From: Hao, Yajing

Sent time: 01/03/2019 05:11:07 PM

To: xiaorui5757@163.com; liang_chen@whu.edu.cn; lixiao5128@gmail.com; zhoubing@ioz.ac.cn; Shao, Changwei; Chen, Jiayu; Lim, Do-Hwan; Liang, Zhengyu

Cc: Fu, Xiang-Dong; Li, Hai

Subject: Re: The storage quota of Fulab's server

Hi, everyone!

This is a reminder Email. Tomorrow the server will delete the data beyond the limit for each user. If your data is beyond the quota, I couldn't guarantee which data will be deleted.

These users are safe: Hairi Li, Jiayu Chen, Yajing Hao, Do-Hwan Lim, Zhengyu Liang, Xiao Li. Liang Chen.

These users may be dangeous,which data beyond the limit: Bing Zhou(628G+7.1T+6.7T), Changwei Shao(2T),Rui Xiao(2.9T+139G).

Best Regards!

Yajing Hao

On Dec 26, 2018, at 7:16 PM, Hao, Yajing <yahao@ucsd.edu> wrote:

Hi, everyone!

Today, our server crashed. I tried a lot of methods to fix it. Finally, It backs up to the normal. But I am so warried about our data. Then I check the reasons and find the main reason is one user produced so many data and exceeded the memory. In order to prevent this terrible things happening again, I will allocate different quota to different users. As for the bioinformatics guys, everyone have 5T storage and for batch workers everyone have 1T. This rule doesn't apply to Dr Li who stored the raw data.

I will give us one week to deal with the data. If you have some reasons to use more larger storage, you can contact with me. We can talk about it. And, If you don't contact with me, the system will delete the exceeded data one week later.

I am sorry about that. As we only have one server, we must try our best to use it more safer.

Best regards!

Yajing Hao

From: journalstaff@pnascentral.org
Sent time: 03/04/2019 11:48:06 AM
To: Fu, Xiang-Dong
Cc: gaochen0813@ucla.edu; weicl@szu.edu.cn; ycxue@ibp.ac.cn; yu.zhou@whu.edu.cn; sren001@ucla.edu; yibinwang@mednet.ucla.edu; Hu, Jing; Shao, Changwei; Hao, Yajing; Gou, Lantao; Zhang, Jianlin; Chen, Ju
Subject: PNAS MS# 2018-22176 Publication Update

Dear Dr. Fu,

PNAS has scheduled publication of your article, "**The RBFox2-miR-34a-Jph2 Axis Contributes to Cardiac Decompensation during Heart Failure**," 2018-22176, in Latest Articles the week of March 11, 2019. Your article may publish in Latest Articles any day during that week. The Latest Articles publication date is the official date of record.

PNAS will not publish your article until the production vendor, Sheridan Journal Services, has incorporated the changes you made on the proofs. If you have requested a second set of proofs, your article will not publish until you have reviewed the edits. If you have questions about proofs, please contact (PNAS_Specialist.djs@sheridan.com).

The press embargo on your article will lift on March 11, 2019 at 3:00 PM U.S. Eastern time. The embargo date is the earliest possible date that your article can publish. Embargoed copies of your accepted article will be available to journalists starting Wednesday, March 6, 2019, on a secure reporters-only web site. Should you or your institution's public relations office have any press- or embargo-related questions, please contact the PNAS News Office at pnasnews@nas.edu or 202-334-1310.

Public Information Officers (PIOs) and authors may post an embargoed press release to EurekAlert! as early as 2:00 PM US ET the Wednesday afternoon before the embargo lifts. Embargo information must be noted in ALL CAPS at the top of the press release. Authors and press officers are responsible for ensuring that embargoed press releases are not published, broadcast, or posted online in any form in the public domain, including any open access site, prior to the embargo date and time. Failure to comply with the PNAS embargo policy may result in author sanctions.

PNAS provides journalists with access to embargoed content through EurekAlert!. Journalists should register with EurekAlert! at http://www.eurekalert.org/register.php and request access to PNAS materials. If they are already registered with EurekAlert!, they can request access to PNAS at http://www.eurekalert.org/account.php.

If you must delay publication for a special reason, please notify the PNAS News Office immediately, no later than noon US ET on Tuesday, March 5, 2019.

PNAS automatically deposits the final, published version of all its content, regardless of funding, in PubMed Central (PMC) and makes it free at both PMC and PNAS within 6 months of publication. For release immediately on publication, the open access surcharge is $1,150 for authors from institutions with a site license/open access membership. For more information, please see our editorial (https://www.pnas.org/cgi/content/full/102/15/5303). For information about the PNAS open access option, including fees and license details, please visit https://www.pnas.org/page/subscriptions/open-access.

Best regards,
PNAS News Office
Phone: 202-334-1310
E-mail: PNASNews@nas.edu

From: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Sent time: 03/13/2019 06:03:14 PM
To: Fu, Xiang-Dong
Subject: USTC

XD:

I wonder if you can join the International Scientific Advisory Committee for University of Science and Technology of China. We plan to have the first meeting on April 15, and I know that you will be there the day before, so can you just stay longer to attend the meeting? The meeting will last until the afternoon of April 16. If you can do it, I will let Linzhao Cheng and Tian Xue know so that they can help you with the logistics. XF

From: davinchen@ustc.edu.cn
Sent time: 03/27/2019 05:39:23 PM
To: Fu, Xiang-Dong
Cc: 王小凡院士 <xiao.fan.wang@duke.edu>; 程临钊-USTC <lzcheng@ustc.edu.cn>; 程临钊-Yahoo <LZcheng@yahoo.com>; 薛天院长 <xuetian@ustc.edu.cn>
Subject: USTC ISAB Member Invitation and First Meeting in Hefei on April 15-16
Attachments: Invitation letter_Professor Fu Xiangdong.pdf

Dear Professor Fu,

Hope this E-mail finds you well.

As Professor Wang Xiaofan told me to contact you, I have attached the USTC ISAB member invitation letter signed by President Bao.
We hope that you can attend the reception dinner on April 14th. If you have any further questions, please feel free to contact me. Looking forward to seeing you in Hefei!

Yours sincerely,

Davin Chen, USTC Life Sciences & Medicine
--
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University of Science and Technology of China
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443 Huangshan Road, Shushan District, Hefei, Anhui 230027
Tel: +86-0551-63601127
E-mail: biomed@ustc.edu.cn
安徽省合肥市黄山路443号中国科大西区科技实验楼709

中国科学技术大学
University of Science and Technology of China
地址：中国 安徽 合肥市金寨路96号　邮编：230026
电话：0551－63602184 传真：0551－63631760 Http://www.ustc.edu.cn

March 22nd, 2019

Dear Esteemed Prof. Xiangdong Fu,

The Division of Life Sciences and Medicine in the University of Science and Technology of China (hereafter referred to as USTC Life Sciences and Medicine) would like to invite you as a member of the International Scientific Advisory Board (ISAB). This multi-disciplinary international board consisting of outstanding scientists with expertise in broad areas of life sciences and medicine will provide independent advice to the Dean on academic and scientific directions of the division. ISAB holds no more than two meetings per year in China; at least one in USTC. The meeting is aimed at strengthening the USTC Life Sciences and Medicine's international orientation and collaborations in its research and teaching activities. USTC will reimburse the ISAB members on expenses incurred and provide an honorarium, consistent with international norm.

Responsibilities of ISAB members are limited strictly to the consulting activities outlined above, and do not involve any administrative duties or research activities. USTC will not provide funding or non-monetary means to the members or their research labs beyond the travel reimbursement and honorarium outlined above. We understand that as an ISAB member, your service on ISAB shall not be conflict with your employment rules or regulations. For example, members of ISAB are not expected to disclose information that is considered confidential and non-public information to USTC, nor transfer privileged materials or intellectual properties to USTC. Meanwhile, members of ISAB shall not disclose proprietary or confidential information of USTC that they acquire while conducting their service as members of ISAB for USTC. Your appointment as an ISAB member is for five years, starting on April 1st, 2019.

The first meeting will be held in USTC located in the City of Hefei, China on April 15-16. We would like to request your arrival in the afternoon of April 14 to join us in a welcoming reception. We plan to assist your lodge in the University guest house or the nearby Crown Plaza Hotel.

Please contact us if you gave any questions or suggestions.

With best regards,

Bao Xi

Professor Xinhe Bao, President of University of Science and Technology of China

From: Fu, Xiang-Dong
Sent time: 03/28/2019 08:59:17 AM
To: davinchen@ustc.edu.cn
Cc: 王小凡院士 <xiao.fan.wang@duke edu>; 程临钊-USTC <lzcheng@ustc.edu.cn>; 程临钊-Yahoo <LZcheng@yahoo.com>; 薛天院长 <xuetian@ustc.edu.cn>
Subject: Re: USTC ISAB Member Invitation and First Meeting in Hefei on April 15-16

Dear Davin,

Thanks for the letter. I am pleased to accept the appointment as a ISAB member. As I have talk Prof Xiaofan Wang, I will attend a Tri-Institutional Symposium at USTC in April 13. Since there will be a lot of interactions during this meeting with colleagues in life science on the campus and given my schedule to leave in the morning of April 14, I will not be able to stay for the April 15-16 meeting this time. I should be available for future meetings.

Best regards,

Fu

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

> On Mar 27, 2019, at 5:39 PM, davinchen@ustc.edu.cn wrote:
>
> Dear Professor Fu,
>
> Hope this E-mail finds you well.
>
> As Professor Wang Xiaofan told me to contact you, I have attached the USTC ISAB member invitation letter signed by President Bao.
> We hope that you can attend the reception dinner on April 14th. If you have any further questions, please feel free to contact me. Looking forward to seeing you in Hefei!
>
> Yours sincerely,
>
> Davin Chen, USTC Life Sciences & Medicine
> --
> Life Sciences and Medicine
> University of Science and Technology of China
> Room 709, Science & Technology Building, West Campus
> 443 Huangshan Road, Shushan District, Hefei, Anhui 230027
> Tel: +86-0551-63601127
> E-mail: biomed@ustc.edu.cn
> 安徽省合肥市黄山路443号中国科大西区科技实验楼709<Invitation letter_Professor Fu Xiangdong.pdf>

From: Linzhao Cheng <lzcheng@yahoo.com>
Sent time: 03/30/2019 04:39:12 AM
To: davinchen@ustc.edu.cn; Fu, Xiang-Dong
Cc: 王小凡院士 <xiao.fan.wang@duke.edu>; 程临钊-USTC <lzcheng@ustc.edu.cn>; 程临钊-Yahoo <LZcheng@yahoo.com>; 薛天院长 <xuetian@ustc.edu.cn>
Subject: Re: USTC ISAB Member Invitation and First Meeting in Hefei on April 15-16

Dear Xiang-Dong,

I am delighted to see that you accept our invitation as an ISAB member. I will attend the symposium on 4/13, and a dinner with you, Don Cleveland, XueBiao and others. Look forward to seeing you in Hefei.

Have a good trip.

程临钊 Linzhao
Sent from Yahoo Mail for iPhone

On Thursday, March 28, 2019, 11:59 PM, Fu, Xiang-Dong <xdfu@ucsd.edu> wrote:

> Dear Davin,
>
> Thanks for the letter. I am pleased to accept the appointment as a ISAB member. As I have talk Prof Xiaofan Wang, I will attend a Tri-Institutional Symposium at USTC in April 13. Since there will be a lot of interactions during this meeting with colleagues in life science on the campus and given my schedule to leave in the morning of April 14, I will not be able to stay for the April 15-16 meeting this time. I should be available for future meetings.
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> Best regards,
>
> Fu
>
> Xiang-Dong Fu, Professor
> Dept. of Cellular and Molecular Medicine
> University of California, San Diego
> George Palade Laboratories
> 9500 Gilman Drive, Room 217
> La Jolla, CA 92093-0651
>
> Phone: 858-534-4937
> Fax: 858-822-6692
> Email: xdfu@ucsd.edu
>
> On Mar 27, 2019, at 5:39 PM, davinchen@ustc.edu.cn wrote:
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Yours sincerely,

Davin Chen, USTC Life Sciences & Medicine
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Life Sciences and Medicine
University of Science and Technology of China
Room 709, Science & Technology Building, West Campus
443 Huangshan Road, Shushan District, Hefei, Anhui 230027
Tel: +86-0551-63601127
E-mail: biomed@ustc.edu.cn
安徽省合肥市黄山路443号中国科大西区科技实验楼709
<Invitation letter_Professor Fu Xiangdong.pdf>

From: Fu, Xiang-Dong
Sent time: 04/02/2019 11:04:27 AM
To: protocols@nature.com
Cc: lixiao5128@gmail.com; 周兵 <bzhou@iozlab.ac.cn>; 罗大极 <luodaji@whu.edu.cn>
Subject: Re: Update on manuscript NP-P180235C

Great! Thanks a lot. We will act in a timely manner once we see the proof. Greatly appreciate your inputs during the review process.

Fu

Sent from my iPhone

On Apr 2, 2019, at 10:17 AM, "protocols@nature.com" <protocols@nature.com> wrote:

> Dear Dr. Fu,
>
> I am pleased to inform you that your protocol, "GRID-seq for Comprehensive Analysis of Global RNA-Chromatin Interactions", has now been accepted and sent to our Production department and should soon be published in Nature Protocols. This message is intended to let you know what to expect from us next and where to address any further questions.
>
> Your protocol will now be copyedited to ensure that it conforms to Nature Protocols style. Assuming there are no major problems, you will be asked to view a set of proofs once your protocol has been laid out into the final PDF format. Once proofs are generated, they will be sent to you electronically and you will be asked to send a corrected version within 24 hours. We realise this is a very tight turnaround but there is usually some flexibility in the system, so please get in touch if you require extra time. It is extremely important that you let us know now if you will be difficult to contact over the next three months. If this is the case, please send us the contact information (email and phone number) of someone who will be able to check the proofs and deal with any last-minute problems.
>
> You should receive a proof of your article within about 3-4 weeks. If you have queries at any point during the production process, then please contact the production team at rjsproduction@springernature.com. Once your paper has been scheduled for online publication, the Nature press office will be in touch to confirm the details.
>
> Please look for emails with the subject line 'Proofs for your article in Nature Protocols' and check spam/junk folders in case emails are redirected.
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>
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>
> Shortly after your protocol has been published, we will be in contact again with details of a code that will enable you to access our content free for a year, as a thank you for all your work in writing.

Once your article is published, please do encourage your colleagues to comment on your protocol on the website, as we hope regular commenting will keep our protocols up to date. To assist our authors in disseminating their research to the broader community, our SharedIt initiative provides you with a unique shareable link that will allow anyone (with or without a subscription) to read the published article. Recipients of the link with a subscription will also be able to download and print the PDF.

As soon as your article is published, you will receive an automated email with your shareable link.

You can now use a single sign-on for all your accounts, view the status of all your manuscript submissions and reviews, access usage statistics for your published articles and download a record of your refereeing activity for the Nature journals.

In addition, Springer Nature encourages all authors and reviewers to associate an Open Researcher and Contributor Identifier (ORCID) to their account. ORCID is a community-based initiative that provides an open, non-proprietary and transparent registry of unique identifiers to help disambiguate research contributions.

Please feel free to contact me at any time with any questions.

Best regards,

Ivanka Kamenova, PhD
Associate Editor, Nature Protocols
Nature Research

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Connecting Research and Researchers

****

From:	davinchen@ustc.edu.cn
Sent time:	04/05/2019 11:46:38 PM
To:	傅海安 <hfu@emory.edu>; Fu, Xiang-Dong; 管俊林 <guanjl@ucmail.uc.edu>; 何川 <chuanhe@uchicago.edu>; 黄教悌 <jiaoti.huang@duke.edu>; 李家洋院士 <jyli@genetics.ac.cn>; 李林院士 <lli@sibs.ac.cn>; 李子海教授 <zihai@musc.edu>; 梁卓伟 <deanmed@hku.hk>; 骆利群院士 <lluo@stanford.edu>; 颜宁 <nyan@princeton.edu>; 杨威院士 <wy7y@nih.gov>; 庄小威 <zhuang@chemistry.harvard.edu>
Cc:	王小凡院士 <xiao.fan.wang@duke.edu>; 程临钊-USTC <lzcheng@ustc.edu.cn>; 薛天院长 <xuetian@ustc.edu.cn>
Subject:	USTC ISAB meeting draft agenda V2_4-6
Attachments:	USTC ISAB meeting draft agenda V2_4-6.doc

Dear Professor,

Hope this E-mail finds you well.

The first meeting of ISAB is coming, I have attached the draft agenda as professor Cheng Linzhao told me.

It is a tentative plan, after discussing with Professor Wang Xiao-fan and USTC leadership. We are open to suggestions to improve. More information will follow by April 10th.

Yours sincerely,

Davin Chen, USTC Life Sciences & Medicine

--
Life Sciences and Medicine
University of Science and Technology of China
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443 Huangshan Road, Shushan District, Hefei, Anhui 230027
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E-mail: biomed@ustc.edu.cn
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A tenatiave plan for The first meeting of
International Advisory Committee for
Division of Life Sciences and Medicine (DLSM), USTC
April 14-16, Hefei, China

April 14: Arrival in hotel (Crown Plaza); dinner starting at 18:30

April 15: Bus will leave from hotel at 8:00 am, to the USTC East Campus

8:30 - 9:00 am: Welcome remark by USTC leadership and CHENG Linzhao, Director of DLSM in USTC

9:00- 10 am: Overview introduction by XUE Tian, Executive Director of DLSM, and Executive Dean for School of Life Sciences, followed by discussion

10:00 – 10:15 am: coffee and tea break

10:15 – 12:00 noon: Plans of new initiatives and discussions

12:00 – 2:00 pm: Lunch break (and visiting USTC campus and mesuem)

2:00 – 5:00 pm: Progress reports by 4 young PIs from School of Life Sciences, including a break in the middle

5:00- 6:00 pm: Other issues (include ceremony of appointments)

6:30 pm: Dinner in the USTC guest house

April 16: Bus will leave from hotel at 8 am, to the South Campus of the USTC 1st affiliated (and Anhui Provincial) Hospital

8:30 am – 10:00 am: tour in the Hospital

10:00 – 11:00 am: ISAB international discussions and with USTC leadership

11:30: ending, followed by lunch in the Hospital Cafe

Planed attendance in person:
WANG Xiaofan (chair), LI Lin (co-chair), GUAN Jun-lin, HUANG Jiaoti, LI Jiayang, LI Zihai, LUO Liqun, YANG Wei, FU Haian
Call-in:
FU Xiangdong, HE Chuan, LEUNG Gabriel, YAN Nien, ZHUAG Xiaowei

A list of four young PIs in the School of Life Sciences who will present their work (25 min each for presentation followed by 15 min Q &A)

孙林峰

https://biox.ustc.edu.cn/2017/0527/c692a370262/page.htm

熊　伟

https://biox.ustc.edu.cn/2014/0224/c692a340190/page.htm

瞿　昆

https://biox.ustc.edu.cn/2016/0221/c692a340185/page.htm

朱　书

https://biox.ustc.edu.cn/2017/0125/c692a340183/page.htm

(More information will follow; this session is NOT determining their promotion)

Roster of the International Advisory Committee for Division of Life Sciences and Medicine, USTC

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Wei.Yang@nih.gov

Xiaowei Zhuang, Ph.D.

Professor and Investigator of HHMI
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Harvard University
Cambridge, MA 02138 USA
617-496-9558
zhuang@chemistry.harvard.edu

From: Li, Zihai <zihai@musc.edu>
Sent time: 04/07/2019 08:11:57 AM
To: davinchen@ustc.edu.cn
Cc: 傅海安 <hfu@emory.edu>; Fu, Xiang-Dong; 管俊林 <guanjl@ucmail.uc.edu>; 何川 <chuanhe@uchicago.edu>; 黄教悌 <jiaoti.huang@duke.edu>; 李家洋院士 <jyli@genetics.ac.cn>; 李林院士 <lli@sibs.ac.cn>; 梁卓伟 <deanmed@hku.hk>; 骆利群院士 <lluo@stanford.edu>; 颜宁 <nyan@princeton.edu>; 杨威院士 <wy7y@nih.gov>; 庄小威 <zhuang@chemistry.harvard.edu>; 王小凡院士 <xiao.fan.wang@duke.edu>; 程临钊-USTC <lzcheng@ustc.edu.cn>; 薛天院长 <xuetian@ustc.edu.cn>
Subject: Re: USTC ISAB meeting draft agenda V2_4-6

Hi Devin,

Thanks. I have just taken a new position. Please update my info and communicate with me using my OSU email address.

Looking forward to meeting with everyone!

Thanks.

Zihai

Zihai Li, MD, PhD
Professor and Founding Director
Institute for Immuno-Oncology
The Ohio State University Comprehensive Cancer Center - James
Biomedical Research Tower - 580
Columbus, Ohio 43210
USA
Zihai.li@osumc.edu
Executive assistant: Tamra Brooks
614-330-1284
Tamra.brooks@osumc.edu

On Apr 6, 2019, at 2:50 AM, "davinchen@ustc.edu.cn" <davinchen@ustc.edu.cn> wrote:

> Dear Professor,
> Hope this E-mail finds you well.
> The first meeting of ISAB is coming, I have attached the draft agenda as professor Cheng Linzhao told me.
> It is a tentative plan, after discussing with Professor Wang Xiao-fan and USTC leadership. We are open to suggestions to improve. More information will follow by April 10th.
> Yours sincerely,
> Davin Chen, USTC Life Sciences & Medicine
>
> --
> Life Sciences and Medicine
> University of Science and Technology of China
> Room 709, Science & Technology Building, West Campus
> 443 Huangshan Road, Shushan District, Hefei, Anhui 230027
> Tel: +86-0551-63601127
> E-mail: biomed@ustc.edu.cn
> 安徽省合肥市黄山路443号中国科大西区科技实验楼709
>
> <USTC ISAB meeting draft agenda V2_4-6.doc>

From:	davinchen@ustc.edu.cn
Sent time:	04/10/2019 05:31:52 AM
To:	傅海安 <hfu@emory.edu>; Fu, Xiang-Dong; 管俊林 <guanjl@ucmail.uc.edu>; 何川 <chuanhe@uchicago.edu>; 黄教悌 <jiaoti.huang@duke.edu>; 李家洋院士 <jyli@genetics.ac.cn>; 李林院士 <lli@sibs.ac.cn>; 李子海教授 <Zihai.li@osumc.edu>; 梁卓伟 <deanmed@hku.hk>; 骆利群院士 <lluo@stanford.edu>; 王小凡院士 <xiao.fan.wang@duke.edu>; 颜宁 <nyan@princeton.edu>; 杨威院士 <wy7y@nih.gov>; 庄小威 <zhuang@chemistry.harvard.edu>
Cc:	程临钊-USTC <lzcheng@ustc.edu.cn>; 薛天院长 <xuetian@ustc.edu.cn>; 翁建平 <wengjp@ustc.edu.cn>
Subject:	USTC ISAB First Meeting Agenda
Attachments:	USTC ISAB First Meeting Agenda 20190410.pdf

Dear Professor,

Hope this E-mail finds you well. The first meeting of ISAB is coming and the agenda is attached.

If you have any further questions and suggestions, please feel free to contact me. Looking forward to seeing you in Hefei!

Yours sincerely,

Davin Chen, USTC Life Sciences & Medicine

Life Sciences and Medicine
University of Science and Technology of China
Room 709, Science & Technology Building, West Campus
443 Huangshan Road, Shushan District, Hefei, Anhui 230027
Tel: +86-0551-63601127
E-mail: biomed@ustc.edu.cn
安徽省合肥市黄山路443号中国科大西区科技实验楼709

The First Meeting of International Scientific Advisory Board (ISAB) for Division of Life Sciences and Medicine (DLSM), USTC
April 14-16, Hefei, China

April 14: Arrival in hotel (Crown Plaza); dinner starting at 18:30 (Sakura VIP Dining Room in Crown Plaza Hotel)

April 15: Bus will leave from hotel at 8:00 am, to the USTC East Campus (Meeting Room in the third floor of USTC guest house)

8:30 - 9:00 am: Welcome remark by USTC President Bao and CHENG Linzhao, Director of DLSM in USTC
9:00 - 9:15 am: Ceremony of appointments and Group photo

9:15 - 10:15 am: Overview of DLSM by XUE Tian (Executive Director of DLSM, and Executive Dean for School of Life Sciences), followed by discussion

10:15 - 10:45 am: coffee and tea break

10:45- 11:45 am: Overview of USTC's medical education and 1st affiliated Hospital by Weng Jianping (Executive Dean for School of Clinical Medicine), followed by discussion

12:00 - 2:00 pm: Lunch break (and visiting USTC campus and museum)

2:00 - 6:20 pm: Progress reports by 6 young PIs from School of Life Sciences, including a 20 min break in the middle

6:30 pm: Dinner in the USTC guest house

April 16: Bus will leave from hotel at 8:30 am, to the South Campus of the USTC 1st affiliated (and Anhui Provincial) Hospital

9:00 am - 10:00 am: tour in the Hospital

10:00 - 12:00 am: ISAB international discussions and feedbacks with USTC leadership

12:30: ending, followed by lunch in the Hospital Cafe

Planed attendance in person:

WANG Xiaofan (chair), LI Lin (co-chair), FU Haian, GUAN Junlin, HUANG Jiaoti, LI Jiayang, LI Zihai, LUO Liqun, YANG Wei,

Call-in:
FU Xiangdong, HE Chuan, LEUNG Gabriel, YAN Nieng, ZHUAG Xiaowei

A list of four young PIs in the School of Life Sciences who will present their work (25 min each for presentation followed by 15 min Q &A)

孙林峰

https://biox.ustc.edu.cn/2017/0527/c692a370262/page.htm

宋晓元

https://biox.ustc.edu.cn/2013/0104/c692a340186/page.htm

熊　伟

https://biox.ustc.edu.cn/2014/0224/c692a340190/page.htm

瞿　昆

https://biox.ustc.edu.cn/2016/0221/c692a340185/page.htm

朱　书

https://biox.ustc.edu.cn/2017/0125/c692a340183/page.htm

丁　勇

https://biox.ustc.edu.cn/2014/0925/c692a340189/page.htm

Roster of the International Scientific Advisory Board for Division of Life Sciences and Medicine, USTC

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From: Yan, Nieng <nyan@princeton.edu>
Sent time: 04/10/2019 06:26:27 PM
To: davinchen@ustc.edu.cn; 傅海安 <hfu@emory.edu>; Fu, Xiang-Dong; 管俊林 <guanjl@ucmail.uc.edu>; 何川 <chuanhe@uchicago.edu>; 黄教悌 <jiaoti.huang@duke.edu>; 李家洋院士 <jyli@genetics.ac.cn>; 李林院士 <lli@sibs.ac.cn>; 李子海教授 <Zihai.li@osumc.edu>; 梁卓伟 <deanmed@hku hk>; 骆利群院士 <lluo@stanford.edu>; 王小凡院士 <xiao fan.wang@duke.edu>; 杨威院士 <wy7y@nih.gov>; 庄小威 <zhuang@chemistry.harvard.edu>
Cc: 程临钊-USTC <lzcheng@ustc.edu.cn>; 薛天院长 <xuetian@ustc.edu.cn>; 翁建平 <wengjp@ustc.edu.cn>
Subject: RE: USTC ISAB First Meeting Agenda

Thanks, Davin!

But I don't think I have received a detailed instruction on how and when to call in.

Thanks,
Nieng

From: davinchen@ustc.edu.cn <davinchen@ustc.edu.cn>
Sent: Wednesday, April 10, 2019 8:32 AM
To: 傅海安 <hfu@emory.edu>; 付向东 <xdfu@ucsd.edu>; 管俊林 <guanjl@ucmail.uc.edu>; 何川 <chuanhe@uchicago.edu>; 黄教悌 <jiaoti.huang@duke.edu>; 李家洋院士 <jyli@genetics.ac.cn>; 李林院士 <lli@sibs.ac.cn>; 李子海教授 <Zihai.li@osumc.edu>; 梁卓伟 <deanmed@hku.hk>; 骆利群院士 <lluo@stanford.edu>; 王小凡院士 <xiao.fan.wang@duke.edu>; Yan, Nieng <nyan@princeton.edu>; 杨威院士 <wy7y@nih.gov>; 庄小威 <zhuang@chemistry.harvard.edu>
Cc: 程临钊-USTC <lzcheng@ustc.edu.cn>; 薛天院长 <xuetian@ustc.edu.cn>; 翁建平 <wengjp@ustc.edu.cn>
Subject: USTC ISAB First Meeting Agenda

Dear Professor,
Hope this E-mail finds you well. The first meeting of ISAB is coming and the agenda is attached.
If you have any further questions and suggestions, please feel free to contact me. Looking forward to seeing you in Hefei!
Yours sincerely,

Davin Chen, USTC Life Sciences & Medicine
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Tel: +86-0551-63601127
E-mail: biomed@ustc.edu.cn
安徽省合肥市黄山路443号中国科大西区科技实验楼709

From: Chuan He <chuanhe@uchicago.edu>
Sent time: 04/14/2019 05:45:28 PM
To: davinchen@ustc.edu.cn; Yan, Nieng <nyan@princeton.edu>; 傅海安 <hfu@emory.edu>; Fu, Xiang-Dong; 管俊林 <guanjl@ucmail.uc.edu>; 黄教悌 <jiaoti.huang@duke.edu>; 李家洋院士 <jyli@genetics.ac.cn>; 李林院士 <lli@sibs.ac.cn>; 李子海教授 <zihai@musc.edu>; 梁卓伟 <deanmed@hku hk>; 骆利群院士 <lluo@stanford.edu>; 杨威院士 <wy7y@nih.gov>; 庄小威 <zhuang@chemistry.harvard.edu>
Cc: 王小凡院士 <xiao.fan.wang@duke.edu>; 程临钊-USTC <lzcheng@ustc.edu.cn>; 薛天院长 <xuetian@ustc.edu.cn>
Subject: Re: USTC ISAB meeting draft agenda V2_4-6

Started...

From: Yan, Nieng <nyan@princeton.edu>
Sent: Sunday, April 14, 2019 7:38:15 PM
To: davinchen@ustc.edu.cn; 傅海安; 付向东; 管俊林; Chuan He; 黄教悌; 李家洋院士; 李林院士; 李子海教授; 梁卓伟; 骆利群院士; 杨威院士; 庄小威
Cc: 王小凡院士; 程临钊-USTC; 薛天院长
Subject: RE: USTC ISAB meeting draft agenda V2_4-6

Hi Davin,

I am totally confused. I called in twice, but there was only the video about USTC. Can you send an updated agenda?

Thanks,
Nieng

From: davinchen@ustc.edu.cn <davinchen@ustc.edu.cn>
Sent: Saturday, April 6, 2019 2:47 AM
To: 傅海安 <hfu@emory.edu>; 付向东 <xdfu@ucsd.edu>; 管俊林 <guanjl@ucmail.uc.edu>; 何川 <chuanhe@uchicago.edu>; 黄教悌 <jiaoti.huang@duke.edu>; 李家洋院士 <jyli@genetics.ac.cn>; 李林院士 <lli@sibs.ac.cn>; 李子海教授 <zihai@musc.edu>; 梁卓伟 <deanmed@hku.hk>; 骆利群院士 <lluo@stanford.edu>; Yan, Nieng <nyan@princeton.edu>; 杨威院士 <wy7y@nih.gov>; 庄小威 <zhuang@chemistry.harvard.edu>
Cc: 王小凡院士 <xiao.fan.wang@duke.edu>; 程临钊-USTC <lzcheng@ustc.edu.cn>; 薛天院长 <xuetian@ustc.edu.cn>
Subject: USTC ISAB meeting draft agenda V2_4-6

Dear Professor,
Hope this E-mail finds you well.
The first meeting of ISAB is coming, I have attached the draft agenda as professor Cheng Linzhao told me.
It is a tentative plan, after discussing with Professor Wang Xiao-fan and USTC leadership. We are open to suggestions to improve. More information will follow by April 10th.
Yours sincerely,
Davin Chen, USTC Life Sciences & Medicine

--
Life Sciences and Medicine
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443 Huangshan Road, Shushan District, Hefei, Anhui 230027
Tel: +86-0551-63601127
E-mail: biomed@ustc.edu.cn
安徽省合肥市黄山路443号中国科大西区科技实验楼709

From: Fu, Xiang-Dong

Sent time: 04/30/2019 07:06:37 AM

To: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>

Cc: xuetian@ustc.edu.cn; davinchen@ustc.edu.cn; Yan, Nieng <nyan@princeton.edu>; Liqun Luo <lluo@stanford.edu>; 傅海安 <hfu@emory.edu>; 管俊林 <guanjl@ucmail.uc.edu>; 何川 <chuanhe@uchicago.edu>; Jiaoti Huang <jiaoti.huang@duke.edu>; 李家洋院士 <jyli@genetics.ac.cn>; 李林院士 <lli@sibs.ac.cn>; 李子海教授 <Zihai.li@osumc.edu>; 梁卓伟 <deanmed@hku.hk>; 杨威院士 <wy7y@nih.gov>; 庄小威 <zhuang@chemistry.harvard.edu>; 程临钊-USTC <lzcheng@ustc.edu.cn>; 翁建平 <wengjp@ustc.edu.cn>; 魏海明书记 <ustcwhm@ustc.edu.cn>; 刘同柱书记 <aqwsltz@163.com>; 刘连新院长 <liulx@ustc.edu.cn>; 周荣斌 <zrb1980@ustc.edu.cn>; 臧建业 <zangjy@ustc.edu.cn>; 胡兵 <bhu@ustc.edu.cn>

Subject: Re: congratulations

---

supper good news! Congrats.

Sent from my iPhone

On Apr 30, 2019, at 7:05 AM, Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu> wrote:

> Congratulations! Well deserved honor!
>
> Best regards, XF
>
> > On Apr 30, 2019, at 9:53 AM, Liqun Luo <lluo@stanford.edu> wrote:
> >
> > Dear Nieng,
> >
> > My hearty congratulations on your election to the National Academy of Sciences!
> >
> > http://www.nasonline.org/news-and-multimedia/news/2019-nas-election.html
> >
> > Best, Liqun

From: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Sent time: 04/30/2019 12:38:31 PM
To: Fu, Xiang-Dong
Subject: a message

XD:

Can you make edits to my message at attached below?

Dear Chunli, Zhongli, and Jianguo:

Today, the National Academy of Sciences (NAS) of USA announced the results of 2019 election for 100 new members and 25 Foreign Associates of NAS. Many of us were disappointed and even disheartened to learn that only one of the 100 new members was originally from Mainland China in all disciplines. This tread has been going on for several years, but the result for this year was even more demoralizing for us since we know that many senior scientists originally from China have made major contributions to their fields and deserve to be elected to this organization. We believe that this result reflected the current general atmosphere in the US making us uncomfortable in many ways, particularly those who have tried to promote the advancement of science and technology for all humankind.

In this context, I appeal to you as leaders of CAS to consider to increase the total number of slots for election of foreign member of CAS in this year's election, as a way to express appreciation to many senior scientists who have devoted their efforts to help the country to modernize in scientific research and higher education. Considering that NAS elects up to 25 new foreign associates each year, the slots for foreign members of CAS should be increased significantly since there is no current rule restricting this number. In addition, I hope that the leadership could explain to CAS members that the general requirement of candidates to be existing members of academies of host countries needs to be relaxed, since many qualified candidates from the US have often been marginalized as evidenced by the fact of disproportionately low numbers of NAS members who are Chinese descent.

Thank you in advance for considering this suggestion.

Best regards, XF

From: Fu, Xiang-Dong
Sent time: 04/30/2019 01:02:21 PM
To: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Subject: Re: a message

Hi Xiaofan,

You are taking a leadership role in the issue. Here I made some minor editions for your consideration.

> On Apr 30, 2019, at 12:38 PM, Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu> wrote:
>
> XD:
>
> Can you make edits to my message at attached below?
>
> Dear Chunli, Zhongli, and Jianguo:
>
> Today, the National Academy of Sciences (NAS) of USA announced the results of 2019 election for 100 new members and 25 Foreign Associates. Many of us were disappointed and even disheartened to learn that only one of the 100 new members was originally from Mainland China in all disciplines. This tread has been going on for several years, but the result for this year was even more demoralizing since we know that many senior scientists originally from China have made major contributions to their fields and thus fully deserve to be elected to this organization. We suspect that this result may have something to do with the current atmosphere in the US that have made many of us increasingly uncomfortable in many ways, particularly those who have tried to promote the advancement of science and technology for humanity in general.
>
> In this context, I appeal to you as leaders of CAS to consider the possibility to increase the total number of slots for electing foreign members of CAS in this year's election. This may be a way to express the appreciation of the Chinese academic community to many senior scientists who have devoted their efforts to help China to modernize in scientific research and higher education. Considering the fact that NAS elects up to 25 new foreign associates each year, the slots for foreign members of CAS may be increased to a reasonable number to reflect the growing number of leading scientists of Chinese origin that have made some major contributions to science in both China and abroad. This should be feasible because there is no current rule that restricts this number. In addition, I hope that the leadership could explain to CAS members that the general requirement of candidates to be existing members of academies of host countries needs to be relaxed, since many qualified candidates from the US have often been marginalized as evidenced by such a disproportion of elected NAS members who are Chinese descent. As China has become a global power, the Chinese academic community should have its confidence in identifying qualified candidates.
>
> Thank you in advance for considering this suggestion.
>
> Best regards, XF

From:	tarpin@cell.com
Sent time:	06/04/2019 08:30:59 AM
To:	xiaorui9@whu.edu.cn; Fu, Xiang-Dong
Subject:	Publishing Agreement completed for your article [CELL_10894]
Attachments:	CELL10894.html

Article title: Pervasive Chromatin-RNA Binding Protein Interactions Enable RNA-based Regulation of Transcription
Article reference: CELL10894
Journal title: Cell
Corresponding author: Dr. Xiang-Dong Fu
First author: Dr. Rui Xiao

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Yours sincerely,
Ms. Trina Arpin
E-mail: tarpin@cell.com
[T-5a-20180404]

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Article:	**Pervasive Chromatin-RNA Binding Protein Interactions Enable RNA-based Regulation of Transcription**
Corresponding author:	**Dr. Xiang-Dong Fu**
E-mail address:	**xdfu@ucsd.edu;xiaorui9@whu.edu.cn**
Journal:	**Cell**
Our reference	**CELL10894**
PII:	**S0092-8674(19)30629-4**
DOI:	**10.1016/j.cell.2019.06.001**

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From:	肖锐 <00031889@whu.edu.cn>
Sent time:	06/05/2019 06:56:09 PM
To:	campbell, tracy (els-cma) <tcampbell@cell.com>
Cc:	Fu, Xiang-Dong
Subject:	Re: Cell article

Dear Tracy,

Good news always comes from you!

We are very glad to hear that our paper will be published soon and happy to resolve any queries you have as soon as we can.

Have a great day!

Rui

> -----原始邮件-----
> **发件人:**"Campbell, Tracy (ELS-CMA)" <tcampbell@cell.com>
> **发送时间:**2019-06-06 02:12:30 (星期四)
> **收件人:** "xiaorui9@whu.edu.cn" <xiaorui9@whu.edu.cn>, "xdfu@ucsd.edu" <xdfu@ucsd.edu>
> **抄送:**
> **主题:** Cell article
>
> Dear Drs. Xiao and Fu,
>
> Good afternoon. I am the copy editor for your upcoming paper in *Cell*, scheduled to publish in print and online at **11 a.m. ET on Thursday, June 27**, which is when the press embargo will lift. I look forward to working with you.
>
> By Friday you will receive any queries I have regarding your article. Once those are resolved, we will move on to the proof stage.
>
> Please let me know if you have any questions.
>
> Best wishes,
> Tracy
>
> **Tracy Campbell**
> Deputy Production Editor, *Cell*
> (617) 386-2168

From: Fu, Xiang-Dong
Sent time: 06/07/2019 08:58:54 AM
To: zhoubing@ioz.ac.cn; Xiao Li <lixiao5128@gmail.com>; 罗大极 <luodaji@whu.edu.cn>; Lim, Do-Hwan
Subject: Fwd: Sharing Information for "GRID-seq for comprehensive analysis of global RNA–chromatin interactions"

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

Begin forwarded message:

From: Springer Nature Sharing <no-reply@email.authors.springernature.com>
Subject: Sharing Information for "GRID-seq for comprehensive analysis of global RNA–chromatin interactions"
Date: June 7, 2019 at 8:33:46 AM PDT
To: <xdfu@ucsd.edu>

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Dear Author,

Congratulations on publishing "GRID-seq for comprehensive analysis of global RNA–chromatin interactions" in Nature Protocols. As part of the Springer Nature Content Sharing Initiative, you can now publicly share full-text access to a view-only version of your paper by using the following SharedIt link:

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From:	Arpin, Trina (ELS-CMA) <tarpin@cell.com>
Sent time:	06/10/2019 08:38:16 AM
To:	xiaorui9@whu.edu.cn; Fu, Xiang-Dong
Cc:	Operations <operations@cell.com>
Subject:	Cell10894 outstanding documentation

Dear Dr. Fu,

I'm sorry to trouble you, but I notice that we have not received a completed Reproduction of Colour Artwork form for your upcoming *Cell* manuscript. It is important that you complete this form to indicate the tax-exempt status of your institution (if appropriate) and to verify the billing address to which we will send your invoice. If you are unable to complete the form prior to publication, we will send the invoice to the address currently available in our database.

Could I ask you to please complete the form by Thursday morning,June 20? (Please note that the form does not require that you have a Purchase Order number ready, even if you intend to pay with a Purchase Order.) I have pasted the link to the form landing page below; please let me know if you have any questions.
https://authors.elsevier.com/authorform/landingpage/selection.do?articleId=CELL10894&md5key=256f75156b0b94e6364b8ebb6345550e&lang=

Best wishes,
Trina

Trina Arpin
Senior Production Editor
Cell
(617) 397-2871 | 50 Hampshire St. | Cambridge, MA 02139

From: tcampbell@cell com
Sent time: 06/11/2019 05:04:09 PM
To: xiaorui9@whu.edu cn; Fu, Xiang-Dong
Subject: Color figures in your article [CELL_10894] in Cell

Our reference: CELL 10894
Article reference: CELL_CELL-D-18-02042
Article title: Pervasive Chromatin-RNA Binding Protein Interactions Enable RNA-based Regulation of Transcription
To be published in: Cell

Dear Dr. Fu,

Our records show that you have not yet completed the Reproduction of Color Artwork form to provide the billing information associated with your color illustrations. Please note that to communicate scientific data most accurately, we require that colour data be displayed in colour both in print and online, and that figures submitted and peer-reviewed in colour also be published in colour.

Please go to the link below as soon as possible for details of your color illustrations, and to provide your preferred billing information:

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(If the above link does not work, please copy the entire URL into your browser, noting that it may run onto a second line.)

Thank you for your cooperation. Please contact us if you have any questions, and quote the reference for your article, CELL 10894, in all of your messages to us.

Kind regards,

Ms Tracy Campbell
Copyeditor
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E-Mail: tcampbell@cell.com

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Attachments: Terms and Conditions of Sale and Purchase.pdf CELL10894C.html

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Article title: Pervasive Chromatin-RNA Binding Protein Interactions Enable RNA-based Regulation of Transcription
Article reference: CELL10894
Journal title: Cell
Corresponding author: Dr. Xiang-Dong Fu
First author: Dr. Rui Xiao

Dear Dr. Fu,

Please find attached a copy of the "Reproduction of Colour Artwork" form you completed online on 12-JUN-2019 for the above article.

WHAT HAPPENS NEXT

If you have placed an order for printed colour, the invoice/receipt will be emailed to you within 5 to 10 days. Check your spam/junk folder in case the email appears there.

If you have any questions, please do not hesitate to contact us, quoting your article reference number CELL10894 in all correspondence.Kind regards,
Ms. Trina Arpin
E-mail: tarpin@cell.com
[T-5b-20152809]

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REPRODUCTION OF COLOUR ARTWORK

Article:	**Pervasive Chromatin-RNA Binding Protein Interactions Enable RNA-based Regulation of Transcription**
Corresponding author:	**Dr. Xiang-Dong Fu**
E-mail address:	**xdfu@ucsd.edu;xiaorui9@whu.edu.cn**
Journal:	**Cell**
Our reference:	**CELL10894**
PII:	**S0092-8674(19)30629-4**
DOI:	**10.1016/j.cell.2019.06.001**

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Order number:
OACSCCELL108947

Order date:
12th June 2019

Figure	Print in colour	Chargeable
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Total number of colour figures is 6
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From: Fu, Xiang-Dong

Sent time: 07/07/2019 12:38:29 PM

To: 唐鹏 <tangpeng@whu.edu.cn>; Li Guangnan <yashinlgn@163.com>; Zhou Yu <yu.zhou@whu.edu.cn>

Subject: A useful paper (review at Cell Rep)

Attachments: APA regulation by CELF2.pdf ATT00001.txt

Here is a useful paper I just reviewed for Cell Rep. In addition, there is a new review on APA in Nat Rev Genetics.

From: 张宇 <yuzhang@sibs.ac.cn>

Sent time: 07/08/2019 07:31:12 PM

To: echenum@med.umich.edu; lim@mskcc.org; wshou@iupui.edu; xutao@ucas.ac.cn; xutao@ibp.ac.cn; xhfeng@zju.edu.cn; Wu, Dan <dianqing.wu@yale.edu>; Fu, Xiang-Dong; Guan, Kun-Liang; Min Han <mhan@colorado.edu>; Guo-Min Li <Guo-Min.Li@UTSouthwestern.edu>; Xiaolong Liu <liux@sibs.ac.cn>

Cc: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>; 李林 <lli@sibs.ac.cn>

Subject: The 2019 annual meeting of SAB-SINH, CAS

Attachments: 1 Preliminary Schedule of 2019 SINH SAB Meeting.pdf 2 Information about Reimbursement of Airfare.docx

---

Dear professors,

Greetings from Shanghai :) The Scientific Advisory Board (SAB) annual meeting of SINH, CAS will be held November 13, 2019 in Shanghai. Attached please kindly find the following documents,

1. Preliminary Schedule
2. Information about Reimbursement of Airfare

If you have any questions or concerns, please feel free to let me know.

Sincerely,
Yu

Yu Zhang, Ph.D.
Director
Science & Technology Development department (STD)
Shanghai Institute of Nutrition and Health (SINH)
Chinese Academy of Sciences (CAS)
320 Yueyang Rd., the Main Building 213
Shanghai 200031, China
E-mail: yuzhang@sibs.ac.cn
Tel: 86-21-54920092, 13818372316
Fax: 86-21-54920078

Preliminary Schedule of
2019 SINH Scientific Advisory Board Meeting

November 12-13, 2019　Shanghai, China

Chair : Prof. Xiao-Fan Wang

Time	Event
Nov. 12	Arrive in Shanghai
Nov. 13	SINH Scientific Advisory Board Meeting
08:30-09:00	SINH Report by Lin Li
Scientific Reports by Research Groups Presentation 20 min，Q&A 15 min	
09:00-09:35	Reported by Wei Lv：Immunometabolism
09:35-10:10	Dynamic evaluation and modification (TBD)
10:10-10:30	Internal discussion of the SAB
10:30-10:40	*Tea Break*
10:40-12:00	Discussion：strategy and direction for SINH research and scientific programs, etc.
12:00-13:30	*Lunch*
Afternoon	Discussion

* 吕伟为到位满 3 年的 PI（2016 年 5 月份入职）。

Information about Reimbursement of Airfare

Please kindly buy airline ticket by yourself. We will reimburse economy class airfare of direct flights. Thanks!

We are grateful to you for providing us the following documents for airfare reimbursement after you return back to your institution.

1. Receipt/invoice & flight itinerary (electronic version)

2. Scan copy of passport (electronic version)

- Pages with personal information and photo, visa, stamps of arrival in and departure from China

3. All boarding passes

- Mobile boarding pass (electronic version) or
- Conventional boarding pass (Please kindly give us your original boarding passes of the flights from USA to Shanghai during the SAB meeting, and email us the scan copy of boarding passes concerning the return trip later on. Thanks!)

.....

Contact Email: kwxue@sibs.ac.cn

Post address :

Ms. Kewen XUE

Room 211, SIBS Main Building, 320 Yueyang Road, Shanghai 200031, China

Tel: +86-21-54920030

When we receive the aforesaid documents, we'll deal with the reimbursement as soon as possible.

Please provide us with your bank account information in the following form. Thanks!

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	Address	

Many thanks for your attention!

From: Elsevier - Article Status <Article_Status@elsevier.com>
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To: xiaorui9@whu.edu.cn; Fu, Xiang-Dong
Subject: The offprints of your article [CELL_10894] have been shipped

---

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If you have any queries we really want to hear from
you via our 24/7 support at http://service.elsevier.com

Article title: Pervasive Chromatin-RNA Binding Protein Interactions Enable RNA-based Regulation of Transcription
Article reference: CELL10894
Journal title: Cell
Corresponding author: Dr. Xiang-Dong Fu
First author: Dr. Rui Xiao
Offprints order dispatch: 9-JUL-2019

Dear Dr. Fu,
The 50 offprints you ordered on 20-JUL-2019 were dispatched on 9-JUL-2019 to:

Dr. Rui Xiao
Wuhan University
Medical Research Institute
Rm 1304, Medical Research Institute
Wuhan University
430071
Wuhan, Hubei
China

Delivery of the offprints can take up to 10 weeks depending on local postal services.

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Kind regards,
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From: 高军涛 <jtgao@mail.tsinghua.edu.cn>

Sent time: 10/10/2019 01:28:43 AM

To: Yijun.Ruan@jax.org; jtl10@cornell.edu; casellar@mail.nih.gov; zhaok@nhlbi.nih.gov; falber@g.ucla.edu; Thomas.Cremer@lrz.uni-muenchen.de; Giacomo.Cavalli@igh.cnrs.fr; vcorces@emory.edu; qiangwu@sjtu.edu.cn; yao_hongjie@gibh.ac.cn; silin.zhong@cuhk.edu.hk; chang.liu@zmbp.uni-tuebingen.de; tanger_009@163.com; gongl100@nenu.edu cn; xingwangli@mail.hzau.edu.cn; xiaorui9@whu.edu.cn; stemcellding@163.com; yan_jiang@fudan.edu.cn; guoliang.li@mail.hzau.edu.cn; sunneyxie@pku.edu.cn; ahe@pku.edu.cn; zengjy@gmail.com; zhangzhihua@big.ac.cn; zsh@amss.ac.cn; zhucheng_chen@mail.tsinghua.edu.cn; xiongji@pku.edu.cn; duzhenhai93220@gmail.com; jingyuwangbio@126 com; lirf@pku.edu.cn; liff@big.ac.cn; liuc@big.ac.cn; xiewei121@tsinghua.edu.cn; liuj@big.ac.cn; dhzhu@pumc.edu.cn; cheng_li@pku edu.cn; qczhang@mail.tsinghua.edu.cn; xshen@tsinghua.edu.cn; zhenhaid@foxmail com; Fu, Xiang-Dong; Yang CHEN <yc@mail.tsinghua.edu.cn>

Cc: michaelzhang <michaelzhang@tsinghua.edu.cn>

Subject: information for speakers

Dear all speakers,
We highly appreciate your contribution for the 6th international Genome Syposium.

For your talk on Oct 11 and 12,
For speakers who have 30 minutes, there will be 25 minutes presentation and 5 minutes discussion;
For speakers who have 20 minutes, there will be 16 minutes presentation and 4 minutes discussion;
For speakers who have 10 minutes, there will be 8 minutes presentation and 2 minutes discussion;

Dinner for tonight and Oct 12:
Suhu Mantogini (Tsinghua Branch) 素虎 漫陀吉尼 (清华店)

Thank you very much.
Best wishes.

Organizing committee

From: USARMY Ft Detrick MEDCOM CDMRP Mailbox CDMRP BCRP <usarmy.detrick.medcom-cdmrp.mbx.cdmrp-bcrp@mail.mil>
Sent time: 11/26/2019 04:00:53 AM
To: xdfu@ucsd.edu
Subject: RESPONSE REQUESTED: Breast Cancer Research Program Award Outcome Survey

Dear **Xiang-Dong Fu,**

The Department of Defense (DoD) Breast Cancer Research Program (BCRP) is conducting a survey of past grant awardees to gather information on the progress and outcomes of their studies funded by the BCRP.

This information will be used by the BCRP to evaluate the success of our program and may be used in informational materials provided to Congress, the DoD, and the public. The survey should only take about 5-10 minutes to complete.

Details of the BCRP-funded award for which we are requesting feedback are below:

Log Number: BC101584
Award Title: Chemical Strategy to Translate Genetic/Epigenetic Mechanisms to Breast Cancer Therapeutics
Award Mechanism: Idea Award: Collaborative Option

Please use the link below to access the online survey. **Please complete the survey by December 6, 2019**. The BCRP greatly appreciates your time and effort in completing the survey.

Survey Link:
https://www.surveymonkey.com/r/BCRP2019

Thank you for your contributions toward the BCRP mission of ending breast cancer.

From: geo@ncbi.nlm.nih.gov
Sent time: 12/21/2019 04:21:44 AM
To: xdfu@ucsd.edu; yu.zhou@whu.edu.cn
Subject: Reminder for GEO data release

Dear Xiang-Dong Fu:

This is a reminder that the following GEO record is scheduled to become public on December 31, 2019:

GSE66021 - Molecular Determinants for RNA Polymerase II Elongation Rate and Acceleration

If you would like to postpone the release date, please:

1. Login to your GEO account at: www.ncbi.nlm.nih.gov/geo/
2. Go to your record:
   http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE66021
3. Select the 'UPDATE' box at the top of the page.
4. Follow the update web forms. On the 'Data Field' page, there is a 'Data Release Date' box you can use to specify the new release date. Changes to Series release date will be automatically propagated to all private Samples contained within that Series.

Alternatively, you may reply to this email with the new release date.

ADD CITATION INFORMATION

If these data have been published, please add the citation to your Series record and link your data to PubMed. There are two ways to add a PubMed identifier (PMID) to your Series:

1. Go to your Series records and follow the instructions next to the "Citation missing" line, or
2. Use the 'UPDATE' forms described above to add the PubMed ID to your Series

If your citation is not included in PubMed, please reply to this e-mail with the full citation including title, authors, journal, issue and page numbers and DOI if available.

Thank you for helping us to keep GEO up-to-date.

Regards,
The GEO Team

From: geo@ncbi.nlm.nih.gov
Sent time: 12/22/2019 10:48:26 PM
To: xdfu@ucsd.edu; yu.zhou@whu.edu.cn
Subject: fulab: update to (private) GSE66021

[sent to: "xdfu@ucsd.edu" "yu.zhou@whu.edu.cn"]

GSM1613033 release_date is changed from 'Dec 31, 2019' to 'Dec 31, 2020
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GSM1613076 release_date is changed from 'Dec 31, 2019' to 'Dec 31, 2020
GSM1613077 release_date is changed from 'Dec 31, 2019' to 'Dec 31, 2020
GSM1613078 release_date is changed from 'Dec 31, 2019' to 'Dec 31, 2020
GSM1613079 release_date is changed from 'Dec 31, 2019' to 'Dec 31, 2020
GSM1613080 release_date is changed from 'Dec 31, 2019' to 'Dec 31, 2020
GSE66021 release_date is changed from 'Dec 31, 2019' to 'Dec 31, 2020'

From: Fan, Jun <jbfan@health.ucsd.edu>

Sent time: 01/09/2020 02:15:52 PM

To: 109288756@qq.com; christoph.burkart@gmail.com; prioncheng@outlook.com; yu.zhou@whu.edu.cn; miyan@ucsd.edu; klaus-peter.knobeloch@uniklinik-freiburg.de; drjeremyrich@gmail.com; hucang@salk.edu; Sayuri Ishida <sishida@ucsd.edu>; Huizhong Xu <hzx1926@gmail.com>; Kim, Jin-Young <jik187@ucsd.edu>; Arimoto, Keiichiro <karimoto@ucsd edu>; Fu, Xiang-Dong <xdfu@ucsd.edu>

Subject: Good news about our manuscript

Dear all,

Happy the new year 2020! As you may be noticed, our manuscript finally got close to the official acceptance for publication on Cancer Discovery. I would like to thank you all for the great help/support on this project and the constructive suggestions for writing the report and for addressing the reviewers' questions. Could you please check your email regarding three electronic forms (author contribution form, copyright form and conflict of interest form) and let me know if you have any questions about them. Thank you again for all the help.

Best wishes,

Junbao

****

Junbao Fan, Ph.D.

Assistant Project Scientist

University of California, San Diego

Moores UCSD Cancer Center

Dong-Er Zhang Laboratory

3855 Health Sciences Drive, #0815

La Jolla, CA 92093-0658

E-Mail: jbfan@ucsd.edu

Tel: 858-822-5327

****

From: Jeremy Rich <drjeremyrich@gmail.com>

Sent time: 01/10/2020 04:30:34 AM

To: Fan, Jun

Cc: 109288756@qq.com; christoph.burkart@gmail.com; prioncheng@outlook.com; yu.zhou@whu.edu.cn; miyan@ucsd.edu; klaus-peter.knobeloch@uniklinik-freiburg.de; hucang@salk.edu; Sayuri Ishida <sishida@ucsd.edu>; Huizhong Xu <hzx1926@gmail.com>; Kim, Jin-Young <jik187@ucsd.edu>; Arimoto, Keiichiro <karimoto@ucsd.edu>; Fu, Xiang-Dong <xdfu@ucsd.edu>

Subject: Re: Good news about our manuscript

Junbao,

Congratulations on your publication! Tremendous work.

Jeremy

Jeremy N. Rich, MD, MHS, MBA
Professor, Department of Medicine, Division of Regenerative Medicine
Professor, Department of Neurosciences
Director, Neuro-Oncology
Director, Brain Tumor Institute

> On Jan 9, 2020, at 2:15 PM, Fan, Jun <jbfan@health.ucsd.edu> wrote:
>
> Dear all,
>
> Happy the new year 2020! As you may be noticed, our manuscript finally got close to the official acceptance for publication on Cancer Discovery. I would like to thank you all for the great help/support on this project and the constructive suggestions for writing the report and for addressing the reviewers' questions. Could you please check your email regarding three electronic forms (author contribution form, copyright form and conflict of interest form) and let me know if you have any questions about them. Thank you again for all the help.
>
> Best wishes,
>
> Junbao
>
> **********
>
> Junbao Fan, Ph.D.
>
> Assistant Project Scientist
>
> University of California, San Diego
>
> Moores UCSD Cancer Center
>
> Dong-Er Zhang Laboratory
>
> 3855 Health Sciences Drive, #0815
>
> La Jolla, CA 92093-0658
>
> E-Mail: jbfan@ucsd.edu
>
> Tel: 858-822-5327
>
> **********

From: Xiao-Fan Wang, Ph D. <xiao.fan.wang@duke.edu>
Sent time: 01/16/2020 01:11:27 PM
To: xdfu@ucsd.edu
Subject: other support
Attachments: Questions for OS.1.docx

This is the form that we all have to produce for Other Supports for the NIH. XF

Questions for Other Support

Many of our federal sponsors are promoting the full disclosure of ***all*** resources being made available to researchers in support of and/or related to ***all*** of their research endeavors, regardless of whether the support has a monetary value and regardless of whether the support is based at the researcher's home institution.

1. Do you have any **positions** or appointments outside of Duke (foreign or domestic), whether full-time or part-time, paid or unpaid, adjunct, visiting or honorary?
    - If so, please list:
        - Date
        - Role
        - Name of funding source

2. Do you receive any funding that currently supports your ongoing research projects, whether provided through a **foreign** organization, or to you, as an individual (including any foreign awards, talent programs, etc.)? This would include any source of funding, regardless of type (government, non-profit, industry, internal, etc.).

    - If so, please provide:
        - Date
        - Role
        - Name of funding source
        - Title of project or funding source
        - Total award amount for the entire project period (including F&A)
        - Number of person months per year, if applicable
        - Description of purpose of funding/goals statement

3. Do you receive any "in kind" support, such as support for laboratory personnel, for example visiting researchers supported by their home institutions or governments, postdocs supported by fellowships or volunteers, and/or provision of high-value materials that are not freely available (e.g., biologics, chemicals, model systems, technology, etc.)?
    - If so, please provide:
        - Type of support (equipment, personnel, etc.)
        - Source of support (industry partner, foreign study abroad scholarship, etc.)

From: no-reply@copyright.com

Sent time: 01/23/2020 12:34:27 AM

To: d7zhang@ucsd.edu

Cc: jbfan@ucsd.edu; sishida@ucsd.edu; hzx1926@gmail.com; 1109288756@qq.com; jik187@ucsd.edu; christoph.burkart@gmail.com; prioncheng@outlook.com; karimoto@ucsd.edu; miyan@ucsd.edu; yu zhou@whu.edu.cn; balgyorf@gmail.com; klaus-peter.knobeloch@uniklinik-freiburg.de; jerich@ucsd.edu; hucang@salk.edu; xdfu@ucsd.edu

Subject: CD-19-0608R2: Please Confirm and Pay Your Publication Order

CANCER DISCOVERY

AACR American Association for Cancer Research

Please confirm and place your publication order.

Dear Dr. Zhang,

Congratulations on being accepted for publication in *Cancer Discovery* for the following manuscript:

Manuscript DOI: 10.1158/2159-8290.CD-19-0608
Manuscript ID: CD-19-0608R2
Manuscript Title: Type I Interferon Regulates a Coordinated Gene Network to Enhance Cytotoxic T Cell-Mediated Tumor Killing
Published by: AACR

To facilitate prompt publication, please place your publication order and agree to your author publication charges using the RightsLink® e-commerce solution from CCC. Any delay in placing your order may result in a delay in publication.

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To review and pay your charge(s), and request an invoice please click here.

To complete a secure transaction, you will need a RightsLink account. If you do not have one already, you will be prompted to register as you are checking out your author charges. This is a very quick process; the majority of your registration form will be pre-populated automatically with information we have already supplied to RightsLink.

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Sincerely,
AACR

Tel.: +1-877-622-5543 / +1-978-646-2777
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www.copyright.com

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From: no-reply@copyright.com

Sent time: 01/30/2020 10:01:48 PM

To: d7zhang@ucsd.edu

Cc: jbfan@ucsd.edu; sishida@ucsd.edu; hzx1926@gmail.com; 1109288756@qq.com; jik187@ucsd.edu; christoph.burkart@gmail.com; prioncheng@outlook.com; karimoto@ucsd.edu; miyan@ucsd.edu; yu zhou@whu.edu.cn; balgyorf@gmail.com; klaus-peter.knobeloch@uniklinik-freiburg.de; jerich@ucsd.edu; hucang@salk.edu; xdfu@ucsd.edu

Subject: CD-19-0608R2: Reminder to Place Your Publication Order

CANCER DISCOVERY

AACR American Association for Cancer Research

Reminder: Please confirm and place your publication order

Dear Dr. Zhang,

Recently we sent you a notification to confirm and place your publication order for the following manuscript:

Manuscript DOI: 10.1158/2159-8290.CD-19-0608
Manuscript ID: CD-19-0608R2
Manuscript Title: Type I Interferon Regulates a Coordinated Gene Network to Enhance Cytotoxic T Cell-Mediated Tumor Killing
Published by: AACR

To facilitate prompt publication, please place your publication order and agree to your author publication charges using the RightsLink® e-commerce solution from CCC. Any delay in placing your order may result in a delay in publication.

Pay charges now / Request an invoice

To review and pay your charge(s), and request an invoice please click here.

To complete a secure transaction, you will need a RightsLink account. If you do not have one already, you will be prompted to register as you are checking out your author charges. This is a very quick process; the majority of your registration form will be pre-populated automatically with information we have already supplied to RightsLink.

If you have any questions about these charges, please contact CCC Customer Service using the information below.

Sincerely,
AACR

Tel.: +1-877-622-5543 / +1-978-646-2777
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From: husnain raza <husnainraza9003@gmail.com>

Sent time: 01/31/2020 07:52:44 AM

To: ashi@hust.edu.cn; duanqhwz@hust.edu.cn; chentianyuzj@163.com; majingwei_pumc@126.com; ketang@hust.edu.cn; tjhuangbo@hotmail.com; jcyxyweb@mails.tjmu.edu.cn; x2sw@scut.edu.cn; tmugraduate@126.com; oec@mail.fjmu.edu.cn; oec@fjmu.edu.cn; hushuang@sdu.edu.cn; chehuiqing@sdu.edu.cn; yjsb@sdu.edu.cn; medcenter@fudan.edu cn; pharmacy_gs@fudan.edu.cn; Sunxunf@shmu.edu.cn; jfhu@fudan.edu.cn; Muqing@fudan.edu.cn; Gxyang@fudan.edu.cn; Jchang@fudan.edu.cn; Pzyu@fudan.edu.cn; Bgwei1974@fudan.edu.cn; Zzhou2003@sina.com; jxiong@fudan.edu.cn; yonghuiwang@fudan.edu.cn; wangyang@shmu.edu.cn; wfu@fudan.edu.cn; Liyx417@fudan.edu.cn; limingshao@fudan.edu cn; yingchen71@fudan.edu.cn; zhoulu@fudan.edu.cn; Zhangqian511@shmu.edu.cn; Zhangw416@fudan.edu.cn; xfgu@fudan.edu.cn; dingning@fudan.edu; zhaoweili@fudan.edu.cn; leixs@fudan.edu.cn; cy110@fudan.edu.cn; xcdong@fudan.edu.cnq; qxie@fudan.edu.cn; tangting@fudan.edu.cn; fmq@fudan.edu.cn; dianwenju@fudan.edu.cn; xunlongshi@fudan.edu.cn; yelil@fudan.edu.cn; haiyanzhu@fudan.edu.cn; lijiyang@fudan.edu.cn; chenjun@fudan.edu.cn; zhuyz@fudan.edu.cn; xuemzhang@fudan.edu.cn; Shxiaoy@fudan.edu.cn; liuxinhua@fudan.edu.cn; blou@shmu.edu.cn; wftan@fudan.edu.cn; liyue@fudan.edu.cn; xinhong@fudan.edu.cn; maoyc@fudan.edu.cn; guowei@fudan.edu.cn; jbdong@shmu.edu.cn; panlilong@fudan.edu.cn; 365213474@qq.com; Jxwang@shmu.edu.cn; qzzhang@fudan.edu.cn; wlu@fudan.edu.cn; wylu@shmu.edu.cn; Jiangchen@shmu.edu.cn; fd_luyi@fudan.edu.cn; liumin@shmu.edu.cn; sunt@fudan.edu.cn; shenteng@fudan.edu.cn; shaxy@fudan.edu.cn; yanyanjiang@shmu edu.cn; qijianping@fudan.edu.cn; rqhuang@fudan.edu.cn; weigang@fudan.edu.cn; liuyu@fudan.edu.cn; qinjing@fudan.edu cn; pharmaxie@aliyun com; lmhan@fudan.edu.cn; weimincai@fudan.edu.cn; mg0328@fudan.edu.cn; xiangxq@fudan.edu.cn; gongqing@fudan.edu.cn; zhengyuanting@fudan.edu.cn; honglan@fudan.edu.cn; danielzhang1992@163.com; houwanwan2008@163.com; phillfee0328@hotmail.com; sungkim@snu.ac.kr; mcbhwj@imcb.a-star.edu.sg; shaomeng@umich.edu; 国际部 <admission@sdu.edu cn>; Wei Wu <wuwei@shmu.edu.cn>; Gao Lirong <zqpang@fudan.edu.cn>; Leming Shi <lemingshi@fudan.edu.cn>; ; ; ; ; ; ; ; ; ; ; 「攀搀甀「㧜济; duanqhwz@hust.edu.cn; ;

Subject: Fwd: Information regarding CORONA VIRUS outbreak

Honorable Professor
Warm greetings
May all peoples of Great Republic of China be happy and healthy ever
I am very grieved to hear about CORONA VIRUS outbreak in Great Republic of CHINA. I love this country as its our neighbor and best friend country of Pakistan I have deep emotions of well being for Chinese Peoples.
I have studies as Pharmacist and also I have good research experience in field of Medicinal Biochemistry so I just want to share a necessary information regarding prevention and cure of CORONA VIRUS signs, symptoms and cure.
Grinded Black Long Pepper powder 1000 mg 0r 1 g along with Amantadine twice daily for one month will leads to cure of signs and symptoms and it will help to improve health and resistance against CORONA VIRUS. It will also minimized even stop mortality.
I can not isolate active ingredient as I have lack of Resources here in Pakistan but please recommend this to healthcare professionals there at CHINA it will really work. I cant communicate to all healthcare professionals please your's Honors communicate with all and use this.
I had applied as Doctoral Candidate and made request for grant of Acceptance Letter and I have only this channel to communicate so I put this E.mail to your Honor
Best Regard
Syed Husnain Raza Shah
Biochemist/Forensic Analyst
Provincial Drugs Testing Laboratory, Multan Punjab-Pakistan

From: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Sent time: 03/14/2020 02:48:33 PM
To: xdfu@ucsd.edu
Subject: Fwd: <no subject>

Begin forwarded message:

From: "Xinnian Dong, Ph.D." <xdong@duke.edu>
Subject: <no subject>
Date: March 14, 2020 at 3:05:32 PM EDT
To: "Xiao-Fan Wang, Ph.D." <xiao.fan.wang@duke.edu>

https://www.wenxuecity.com/news/2020/03/14/9236624.html

From: Fu, Xiang-Dong
Sent time: 03/27/2020 12:21:40 PM
To: 田泃 <ttian@whu.edu.cn>
Subject: Re: Be careful with the spread of newvirus

Many many thanks, Tian. I am doing well here, largely working at home now. God knows when we will be able to go back to work in a normal way.

Fu

Xiang-Dong Fu,
Distinguished Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

> On Mar 18, 2020, at 10:41 PM, 田泃 wrote:
>
> Dear Prof. Fu:
> I am Tian from Wuhan. I hope you are not too disrupted by the newly emerging virus. I am following the news intently since Wuhan is still recovering from the outbreak!
> The number of cases in the US is not very big, but increasing quickly. It may become much worse if not controlled strictly. I hope you will be careful! Wash hands ASAP after contact with elevator buttons. Open public doors with an elbow. The best way to prevent illness is to avoid being exposed to this virus.
>
> I wish you all best and good health!
>
> With my best regards!
> Tian
> ------------------------------
> Tian Tian, Ph.D.Professor of Chemistry and Chemical BiologyKey Laboratory of Biomedical Polymers of Ministry of EducationCollege of Chemistry and Molecular SciencesWuhan UniversityWuhan, 430072, ChinaEmail:ttian@whu.edu.cnhttp://faculty.whu.edu.cn/show.jsp?lang=cn&n=Tian%20Tian

From: cxdeng <cxdeng@um.edu.mo>
Sent time: 05/18/2020 06:34:29 AM
To: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>; 强伯勤 <qiang.boqin@imicams.ac.cn>; 何川 <chuanhe@uchicago.edu>; Fu, Xiang-Dong; 陈晔光 <chen_yeguang@grmh-gdl.cn>; 孟安明 <mengam@mail.tsinghua.edu.cn>; Mingjie ZHANG <mzhang@ust.hk>; 徐国良 <glxu@sibcb.ac.cn>
Subject: Re: Discussion of centers for GDL

Dear Xiao-Fan,
Will do.
Thanks
Chuxia

Chu-Xia Deng, Ph.D.
Dean and Chair Professor
E12, Room 4041
Faculty of Health Sciences
University of Macau
Macau SAR, China
Phone: (853) 8822 4997
Fax: 8822 2314
Email: cxdeng@umac.mo
https://fhs.umac.mo/staff/academic-staff/chuxia-deng/

From: "Xiao-Fan Wang, Ph.D." <xiao.fan.wang@duke.edu>
Date: Monday, 18 May 2020 at 9:22 PM
To: "Xiao-Fan Wang, Ph.D." <xiao.fan.wang@duke.edu>, 强伯勤 <qiang.boqin@imicams.ac.cn>, 何川 <chuanhe@uchicago.edu>, 付向东 <xdfu@health.ucsd.edu>, 陈晔光 <chen_yeguang@grmh-gdl.cn>, 孟安明 <mengam@mail.tsinghua.edu.cn>, Mingjie ZHANG <mzhang@ust.hk>, cxdeng <cxdeng@um.edu.mo>, 徐国良 <glxu@sibcb.ac.cn>
Subject: Discussion of centers for GDL

Dear Friends:

Thank you all again for taking the time to help with this task for GDL. I hope you have all seen the minutes for our first online meeting and we will go through the points to see if specific changes are needed before making it a formal document that will be sent to relevant people.

For discussion of the eight centers in our next meeting (Tuesday evening at 10 pm Beijing Time, Tuesday morning at 10 am EST, 9 am CST, 7 am PST), Tao Xu will not attend the meeting so that we can discuss his center in his absence (we will discuss Yeguang's center in the last so that YG can leave the meeting). I think that it will be more helpful if one of us leads the discussion for one of the centers so that the process will be more efficient. Although everyone of us is supposed to read the documents for all centers, the person in charge can put more thoughts into the assigned center. I have made assignments to each of you, and I understand that we are not experts for all of the topics, but will try to use our scientific judgements to make suggestions and recommendations to the leadership of GDL.

For contents, I think that we should follow the document generated from our first online meeting with the main principle points covered with link to the specifics of each center to come up specific suggestions if deficiencies are identified (strengths are also identified).

If you have any questions before the meeting, please let me know.

Best regards, XF

From: Chuan He <chuanhe@uchicago.edu>
Sent time: 05/18/2020 08:57:52 AM
To: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Cc: xdfu <xdfu@ucsd.edu>
Subject: Re: Discussion of centers for GDL

I feel just cut those. Focus resources to do two things, regeneration medicine (everything into one center) and medical device .

Chuan

From: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Sent: Monday, May 18, 2020 10:52 AM
To: Chuan He <chuanhe@uchicago.edu>
Cc: xdfu <xdfu@ucsd.edu>
Subject: Re: Discussion of centers for GDL

I do feel that they need to have short term (three years) and long term strategies, and each center should have specific focused areas, rather than the whole field. I was reading the center for anti-aging, and it will cover everything, from basic research all the way to treating multiple diseases, totally unrealistic. It is one thing that they need to tell politicians that they will get the moon, it is another for doing real science/research that has to be focused. We will raise these issues during discussion and for recommendations. XF

> On May 18, 2020, at 11:45 AM, Chuan He <chuanhe@uchicago.edu> wrote:
>
> Dear Xiao-Fan,
>
> If it is up to me, I would just recommend them doing one thing, this biomedical device center. That is it. Maybe add stem cell research and therapies. Cut everything else. That to me is the best way to move forward. They just need to do one thing well. They indeed have advantage on the device part based on location and expertise.
>
> Chuan
>
> ---
>
> **From:** Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
> **Sent:** Monday, May 18, 2020 10:04 AM
> **To:** Chuan He <chuanhe@uchicago.edu>
> **Subject:** Re: Discussion of centers for GDL
>
> Thanks! Phone will be fine and your presentation will be later using the current list. XF
>
> > On May 18, 2020, at 10:49 AM, Chuan He <chuanhe@uchicago.edu> wrote:
> >
> > Thanks Xiao-Fan,
> >
> > I will evaluate the last one. I may use phone for early presentations. I am in a COVID-19 study group here on campus. Life gets a bit busy now.
> >
> > Best,
> >
> > Chuan
> >
> > ---
> >
> > **From:** Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
> > **Sent:** Monday, May 18, 2020 8:15 AM
> > **To:** Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>; 强伯勤 <qiang.boqin@imicams.ac.cn>; Chuan He <chuanhe@uchicago.edu>; 付向东 <xdfu@health.ucsd.edu>; 陈晔光 <chen_yeguang@grmh-gdl.cn>; 孟安明 <mengam@mail.tsinghua.edu.cn>; Mingjie ZHANG <mzhang@ust.hk>; 邓初夏 <cxdeng@um.edu.mo>; 徐国良 <glxu@sibcb.ac.cn>
> > **Subject:** Discussion of centers for GDL

Dear Friends:

Thank you all again for taking the time to help with this task for GDL. I hope you have all seen the minutes for our first online meeting and we will go through the points to see if specific changes are needed before making it a formal document that will be sent to relevant people.

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For contents, I think that we should follow the document generated from our first online meeting with the main principle points covered with link to the specifics of each center to come up specific suggestions if deficiencies are identified (strengths are also identified).

If you have any questions before the meeting, please let me know.

Best regards, XF

From: mfliu <mfliu@sibcb.ac.cn>
Sent time: 06/08/2020 01:29:41 AM
To: chengqi.yi <chengqi.yi@pku.edu.cn>; Fu, Xiang-Dong; 惠静毅 <jyhui@sibcb.ac.cn>; 程红 <hcheng@sibcb.ac.cn>; Zefeng Wang <wangzefeng@picb.ac.cn>; 陈炜(CHEN Wei) <chenw@sustech.edu.cn>; shange <shange@ustc.edu.cn>; yangming.wang <yangming.wang@pku.edu.cn>; guifangjia <guifangjia@pku.edu.cn>; Yu Zhou <yu.zhou@whu.edu.cn>; 薛愿超 <ycxue@ibp.ac.cn>; 杨建华 <yangjh7@mail.sysu.edu.cn>
Cc: 付向东 <xdfu@ucsd.edu>; mfliu <mfliu@sibs.ac.cn>; ygyang <ygyang@big.ac.cn>; chengqi.yi <chengqi.yi@pku.edu.cn>; jypengpku <jypengpku@pku.edu.cn>
Subject: 回复: Postpone 2020 Sino-German RNA meeting

Dear Chengqi,

The new date works for me. I am looking forward to going to Regensburg with you all. Thanks a lot!

Best wishes
Mofang

Mofang Liu, Ph.D.
Principle Investigator
Institute of Biochemistry and Cell Biology
Shanghai Institutes of Biological Sciences
Chinese Academy of Sciences
320 Yue Yang Road
Shanghai 200031 China
Tel: +86-21-54921146
Email: mfliu@sibcb.ac.cn

发件人: chengqi.yi@pku.edu.cn
发送时间: 2020-06-08 16:03
收件人: Fu, Xiang-Dong; jyhui; hcheng; wangzefeng; chenw; shange; 汪阳明; guifangjia; yu.zhou; ycxue; yangjh7
抄送: xdfu; mfliu; Yungui Yang/杨运桂; chengqi.yi; jypengpku
主题: Postpone 2020 Sino-German RNA meeting

Dear All,

I hope everything is getting back to normal for you already.

And thank you for agreeing to join us for the Sino-German meeting on RNA biology, which was originally planned to take place in Regensburg, Germany from Sep. 13.-16, 2020. However, considering the uncertainties for international travel and accomendations, we have decided to postpone the meeting to the last week of April, 2021. The tentative plan suggested from our German paterners is that we could arrive in Germany maybe on Sunday, have conferences on Monday, Tuesday and Wednesday, and then depart on Thursday. You don't have to do anything right now; please just save the dates and I will get back to you with more information later on. If there is any conflicts with your schedule, please also let us know.

Best,

Chengqi

From: liangyi@whu.edu.cn
Sent time: 06/11/2020 06:43:09 PM
To: xdfu <xdfu@ucsd.edu>
Subject: JMB Neutralizing Mutations Significantly Inhibit Amyloid Formation by Human Prion Protein and Decrease Its Cytotoxicity
Attachments: JMB Neutralizing Mutations Significantly Inhibit Amyloid Formation by Human Prion Protein and Decrease Its Cytotoxicity.pdf JMB Phase Separation and Cytotoxicity of Tau are Modulated by Protein Disulfide Isomerase and S-nitrosylation of this Molecular Chaperone.pdf

Dear Xiangdong Fu,

Thank you very much for your continuous encouragement to my work during the past so many years.
Welcome you visiting Wuhan University again this year!

Enclosed please find two PDF files of our two Journal of Molecular Biology articles titled "Phase Separation and Cytotoxicity of Tau Are Modulated by Protein Disulfide Isomerase and S-nitrosylation of this Molecular Chaperone"
and "Neutralizing Mutations Significantly Inhibit Amyloid Formation by Human Prion Protein and Decrease Its Cytotoxicity".

Celebrating 60 Years of *Journal of Molecular Biology*

Best wishes.
Have a nice day!

Yi Liang

Dr. Yi Liang, Professor of Structural Biology
Hubei Key Laboratory of Cell Homeostasis
College of Life Sciences, Wuhan University
Wuhan 430072, China
Fax: +86-27-68754902, Tel: +86-27-68754902

liangyi@whu.edu.cn

From: liangyi@whu.edu.cn
Sent time: 06/11/2020 07:08:32 PM
To: xdfu <xdfu@ucsd.edu>
Subject: NSMB Cryo-EM structure of an amyloid fibril formed by full-length human prion protein
Attachments: NSMB Cryo-EM structure of an amyloid fibril formed by full-length human prion protein.pdf

---

Dear Xiangdong Fu,

Thank you very much for your continuous encouragement to my work during the past so many years. Welcome you visiting Wuhan University again this year!

Enclosed please find one PDF file of our our Nature Structural & Molecular Biology article titled "Cryo-EM structure of an amyloid fibril formed by full-length human prion protein"

Nature Structural & Molecular Biology | VOL 27 | June 2020 | 598–602

Best wishes.
Have a nice day!

Yi Liang

Dr. Yi Liang, Professor of Structural Biology
Hubei Key Laboratory of Cell Homeostasis
College of Life Sciences, Wuhan University
Wuhan 430072, China
Fax: +86-27-68754902, Tel: +86-27-68754902

liangyi@whu.edu.cn

From: Yu Zhou <yu.zhou@whu.edu.cn>
Sent time: 06/11/2020 09:43:02 PM
To: Fu, Xiang-Dong
Subject: Re: response suggestion

Thanks a lot!

Best,
Yu

在 2020年6月12日，上午11:37，Fu, Xiang-Dong <xdfu@health.ucsd.edu> 写道：

Here is my edits for your consideration

Fu

Xiang-Dong Fu,
Distinguished Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@ucsd.edu

> On Jun 11, 2020, at 7:56 PM, Yu Zhou <yu.zhou@whu.edu.cn> wrote:
>
> <ResponseToEditor.docx>

<Edited resp;onse.docx>

From: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Sent time: 06/15/2020 02:05:41 PM
To: xdfu@ucsd.edu
Subject: phone call

Did you call me earlier? I tried to call back several times but could not get through or even a busy tone, something was wrong? XF

From: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Sent time: 06/23/2020 05:54:38 AM
To: Fu, Xiang-Dong
Subject: Re: interview for CAMS candidates

Thanks! XF
> On Jun 23, 2020, at 1:01 AM, Fu, Xiang-Dong wrote:
>
> Sure. Send the material in.
>
> Xiang-Dong Fu,
> Distinguished Professor
> Dept. of Cellular and Molecular Medicine
> University of California, San Diego
> George Palade Laboratories
> 9500 Gilman Drive, Room 217
> La Jolla, CA 92093-0651
>
> Phone: 858-534-4937
> Email: xdfu@ucsd.edu
>
>
>
>> On Jun 22, 2020, at 7:32 PM, Xiao-Fan Wang, Ph.D. wrote:
>>
>> Hi XD:
>>
>> We need to conduct an online interview for six candidates for Chinese Academy of Medical Sciences, and the schedule will be BJ time 8 am to 10:30 am on two days, June 30 and July 1, so the time will be 5 pm to 7:30 pm PST on June 29 and 30. We will need to use the 腾讯 system instead of Zoom and they will help us to set it up before the online interview. If you can help, I will let CAMS know to send you relevant documents.
>>
>> Thank you very much! XF
>

From: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Sent time: 07/13/2020 12:30:07 PM
To: Feng, Gen-Sheng
Cc: Fu, Xiang-Dong
Subject: Re:

Thanks!

Sent from my iPhone

> On Jul 13, 2020, at 2:58 PM, Feng, Gen-Sheng <gfeng@health.ucsd.edu> wrote:
>
> This article mentioned Kang Zhang's case:
>
> > Dr. Michael Lauer, NIH's Deputy Director for Extramural Research, wrote a summary on the latest information about foreign engagement: https://nexus.od.nih.gov/all/2020/07/08/addressing-foreign-interference-and-associated-risks-to-the-integrity-of-biomedical-research-and-how-you-can-help/.

From: Fu, Xiang-Dong
Sent time: 04/06/2020 07:01:07 PM
To: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Subject: Re: bai's email

Got it.

Xiang-Dong Fu,
Distinguished Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

> On Apr 6, 2020, at 6:58 PM, Xiao-Fan Wang, Ph.D. wrote:
>
> clbai@cas.cn

From: Yi Rao <yrao@pku.edu.cn>
Sent time: 04/06/2020 07:44:19 PM
To: Fu, Xiang-Dong; Shi, Yigong <shi-lab@tsinghua.edu.cn>
Cc: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Subject: Re: A serious ethical issue

I hope that it will change this time…

My experience:
I gave talk at ION on SDF and neuronal migration. ION (with Poo as the corresponding author) sent out one on SDF and neuronal migration to *Nature Cell Biology*, which I reviewed and accepted
Another paper which I do not remember so well at the moment
Then a Cell paper by Chenbing Guan (grad student) and Poo (corresponding author): on Slit and neuronal migration mechanisms. This was a project that I gave as a test question for ION students, and Guan was a rotating student in my lab, working with Hui Jiang, on this project. He then went to the Poo lab, and finished it. There were suggestions by Poo, I am sure, later in his lab. But the idea and the gene (and protein) Slit were both mine.
I never complaint about any of these.

This kind of things have happened to me more than once and from more than one person, including some quite junior to us (there was one at NIBS too). Each time, I moved on, without complaint. So, most of these people thought that I am simply dumb and did not realize it.

在 4/7/20, 10:26 AM, "Fu, Xiang-Dong" <xdfu@health.ucsd.edu> 写入:

Dear Yi and Yigong,

This email may be unexpected, which is about a problem I just encountered today.

This morning, I was informed that our work in the past 8 years (review started in 2017) on neuronal reprogramming was largely stolen by a group of scientists in the Institute of Neuroscience in Shanghai. Their paper will come online at Cell this Thursday. I am quite upset because I have given seminars on this topics multiple times in China, including ION. I am now rushing our revised manuscript to Nature tonight. Once submitted, I will send it to you.

I sense that this reflects a general problem in China. For this reason, I wrote an email to Dr. Mu-Ming Poo, which I copy here for your reference:

Dear Mu-Ming,

Today, I am informed for an upcoming paper from Cell, which are authored by a large number of scientists from your institute. This paper basically stole our experimental approach, ideas, and positive results, which I have presented several times in your place. If they wish to replicate our data, they are certainly welcome to do so, but according to the normal scientific ethics, they should let us know and coordinate. In this case, it is clear that they have been pursuing the project with our unpublished findings as the basis, but completely behind us. It basically damages the reputation of Chinese scientists in general by ruthlessly chasing "hot" topics and grabbing scientific ideas and data from public seminars to out compete original scientists.

We are in the final stage of publishing our results at Nature. In fact, I plan to propose collaboration with you on non-human primate models with our approach for future studies. Although you are not part of the authorship, I seriously believe that you are responsible for educating your PIs on scientific ethics.

Sincerely yours,

Fu
Xiang-Dong Fu,
Distinguished Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

From: Fu, Xiang-Dong
Sent time: 04/06/2020 10:33:00 PM
To: Yi Rao <yrao@pku.edu.cn>; Shi, Yigong <shi-lab@tsinghua.edu.cn>; Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Subject: Mu-Ming's response

I will respond and then forward my response to you.

Begin forwarded message:

From: "mpoo@ion.ac.cn" <mpoo@ion.ac.cn>
Subject: Re: a major upsetting matter
Date: April 6, 2020 at 9:18:40 PM PDT
To: Fu, Xiang-Dong <xdfu@health.ucsd.edu>
Cc: "Don Cleveland" <dcleveland@health.ucsd.edu>, "Mobley Bill" <wmobley@ucsd.edu>

Dear Xiang-Dong:

Thank you for your letter raising the issue about Yang Hui's recent paper in Cell. Yang's lab has been interested in using gene-editing approach for translational applications, including transdifferentiation of non-neuronal cells into neurons since his joining of IoN, as shown by his paper in 2018 in Nature Neuroscience using CRISPR activation system in transdifferenting astrocytes in striatum. Your discovery of the importance of PTBP1 in regulating neuronal gene expression published in Cell (2013) must be inspirational to him , and triggering his effort in using the gene-editing approach to induce transdifferentiation in a variety of neurodegenerative diseases. Since you did give a talk at IoN, and Yang had learned that you are working on transforming non-neuronal cells in SNc using small molecules, he should have talked to you about his findings in striatum and retina (which is the major part of his Cell paper), before submitting the paper, even though his approach is different from yours (using gene-editing rather than small molecule) and the work was done in different brain areas. I have just checked his paper, and noted that he has cited all your earlier papers on PTBP1,

All these said, for proper scientific communication, Yang should have informed you that he is working on transdifferentiation in the striatum. However, I also suspect that the reason he did not inform you is becuase he is a young investigator and had a very bad experience a few years ago. In the latter case, he had informed a senior investigator working on similar base-editing on human embryos and obtained the agreement to co-submit the papers, but later found out that this person quickly published his paper before he is ready in violation of the agreement. Intense competition in hot fields had led to many young investigators refraining from informing others about their work before publication. Nevertheless, I agreed with you that Yang should have inform you that he is working a problem closely related to your work on SNc and potentially coordinate the publication with you. This is a problem in what I refer to as the Gray Zone, and there are so many scientists who compete with each other and show such gray zone behavior (without communicating unpublished results). This phenomenon is bad for scientific communication, and it is widespread. I have made much effort to warn people in our institute against it.

You begin your letter by saying that Yang basically "stole our experimental approach, ideas, and positive results". This is a very serious accusation, and if true , Yang has committed scientific misconduct, and we will need to proceed with formal investigation on this matter. At this moment, I am unable to find any potential evidence of misconducts. (Failure to communicate is a mistake but not a misconduct). I noted that the idea of transdifferentiation is not new, many people are working on this, including Cheng Leping (formerly at IoN) and Chen Gong, as well as Yang Hui. The PTBP1 protein as an important regulator was published by you years ago. All other aspects of their work are different from yours. So, I need to be enlightened if I have missed something, besides his failure of prior communication.

Best wishes,
Mu-ming

PS. I am indeed looking forward to collaborate with you on using monkey model of PD. We are still working hard in generating a good model with slow degeneration (unlike MPTP)

---

mpoo@ion.ac.cn

From: Fu, Xiang-Dong
Date: 2020-04-07 07:42
To: mpoo
CC: Don Cleveland; Mobley Bill
Subject: a major upsetting matter

Dear Mu-Ming,

Today, I am informed for an upcoming paper from Cell, which are authored by a large number of scientists from your institute. This paper basically stole our experimental approach, ideas, and positive results, which I have presented several time in your place. If they wish to replicate our data, they are certainly welcome to do so, but according to the normal scientific ethics, they should let us know and coordinate. In this case, it is clear that they have been pursuing the project with our unpublished findings as the basis, but completely behind us. It basically damages the reputation of Chinese scientists in general by ruthlessly chasing “hot” topics and grabbing scientific ideas and data from public seminars to out compete with original scientists.

We are in the final stage of publishing our results at Nature. In fact, I plan to propose collaboration with you on non-human primate models with our approach for future studies. Although you are not part of the authorship, I seriously believe that you are responsible for educating your PIs on scientific ethics.

Sincerely,

Fu

Xiang-Dong Fu,
Distinguished Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

From: Fu, Xiang-Dong
Sent time: 04/06/2020 10:45:24 PM
To: Yi Rao <yrao@pku.edu.cn>; Shi, Yigong <shi-lab@tsinghua.edu.cn>
Cc: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Subject: Re: A serious ethical issue

Hi Yi and Yigong,

What you both said is precisely the problem now widespread in China. Basically, this reflects the lack of ethical education for young PIs. As we all know, people use their cell phones to take pictures during seminars and meetings, even though it is made clear not to do so. People do not seem to feel any thing wrong by steeling others' ideas and sometime directly data. In fact, several so-called rising stars are doing that shamelessly. This creates a wrong culture among Chinese scientists, and consequently, people do not share ideas and unpublished findings, even within the same institutes, the same departments, or the same labs! All seminars and meeting presentations now become opportunities to show off, rather than for the purpose of scientific exchange. We, as senior scientists, need to do something on this problem for China.

Fu

> On Apr 6, 2020, at 9:10 PM, Yi Rao <yrao@pku.edu.cn> wrote:
>
> Xiangdong would be hard pressed to believe what Yigong just said, but it happened to my twice, once in an institute. I suggested a collaboration with a junior PI, but did not hear back. Then I found out that he did the experiments (in the wrong way). I did not complain but never treated him seriously from then on
>
> Recently, a even younger person asked me for reagents. I asked what he planed to do. It turned out to be the same as I already gave internal talks about what we are doing, which is why we have collected those reagents, and also how he learned that we have the reagents. I told him that there can be competitions between institutions, but not within the same dept or institute, not knowingly. If such things happen, then there can be no discussions within depts or institutes.
>
> Basic conventions are to be established.

> 在 4/7/20, 11:39 AM, "shi-lab@tsinghua.edu.cn" <shi-lab@tsinghua.edu.cn> 写入:
>
> Hi Xiang-Dong,
>
> I am very sympathetic to your situation! What you have encountered again signifies how messed up our community is in terms of research ethics. I believe such cases are widespread in China, more so than in the US. I had to warn my own students not to share unpublished information for any competitive projects.
>
> Just two days ago, I learned that someone at Tsinghua began to work on a project that we have been working on for nearly 10 years. In this case, we just published our results after struggling with Nature and Science. This group told others that they were "scooped" - and I learned their effort for the first time and felt speechless.
>
> Wait to see what you get from Mu-ming.
>
> Best,
> Yigong
>
> -----邮件原件-----
> 发件人: Fu, Xiang-Dong <xdfu@health.ucsd.edu>
> 发送时间: 2020年4月7日 10:56
> 收件人: Yi Rao <yrao@pku.edu.cn>; Shi, Yigong <shi-lab@tsinghua.edu.cn>
> 主题: Re: A serious ethical issue
>
> Thanks for your quick response. If Mu-Ming is such kind of person, he will completely loss my respect of him. I raised the issue not because I

was offended, but because I realize that this is a common problem in China. No wonder few people give seminars on unpublished results. I will see how Mu-Ming will respond, if not at all, and will let you know.

Fu

Xiang-Dong Fu,
Distinguished Professor
Dept. of Cellular and Molecular Medicine University of California, San Diego George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

> On Apr 6, 2020, at 7:26 PM, Fu, Xiang-Dong <xdfu@health.ucsd.edu> wrote:
> Dear Yi and Yigong,
> This email may be unexpected, which is about a problem I just encountered today.
> This morning, I was informed that our work in the past 8 years (review started in 2017) on neuronal reprogramming was largely stolen by a group of scientists in the Institute of Neuroscience in Shanghai. Their paper will come online at Cell this Thursday. I am quite upset because I have given seminars on this topics multiple times in China, including ION. I am now rushing our revised manuscript to Nature tonight. Once submitted, I will send it to you.
> I sense that this reflects a general problem in China. For this reason, I wrote an email to Dr. Mu-Ming Poo, which I copy here for your reference:
> Dear Mu-Ming,
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> We are in the final stage of publishing our results at Nature. In fact, I plan to propose collaboration with you on non-human primate models with our approach for future studies. Although you are not part of the authorship, I seriously believe that you are responsible for educating your PIs on scientific ethics.
> Sincerely yours,
> Fu
> Xiang-Dong Fu,
> Distinguished Professor
> Dept. of Cellular and Molecular Medicine University of California, San
> Diego George Palade Laboratories
> 9500 Gilman Drive, Room 217
> La Jolla, CA 92093-0651
> Phone: 858-534-4937
> Email: xdfu@health.ucsd.edu

From: Fu, Xiang-Dong
Sent time: 04/06/2020 11:30:25 PM
To: Yi Rao <yrao@pku.edu.cn>; Shi, Yigong <shi-lab@tsinghua.edu.cn>; Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Subject: my response to Mu-Ming

Dear Mu-Ming,

Thanks for your rapid rely. The issue has triggered intensive discussion among several of my close colleagues because of the commonality now days in China that people treat "gray zone" as norm. Consequently, most people just talk about published works in seminars and meetings where the whole thing becomes show-off, thus losing the intended purposes. In fact, people do not talk about their unpublished works even in the same institutes, the same departments, and even the same labs. There is no such thing as in MRC and many institutions in the US where people brainstorm over coffee or tie. Scientists in China basically use science for material gains, rather than for pursuing their passions. Something seriously wrong.

In this specific case, I gave my seminar on the topic at the time he just joint ION as a faculty. I even talked to him during my visit. He never mentioned their intension during our conversation. You mentioned that he has been following our published works. The fact is that REST has been known for at least two decades as a master suppressor of neurogenesis. As I explained in my seminar, inactivating REST will deplete neuronal progenitors and compromise the viability of induced neurons, which is in contrast to the PTB-regulated circuit where once activated, it becomes self-enforced and homeostatic as during neurogenesis. He is clearly very smart and he learned not just the approach but also the feasibility to reprogram directly in the brain. Without knowing that the strategy works in the brain, how would he be so smart to guess it out which is a better target to begin with? As you indicated, he should at least inform me for his intension. In fact, during my presentation, I also mentioned that we have been collaborating with Kang Zhang's group on the retina system and show that PTB kd is sufficient to restore vision on blind mice. It would be too much a coincidence that he happened to think about the same approach and the same biological systems for his own studies.

Of course, I would expect him to deny the whole thing if questioned. You mentioned Leping and Gang Chen for their work in trans-differentiation. In fact, we have been in close contact and Gang and I even plan to collaborate, which is expected from basic collegiality. Distinct from the common approach by overexposing a TF(s) in the field, our approach has a unique advantage from the therapeutic point of view, as kd is alway easier than overexpression. Cooperation among scientists should be encouraged, but the current culture in the Chinese scientific community is just opposite. Given such a bad culture, should we, as senior scientists, do things to educate young scientists in China? As you know, everyone has to gone through a series of ethics training in the US. As far as I know, there is no such thing in China.

Finally, you mentioned your interest to collaborate on monkey models. He would be more convenient to jump on top again. Do you even know his intension for the nest step?

As writing email is tedious, hope we can talk in person in the near future.

Best regards,

Fu

Xiang-Dong Fu,
Distinguished Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217

La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

On Apr 6, 2020, at 9:18 PM, mpoo@ion.ac.cn wrote:

Dear Xiang-Dong:

Thank you for your letter raising the issue about Yang Hui's recent paper in Cell. Yang's lab has been interested in using gene-editing approach for translational applications, including transdifferentiation of non-neuronal cells into neurons since his joining of IoN, as shown by his paper in 2018 in Nature Neuroscience using CRISPR activation system in transdifferenting astrocytes in striatum. Your discovery of the importance of PTBP1 in regulating neuronal gene expression published in Cell (2013) must be inspirational to him , and triggering his effort in using the gene-editing approach to induce transdifferentiation in a variety of neurodegenerative diseases. Since you did give a talk at IoN, and Yang had learned that you are working on transforming non-neuronal cells in SNc using small molecules, he should have talked to you about his findings in striatum and retina (which is the major part of his Cell paper), before submitting the paper, even though his approach is different from yours (using gene-editing rather than small molecule) and the work was done in different brain areas. I have just checked his paper, and noted that he has cited all your earlier papers on PTBP1,

All these said, for proper scientific communication, Yang should have informed you that he is working on transdifferentiation in the striatum. However, I also suspect that the reason he did not inform you is becuase he is a young investigator and had a very bad experience a few years ago. In the latter case, he had informed a senior investigator working on similar base-editing on human embryos and obtained the agreement to co-submit the papers, but later found out that this person quickly published his paper before he is ready in violation of the agreement. Intense competition in hot fields had led to many young investigators refraining from informing others about their work before publication. Nevertheless, I agreed with you that Yang should have inform you that he is working a problem closely related to your work on SNc and potentially coordinate the publication with you. This is a problem in what I refer to as the Gray Zone, and there are so many scientists who compete with each other and show such gray zone behavior (without communicating unpublished results). This phenomenon is bad for scientific communication, and it is widespread. I have made much effort to warn people in our institute against it.

You begin your letter by saying that Yang basically "stole our experimental approach, ideas, and positive results". This is a very serious accusation, and if true , Yang has committed scientific misconduct, and we will need to proceed with formal investigation on this matter. At this moment, I am unable to find any potential evidence of misconducts. (Failure to communicate is a mistake but not a misconduct). I noted that the idea of transdifferentiation is not new, many people are working on this, including Cheng Leping (formerly at IoN) and Chen Gong, as well as Yang Hui. The PTBP1 protein as an important regulator was published by you years ago. All other aspects of their work are different from yours. So, I need to be enlightened if I have missed something, besides his failure of prior communication.

Best wishes,

Mu-ming

PS. I am indeed looking forward to collaborate with you on using monkey model of PD. We are still working hard in generating a good model with slow degeneration (unlike MPTP)

---

mpoo@ion.ac.cn

From: Fu, Xiang-Dong
Date: 2020-04-07 07:42
To: mpoo
CC: Don Cleveland; Mobley Bill
Subject: a major upsetting matter

Dear Mu-Ming,

Today, I am informed for an upcoming paper from Cell, which are authored by a large number of scientists from your institute. This paper basically stole our experimental approach, ideas, and positive results, which I have presented several time in your place. If they wish to replicate our data, they are certainly welcome to do so, but according to the normal scientific ethics, they should let us know and coordinate. In this case, it is clear that they have been pursuing the project with our unpublished findings as the basis, but completely behind us. It basically damages the reputation of Chinese scientists in general by ruthlessly chasing "hot" topics and grabbing scientific ideas and data from public seminars to out compete with original scientists.

We are in the final stage of publishing our results at Nature. In fact, I plan to propose collaboration with you on non-human primate models with our approach for future studies. Although you are not part of the authorship, I seriously believe that you are responsible for educating your PIs on scientific ethics.

Sincerely,

Fu

Xiang-Dong Fu,
Distinguished Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

From: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Sent time: 04/07/2020 05:56:11 AM
To: Fu, Xiang-Dong
Subject: Re: Mu-Ming's response

MM sent his response to your message to the three of us, did you let him know that you shared the message with us in addition to cced to Don and Bill? It was just intriguing if you did not tell him that. Let's see if he will respond to your reply. XF

On Apr 7, 2020, at 1:33 AM, Fu, Xiang-Dong <xdfu@health.ucsd.edu> wrote:

I will respond and then forward my response to you.

Begin forwarded message:

From: "mpoo@ion.ac.cn" <mpoo@ion.ac.cn>
Subject: Re: a major upsetting matter
Date: April 6, 2020 at 9:18:40 PM PDT
To: Fu, Xiang-Dong <xdfu@health.ucsd.edu>
Cc: "Don Cleveland" <dcleveland@health.ucsd.edu>, "Mobley Bill" <wmobley@ucsd.edu>

Dear Xiang-Dong:

Thank you for your letter raising the issue about Yang Hui's recent paper in Cell. Yang's lab has been interested in using gene-editing approach for translational applications, including transdifferentiation of non-neuronal cells into neurons since his joining of IoN, as shown by his paper in 2018 in Nature Neuroscience using CRISPR activation system in transdifferenting astrocytes in striatum. Your discovery of the importance of PTBP1 in regulating neuronal gene expression published in Cell (2013) must be inspirational to him , and triggering his effort in using the gene-editing approach to induce transdifferentiation in a variety of neurodegenerative diseases. Since you did give a talk at IoN, and Yang had learned that you are working on transforming non-neuronal cells in SNc using small molecules, he should have talked to you about his findings in striatum and retina (which is the major part of his Cell paper), before submitting the paper, even though his approach is different from yours (using gene-editing rather than small molecule) and the work was done in different brain areas. I have just checked his paper, and noted that he has cited all your earlier papers on PTBP1,

All these said, for proper scientific communication, Yang should have informed you that he is working on transdifferentiation in the striatum. However, I also suspect that the reason he did not inform you is becuase he is a young investigator and had a very bad experience a few years ago. In the latter case, he had informed a senior investigator working on similar base-editing on human embryos and obtained the agreement to co-submit the papers, but later found out that this person quickly published his paper before he is ready in violation of the agreement. Intense competition in hot fields had led to many young investigators refraining from informing others about their work before publication. Nevertheless, I agreed with you that Yang should have inform you that he is working a problem closely related to your work on SNc and potentially coordinate the publication with you. This is a problem in what I refer to as the Gray Zone, and there are so many scientists who compete with each other and show such gray zone behavior (without communicating unpublished results). This phenomenon is bad for scientific communication, and it is widespread. I have made much effort to warn people in our institute against it.

You begin your letter by saying that Yang basically "stole our experimental approach, ideas,

and positive results". This is a very serious accusation, and if true , Yang has committed scientific misconduct, and we will need to proceed with formal investigation on this matter. At this moment, I am unable to find any potential evidence of misconducts. (Failure to communicate is a mistake but not a misconduct). I noted that the idea of transdifferentiation is not new, many people are working on this, including Cheng Leping (formerly at IoN) and Chen Gong, as well as Yang Hui. The PTBP1 protein as an important regulator was published by you years ago. All other aspects of their work are different from yours. So, I need to be enlightened if I have missed something, besides his failure of prior communication.

Best wishes,
Mu-ming

PS. I am indeed looking forward to collaborate with you on using monkey model of PD. We are still working hard in generating a good model with slow degeneration (unlike MPTP)

---

mpoo@ion.ac.cn

From: Fu, Xiang-Dong
Date: 2020-04-07 07:42
To: mpoo
CC: Don Cleveland; Mobley Bill
Subject: a major upsetting matter

Dear Mu-Ming,

Today, I am informed for an upcoming paper from Cell, which are authored by a large number of scientists from your institute. This paper basically stole our experimental approach, ideas, and positive results, which I have presented several time in your place. If they wish to replicate our data, they are certainly welcome to do so, but according to the normal scientific ethics, they should let us know and coordinate. In this case, it is clear that they have been pursuing the project with our unpublished findings as the basis, but completely behind us. It basically damages the reputation of Chinese scientists in general by ruthlessly chasing “hot” topics and grabbing scientific ideas and data from public seminars to out compete with original scientists.

We are in the final stage of publishing our results at Nature. In fact, I plan to propose collaboration with you on non-human primate models with our approach for future studies. Although you are not part of the authorship, I seriously believe that you are responsible for educating your PIs on scientific ethics.

Sincerely,

Fu

Xiang-Dong Fu,
Distinguished Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

From: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Sent time: 04/07/2020 08:33:04 AM
To: xdfu@ucsd.edu
Subject: Fwd: a major upsetting matter

As you can see, MM sent his response to you directly to the three of us, the reason that I thought the consequence of Chunli Bai forwarding your message to MM. XF

Begin forwarded message:

From: "mpoo@ion.ac.cn" <mpoo@ion.ac.cn>
Subject: Fw: Re: a major upsetting matter
Date: April 7, 2020 at 12:34:47 AM EDT
To: "yrao@pku.edu.cn" <yrao@pku.edu.cn>, "shi-lab@tsinghua.edu.cn" <shi-lab@tsinghua.edu.cn>, "xiao.fan.wang@duke.edu" <xiao.fan.wang@duke.edu>

mpoo@ion.ac.cn

From: mpoo@ion.ac.cn
Date: 2020-04-07 12:18
To: Fu, Xiang-Dong
CC: Don Cleveland; Mobley Bill
Subject: Re: a major upsetting matter

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Xiang-Dong Fu,
Distinguished Professor
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University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937

Email: xdfu@health.ucsd.edu

From: Yi Rao <yrao@pku.edu.cn>
Sent time: 04/07/2020 05:13:12 PM
To: Fu, Xiang-Dong
Cc: Shi, Yigong <shi-lab@tsinghua.edu.cn>; Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Subject: Re: Submitted ms yesterday

It is so obvious that he was good at a technique invented by others but was looking for an application, so he grabbed your idea. The original surprise was still your 2013 paper. Everyone was looking at transcription factors but you had a surprise
When one looks at the trail of papers, yours would still be the first

发自我的iPhone

在 2020年4月8日，上午12:39，Fu, Xiang-Dong <xdfu@health.ucsd.edu> 写道：

Hi Yi, Yigong and Xiaofan,

Here is our manuscript we uploaded to the Nature website yesterday. Because of the large size for 20 supplementary figures, I only send you the main text with 7 main figures.

Fu

Xiang-Dong Fu,
Distinguished Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

<Submitted PTB PD ms 472020.pdf>

From: Fu, Xiang-Dong
Sent time: 04/08/2020 08:04:04 AM
To: Pham, John W. (ELS-CMA) <jpham@cell.com>
Cc: dsweet@cell.com; Yi Rao <yrao@pku.edu.cn>; Shi, Yigong <shi-lab@tsinghua.edu.cn>; Xiao-Fan Wang, Ph.D. <xiao fan.wang@duke.edu>
Subject: Re: A potential ethical issue related to an upcoming paper in Cell

---

Dear John,

Although we will have a conversation this Friday and given the paper I questioned for a potential ethical issue that will appear online in Cell tonight, I am writing to formally request holding of the paper until the issue is resolved.

I make this request because I have informed the director of the Institute Dr. Mu-Ming Poo about my concern and complained about this clear scientific breach case. Consequently, Dr. Poo has started an investigation of this serious problem. I thus feel that it would be the best interest of all parties involved to request Cell to hold the paper.

I know you are in the middle of the important annual strategic meeting for Cell and you may feel awkward to make a decision. I thus carbon copy this email to Dr. Deborah Sweet at the Cell press.

Best regards,

Fu

Xiang-Dong Fu,
Distinguished Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

> On Apr 7, 2020, at 9:09 AM, Fu, Xiang-Dong wrote:
>
> Dear John,
>
> Yesterday, I was told about a paper from Hui Yang's lab from Shanghai Institute of Neuroscience, which will appear online this Thursday at Cell. You probably know that this work is highly related to our work on PTB knockdown-induced neuronal regeneration in the brain. The fact is that they essentially copied our approach on slightly distinct brain areas after knowing our positive results.
>
> We started developing our in vivo reprogramming project after we published our initial findings on PTB-regulated neuronal trans-differentiation in Cell in 2013. Invited by the institute director Mu-Ming Poo, I gave a seminal there in 2017 when Yang just joined the institute as a new faculty member. I showed a series of data on both the Retinitis Pigmentosa model in retina and the Parkinson's diseases in the brain. He immediately tried to duplicate our work behind us (of course using different, but similar disease models in both systems to bypass the obvious).
>
> We actually started the publication process in 2017, and while we always received glowing reviews from most of reviewers, there is always one reviewer who thought that the behavioral benefits might be due to indirect efforts after inducing new neurons, despite the fact that we proved otherwise through a set of elaborated chemical genetic experiments to demonstrate that it is the reprogrammed new neurons that directly contribute to the final functional outcome. In fact, this concern applies to the current Cell paper.
>
> I am not sure what you can do or will do in this case of scientific breach, which discourages sharing unpublished results in public seminars and meetings. Does Cell have any moral obligation to safeguard proper scientific conduct?
>
> Best regards,
>

> Fu
>
> Xiang-Dong Fu,
> Distinguished Professor
> Dept. of Cellular and Molecular Medicine
> University of California, San Diego
> George Palade Laboratories
> 9500 Gilman Drive, Room 217
> La Jolla, CA 92093-0651
>
> Phone: 858-534-4937
> Email: xdfu@health.ucsd.edu
>
>
>

From: Fu, Xiang-Dong

Sent time: 04/08/2020 12:57:21 PM

To: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>; Xinnian Dong, Ph.D. <xdong@duke.edu>

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http://mp.weixin.qq.com/s?__biz=MzA3MzQyNjY1MQ==&mid=2652483148&idx=1&sn=dd50147d903d4568395e2477147526df&chksm=84e23df8b395b4eed1fa0d85c9797b5cc0fe3d4975a818ae789d1f6388bf6548f756adbda841&mpshare=1&scene=1&srcid=&sharer_sharetime=1586365661812&sharer_shareid=0fc6e84eba1c053b5f5d6d4184d30124#rd

Xiang-Dong Fu,
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University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

From: Fu, Xiang-Dong
Sent time: 04/08/2020 12:58:55 PM
To: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Subject: Fwd: personal message

Xiang-Dong Fu,
Distinguished Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

Begin forwarded message:

From: "Fu, Xiang-Dong" <xdfu@health.ucsd.edu>
Subject: personal message
Date: April 8, 2020 at 11:12:25 AM PDT
To: mpoo@ion.ac.cn

Hi Mu-Ming,

I have been communicating with you on the problem, which has been cc'd to a few key scientists in our small circle. Here I want to write you this primate email.

I know, as the director of the Institute, you are doing your job in defending your PI. However, I am also your friend and past colleague at UCSD. Given our friendship and mutual respect, I hope that you understand why I approach you in the very upsetting incidence.

You know well that we have been working on this new frontier for years. I am trying to learn neuroscience, which is not easy for a molecular biologist pretty much throughout my scientific career. Because of my academic activities in China, I am now officially banned for NIH fundings for the next 4 years. Tom Maniatis, my postdoc advisor, advised me to abandon my comfortable zone and instead focus on the neuronal reprogramming strategy we discovered. I thus intend to make this switch in my remaining productive years of my career. As you can see, how upset I am to see the Cell paper, which gets ahead of us, claiming their original discoveries, but the truth is that they learned our positive results, which of course will expedite their duplication of our work in a different disease model and a different brain region. I guess that I now learn my own lessons for being openness in scientific exchange.

We have started the publication process since 2017. Now, the paper is still at Nature. There are 4 reviewers. Three highly praised our work for the originality and thoroughness (7 main figures and 20 supplementary figures in the current version). One reviewer specifically asked the Nature editor to give us extra space to fully and clearly describe our findings, not to confine with the general guide of Nature for the length of typical articles. However, one reviewer asked for endless extension of our work. In fact, the data have been tripled during the last revision. Now, with the Cell paper, it is unclear whether they will now raise the novelty issue.

Therefore, if you try to feel in my shoes, you can imagine how upset I am. Additionally, as my work involves collaborators at UCSD, there is a chance for raising the breach issue, thus triggering FBI investigation. This is the last thing I want to see, as I will be crushed in the middle because I gave seminars on our unpublished work in China, now causing the current trouble.

In any case, what would by your personal advice on this?

Fu

Xiang-Dong Fu,
Distinguished Professor
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Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

From: Fu, Xiang-Dong
Sent time: 04/08/2020 06:07:51 PM
To: Yi Rao <yrao@pku.edu.cn>; Shi, Yigong <shi-lab@tsinghua.edu.cn>; Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>

Now the paper is out and everyone interested is reading. Their work on PD appears to be totally wrong and every images presented are questionable. If you look at Fig 6, you will see why. The neurons have no axons and the cell body size is the same as astrocytes, which is wrong. They claimed that 50% of converted neurons are TH+ dopaminergic neurons, but the vest majority cannot take uptake the dopamine derivative FFN206, which is supposed to bind VMAT2. Strangely, whatever signals they detected are around cells bodies, not neuronal processes. Many people now start to question whether many parts of the story are fabricated!

As a neuroscientist, you should take a look at the data.

Xiang-Dong Fu,
Distinguished Professor
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> On Apr 8, 2020, at 3:07 PM, Yi Rao wrote:
>
> https://mp.weixin.qq.com/s/URIUbwcIUd24YacsKnohfQ
>
>
> 发自我的iPhone

From: Yi Rao <yrao@pku.edu.cn>
Sent time: 04/08/2020 06:49:24 PM
To: Fu, Xiang-Dong
Cc: Shi, Yigong <shi-lab@tsinghua.edu.cn>; Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Subject: Re:

Gave you an example
I will read Yang later (I was in a car, not able to download)

在 4/9/20, 9:48 AM, "Fu, Xiang-Dong" 写入:

>Hi Yi,
>
>Why did you talked about Hailan Hu, rather Hui Yang?
>
>Xiang-Dong Fu,
>Distinguished Professor
>Dept. of Cellular and Molecular Medicine
>University of California, San Diego
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>Phone: 858-534-4937
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>> On Apr 8, 2020, at 6:24 PM, Yi Rao wrote:
>>
>> Not the first time
>> Hailan Hu published 4-5 N/S papers, none is believed
>> Evan Poo does not
>> Labs in her field could not reproduce
>> Her papers on ketamine happen to overlap with ours. We use the same
>>drug on the same brain area. Her "discoveries " were due to leakage in
>>their electrodes, my postdocs concluded. That is why they "observed"
>>what they reported. They were basically wrong, cheating themselves (and
>>getting papers), but missed what are more important
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>>> 在 2020年4月9日, 上午9:08, Fu, Xiang-Dong 写道:
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>>>have no axons and the cell body size is the same as astrocytes, which
>>>is wrong. They claimed that 50% of converted neurons are TH+
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From: Shi, Yigong <shi-lab@mail.tsinghua.edu.cn>
Sent time: 04/09/2020 02:12:11 AM
To: Fu, Xiang-Dong
Cc: Yi Rao <yrao@pku.edu.cn>; Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Subject: Re: Re:

Hi Xiang-Dong,

After digesting the information, I also believe there are issues here that should be investigated seriously by ION. I am not sure how to proceed from here. Maybe Xiao-Fan has some idea?

Yigong

> -----原始邮件-----
> 发件人: "Fu, Xiang-Dong"
> 发送时间: 2020-04-09 09:48:21 (星期四)
> 收件人: "Yi Rao"
> 抄送: "Shi, Yigong" , "Xiao-Fan Wang, Ph.D."
> 主题: Re:
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> Hi Yi,
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From: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Sent time: 04/09/2020 06:12:44 AM
To: Shi, Yigong <shi-lab@mail.tsinghua.edu.cn>
Cc: Fu, Xiang-Dong; Yi Rao <yrao@pku.edu.cn>
Subject: Re:

Since Xiang-Dong sent his original message to MMP to the three of us and also Chunli, apparently Chunli immediately forwarded it to MMP, the reason that MMP sent his reply message specifically to the three of us. What we heard was that CAS immediately asked ION to conduct an investigation, so they knew from the start of this situation. Now the issue is getting more complicated, no longer just serious breach of ethical standard, but suspicion of data manipulation, which is in the area of misconduct. I think that, after Xiang-Dong consults with a few experts who have now looked at the published data and raised the same questions as the ones by others forwarded by Yi, then Xiang-Dong can decide the next step, including writing a formal letter to both CAS and Cell requesting investigation.

I will talk to Xiang-Dong later today about this. XF

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发自我的iPhone

在 2020年4月9日，上午9:08，Fu, Xiang-Dong <xdfu@health.ucsd.edu> 写道：

Now the paper is out and everyone interested is reading. Their work on PD appears to be totally wrong and every images presented are questionable. If you look at Fig 6, you will see why. The neurons have no axons and the cell body size is the same as astrocytes, which is wrong. They claimed that 50% of converted neurons are TH+ dopaminergic neurons, but the vest majority cannot take uptake the dopamine derivative FFN206, which is supposed to bind VMAT2. Strangely, whatever signals they detected are around cells bodies, not neuronal processes. Many people now start to question whether many parts of the story are fabricated!

As a neuroscientist, you should take a look at the data.

Xiang-Dong Fu,
Distinguished Professor
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9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

> On Apr 8, 2020, at 3:07 PM, Yi Rao <yrao@pku.edu.cn> wrote:
>
> https://urldefense.com/v3/__https://mp.weixin.qq.com/s/URIUbwcIUd24YacsKnohfQ__;!!OToaGQ!-U3bfPNEO2JTRKuyz3AoBfr2d99xadI_lwouWfGFlM0lpKzL_Rur0yN9Vq7Gl4L9AhWi$
>
> 发自我的iPhone

From: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Sent time: 04/09/2020 08:48:50 AM
To: Fu, Xiang-Dong
Subject: Re: urgent

I am glad that they will move forward to publishing your paper there which they should have done a long time ago knowing that your work was better and stronger!

I have also read MM's response, and hoped he would have paid more attention to his own young investigators while lecturing to the rest using his status. At the least, he should have insisted that Yang communicated with you after they got the positive review from Cell.

Hope we can take the opportunity in the near future to push for the ethics education on this point.

In regard of the data quality from the Cell paper, I think that we can wait for more people in the field to evaluate and raise issues if there are serious problems, as the points sent by Yi by one scientist were not at the level that an accusation of misconduct occurred by Yang since missing proper controls can ben considered as weaknesses or deficiencies of a study that may have led to the wrong or unsupported conclusions, but not be used as sufficient evidence for misconduct which is a very serious matter. What do you think? I wished Yi had used his own judgement in informing us on this point. XF

> On Apr 9, 2020, at 11:15 AM, Fu, Xiang-Dong <xdfu@health.ucsd.edu> wrote:
>
> Sent from my iPhone
>
> Begin forwarded message:
>
> **From:** Marie-Therese Heemels <T.Heemels@nature.com>
> **Date:** April 9, 2020 at 1:34:31 AM PDT
> **To:** "Fu, Xiang-Dong" <xdfu@health.ucsd.edu>
> **Cc:** Don Cleveland <dcleveland@health.ucsd.edu>, Mobley Bill <wmobley@ucsd.edu>
> **Subject: RE: urgent**
>
> Dear Fu,
> Thank you very much for your message. I do appreciate your disappointment.
> In our experience, better, stronger, is far more important than a couple of weeks sooner or later.
> We knew the paper was coming. We know your work is better, stronger. We'll go ahead as planned.
> Moving swiftly. I have now contacted the reviewers to make them aware of the paper. Your original submission date and the strength of the data will speak for itself.
>
> Best regards, Therese
>
> Marie-Therese Heemels, PhD
> Senior Editor nature
> Follow me on twitter @TeeHeemels
>
> -----Original Message-----
> From: Fu, Xiang-Dong <xdfu@health.ucsd.edu>
> Sent: 08 April 2020 21:42

To: Marie-Therese Heemels <T.Heemels@nature.com>
Cc: Don Cleveland <dcleveland@health.ucsd.edu>; Mobley Bill <wmobley@ucsd.edu>
Subject: Re: urgent

Der Therese,

The competing paper is online now at Cell. As a deeply wounded author, I hope that your "cautious" referee #2 will now realize how he or she has done a major disfavor to Nature, as this news is supposed to be first announced by Nature.

The our referees have the chance to compare ours with the Cell paper, they note right away how little evidence presented in the Cell paper and how extensive and thorough evidence conveyed in our manuscript. Nonetheless, as demanded by referee #2 for independent replication of our findings, this would be the one, but not the one I would be prude of if I were the author.

In fact, a scientific misconduct investigation is under the way for the Cell paper because I gave a seminar in the authors' institution after we entered the publication process for our work. The authors basically used our positive results (both in the retina system and in the brain) as the basis to replicate our works completely without our knowledge (of course using a different disease model or a different brain region). To me, this is the shameless act on their part.

Scientifically, the community will judge, as our findings are the first ever to demonstrate the reconstitution of the nigro-striatal pathway to achieve life long benefits (the same phenotype persists in lesioned animals and remains fully rescued in reprogrammed animals 1.5 years later). In the Cell paper, they claimed they achieved 50% conversion from astrocytes to TH+ neurons in striatum, which is not even the brain area where most dopaminergic neurons originate, and our data show that this rarely happens. If you take a close look at their images, there are hardly any axons from those TH+ cells. Notably, they used AAV-GFAP-Cre in their study, which is much more leaky than the knock-in Cre gene under the endogenous GFAP promoter.

Of course, as you can imagine, I am quite upset by this expected competition from people who basically stole our ideas and data. Behaviors like this will discourage sharing unpublished data in seminars and meetings, which is not good for science in general. Now, the only thing I remain hopeful is that you will go through the due process soon.

Best regards,

Fu

Xiang-Dong Fu,
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Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

From: Fu, Xiang-Dong
Sent time: 04/09/2020 11:16:50 AM
To: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>; Yi Rao <yrao@pku.edu.cn>; Shi, Yigong <shi-lab@tsinghua.edu.cn>
Subject: Fwd: personal message

This is my response to MMP. Because this is supposed to be my "primate" communication, please keep it to yourself.

Fu

Begin forwarded message:

From: "Fu, Xiang-Dong" <xdfu@health.ucsd.edu>
Subject: Re: personal message
Date: April 9, 2020 at 11:14:59 AM PDT
To: mpoo@ion.ac.cn

Dear Mu-Ming,

Thanks for your message. I could not agree more with what you said in term of emphasizing original ideas. You are right that this is not unique in China, quite widespread in the US and elsewhere. To some extent, many top Chinese scientists in both China and US are contributing to this bad culture.

As you can imagine, a lot of information has been funneled to me in the past couple of days. As an advocator for higher moral standard, you are doing the right thing for the country. On the other hand, as the director of the Institute, you are probably enjoying the publicity, at least among the media in China, which is based on the shameless claim of their original invention (even with respect to the application in the retina system, which I described during my seminars).

If you happen to see comments so far from the scientific community outside China, all are rather negative, questioning not only the quality of the work, but also the theoretical ground for the observations as reported. If I were you, I would take a close look at the actual data, which I am sure you can tell as a leading neuroscientist. If you wish to lead ION to become a reputable institution at the international stage, I am not even sure that this short-term gain of publicity will be positive or negative from the eyes of the international community where most top leaders in the field know our work quite well.

In any case, I hope we will continue to maintain our friendship after this.

Best wishes,

Fu

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Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

On Apr 9, 2020, at 4:19 AM, mpoo@ion.ac.cn wrote:

Dear Xiang-Dong:

I must say that I do feel very sorry about this incident. In fact, I have talked to Yang and his postdoc about communicating with you when they showed me the preprint of their paper, specifically about coordinating the publication of their work with you. My understanding was that your paper is about to be published in Nature, given the fact that you have done such a thorough job in providing all the data (based on our last communication in Shanghai), thus having back-to-back publication is probably the best approach. Thus, for proper scientific communication, they should coordinate with you about coordinating the publication.

I have talked about the importance of communicating unpublished results and respect the work of others for so many times, in my annual meetings at IoN and in my recent billibilli online lecture on scientific conducts last month on the gray zone problems. This is my current personal mission - to fight against the the tide of scientific competition overwhelming the respect of the norm of scientific communication. Apparently, I have not been able to have much effect on the behavior of young investigators, who always argue that they are the victims of such competition. This is a culture that is pervasive in China and equally pervasive in the US. After all, they were mostly trained by the US culture. In fact, I have known several cases of senior Chinese-American scientists who gained the information on the work done by young colleagues in China or hearing their work in meetings (even lab meetings that presumably providing advice), and went back to US to pursue the work and publish the results first. I can tell you the stories next time we meet with real names.

I fully understand how upsetting this Cell paper appears before your paper. I think the Nature editor has made a big mistake in taking only one reviewer's view too seriously. I wonder whether the Nature editor now can be persuaded to speed up the publication of your paper and ignore the odd review, given the fact that the delay in their review process is a main cause of the current situation, the site you chose to do the conversion is more appropriate for PD, and that the Cell paper is mainly on the conversion in the retina.

Finally, I should say that I will not be protective of IoN PIs if I find clear evidence of misconducts. In fact, IoN is the only institute that fired a PI within months (in the case of Ding Yu-xiang) after an investigative committee decided that misconduct was committed. In the present case (like the two sample cases you mentioned in your previous letter) it will be very difficult to initiate an investigation. Gray zone problems are particularly sticky, because one can always claim that he(she) had the idea (cannot be documented) already in his head before he heard the unpublished results. I have personal experience in such a dispute in the neuronal migration field (because I knew both parties very well, and were given all the communications during the dispute).

Best wishes,
Mu-ming

---

mpoo@ion.ac.cn

From: Fu, Xiang-Dong
Date: 2020-04-09 02:12
To: mpoo@ion.ac.cn

Subject: personal message

Hi Mu-Ming,

I have been communicating with you on the problem, which has been cc'd to a few key scientists in our small circle. Here I want to write you this primate email.

I know, as the director of the Institute, you are doing your job in defending your PI. However, I am also your friend and past colleague at UCSD. Given our friendship and mutual respect, I hope that you understand why I approach you in the very upsetting incidence.

You know well that we have been working on this new frontier for years. I am trying to learn neuroscience, which is not easy for a molecular biologist pretty much throughout my scientific career. Because of my academic activities in China, I am now officially banned for NIH fundings for the next 4 years. Tom Maniatis, my postdoc advisor, advised me to abandon my comfortable zone and instead focus on the neuronal reprogramming strategy we discovered. I thus intend to make this switch in my remaining productive years of my career. As you can see, how upset I am to see the Cell paper, which gets ahead of us, claiming their original discoveries, but the truth is that they learned our positive results, which of course will expedite their duplication of our work in a different disease model and a different brain region. I guess that I now learn my own lessons for being openness in scientific exchange.

We have started the publication process since 2017. Now, the paper is still at Nature. There are 4 reviewers. Three highly praised our work for the originality and thoroughness (7 main figures and 20 supplementary figures in the current version). One reviewer specifically asked the Nature editor to give us extra space to fully and clearly describe our findings, not to confine with the general guide of Nature for the length of typical articles. However, one reviewer asked for endless extension of our work. In fact, the data have been tripled during the last revision. Now, with the Cell paper, it is unclear whether they will now raise the novelty issue.

Therefore, if you try to feel in my shoes, you can image how upset I am. Additionally, as my work involves collaborators at UCSD, there is a chance for raising the breach issue, thus triggering FBI investigation. This is the last thing I want to see, as I will be crushed in the middle because I gave seminars on our unpublished work in China, now causing the current trouble.

In any case, what would by your personal advice on this?

Fu

Xiang-Dong Fu,
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Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

From: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Sent time: 04/10/2020 08:54:43 AM
To: Fu, Xiang-Dong
Subject: Re: WeChat record

Thanks! It is clear when he knew and started to work on this project, which contradicted his statement in response to your questions. It is often the case that an initial lie would lead to more lies. XF

> On Apr 10, 2020, at 11:17 AM, Fu, Xiang-Dong <xdfu@health.ucsd.edu> wrote:
>
> Hi Xiaofan,
>
> Here are two screen shots, showing that he did not even know what is PTB after my seminar at ION in 7/6/2018 and began to tell his students in 7/8/2018 when he still did not remember the name of PTB.
>
> As you see in the last email, they claimed that they initiated the experiments at least before May of 2018. The whole things are made up. The dates they provided as evidence for their efforts before hearing my seminar are not related to PTB at all.
>
> Fu
>
> Xiang-Dong Fu,
> Distinguished Professor
> Dept. of Cellular and Molecular Medicine
> University of California, San Diego
> George Palade Laboratories
> 9500 Gilman Drive, Room 217
> La Jolla, CA 92093-0651
>
> Phone: 858-534-4937
> Email: xdfu@health.ucsd.edu
>
> <1_Screen Shot 2020-04-10 at 10.54.57 AM.pdf><2_Screen Shot 2020-04-10 at 10.55.50 AM.pdf>

From: Fu, Xiang-Dong
Sent time: 04/11/2020 11:51:36 AM
To: yrao <yrao@pku.edu.cn>; shi-lab <shi-lab@tsinghua.edu.cn>; Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>; clbai <clbai@cas.cn>
Subject: Forget to pass this email to you as a record

Begin forwarded message:

From: "Fu, Xiang-Dong" <xdfu@health.ucsd.edu>
Subject: Re: personal message
Date: April 9, 2020 at 11:14:59 AM PDT
To: mpoo@ion.ac.cn

Dear Mu-Ming,

Thanks for your message. I could not agree more with what you said in term of emphasizing original ideas. You are right that this is not unique in China, quite widespread in the US and elsewhere. To some extent, many top Chinese scientists in both China and US are contributing to this bad culture.

As you can imagine, a lot of information has been funneled to me in the past couple of days. As an advocator for higher moral standard, you are doing the right thing for the country. On the other hand, as the director of the Institute, you are probably enjoying the publicity, at least among the media in China, which is based on the shameless claim of their original invention (even with respect to the application in the retina system, which I described during my seminars).

If you happen to see comments so far from the scientific community outside China, all are rather negative, questioning not only the quality of the work, but also the theoretical ground for the observations as reported. If I were you, I would take a close look at the actual data, which I am sure you can tell as a leading neuroscientist. If you wish to lead ION to become a reputable institution at the international stage, I am not even sure that this short-term gain of publicity will be positive or negative from the eyes of the international community where most top leaders in the field know our work quite well.

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Best wishes,

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Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

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>
> Dear Xiang-Dong:

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Best wishes,
Mu-ming

---

mpoo@ion.ac.cn

From: Fu, Xiang-Dong
Date: 2020-04-09 02:12
To: mpoo@ion.ac.cn
Subject: personal message

Hi Mu-Ming,

I have been communicating with you on the problem, which has been cc'd to a few key scientists in our small circle. Here I want to write you this primate email.

I know, as the director of the Institute, you are doing your job in defending your PI. However, I am also your friend and past colleague at UCSD. Given our friendship and mutual respect, I hope that you understand why I approach you in the very upsetting incidence.

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In any case, what would by your personal advice on this?

Fu

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La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

From: Fu, Xiang-Dong
Sent time: 05/09/2020 09:41:55 AM
To: shi-lab@tsinghua.edu.cn
Cc: Yi Rao <yrao@pku.edu.cn>; Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Subject: Re: Yigong

Dear Yigong,

Thanks for forwarding this string of emails to me. Now, as you know, our paper has been accepted by Nature. Once the paper appears in print, people will tell how much difference between our work and Yang Hui's Cell paper. As you and Yi have noticed, many experts have expressed concerns on their work. To me, most of their data can be explained by leaked Cre expression driven by the minimal GFAP promoter in their AAV vector. Gong Chen was the first to use this approach and he has hard time publishing his work because of the same concern from the field. Gong noticed that they used 1000X more AAV-GFAP-Cre than his study, and according to his experience, the leakage would be dramatic. By the way, we tried their gene editing strategy to generate conditional ko mice with zero success, while we are highly successful in introducing point mutation one at time using the same approach.

This brought the issue of how they obtained the "anticipated" behavioral benefits. As pointed out by Zhigong He, the chemical-induced disease model is highly variable and mice show a significant degree in recovering by themselves. In our experiments, we had to monitor the establishment of stable phenotype before reprogramming and following behavioral changes in time course experiments with one set of mice for up to 2 years. In comparison, they did not have time to repeat their animal experiments even once (their paper was submitted to Nature 6 months after hearing my talk at ION, rejected and then to Cell). Thus, the most plausible explanation is their cherry picking of the data to fit the conclusions. This is precisely the core problem of data manipulation, which is beyond the gray zone as Mu-Ming tried to shrug under the rug. In my mind, Yang Hui has shown a consistent pattern of scientific dishonesty.

After fully cooling down, I intend to write an open letter to use this specific case to reflect the current lack of scientific ethics eduction to the current generation of young scientists. I am afraid that Mu-Ming is contributing, and in many cases especially when involved people in ION, nurturing short-cut approaches to hot topics, quickly pouching a hole, and then moving to the next target, rather than attacking a fundamental problem by making systematic efforts. He probably thinks nothing wrong with it, which would be a great strategy to use the manpower and resources to beat original scientists. This is clearly a wrong way to do science, as once the outcome is already known, what is the point to investigate? Once my letter is drafted, I will circulate among our small circle before deciding on the next step.

Fu

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Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

> On May 9, 2020, at 2:17 AM, shi-lab@tsinghua.edu.cn wrote:
>
> Hi Fu,
> I wrote to Mu-ming about Hui YANG's scientific integrity. Mu-ming forwarded my email to him. He sent the following reply to me. I did not reply to his email.
> His explanation is pale compared to the scale of the problem he faces.
> Best,

Yigong

发件人: 杨辉 <huiyang@ion.ac.cn>
发送时间: 2020年5月1日 17:13
收件人: mpoo@ion.ac.cn
抄送: shi-lab@mail.tsinghua.edu.cn; yrao@pku.edu.cn
主题: Re: Yigong

施老师，您好，

1. 关于我postdoc的文章，质疑文章一在线我已于editor取得联系，也与Rudolf Jaenisch交流过，同时做了一些实验再次验证我们数据和结论没有任何问题。详细见附件，有很多已经发表的文献可以重复我们的数据或者方法。与editor私下交流，也确实有一些reviewer也可以重复我们的实验，这个您可以和editor去确认，邮箱见下面附文。Yixin Yao <yixin.yao@biomedcentral.com>
您也可以找您信赖的人评价一下我们回应的文章，看看是否有问题。

我们这一方法许多人无法重复确实可以理解，实验平台和各方面技能都有一定要求，要把我们这一系统做好，需要在专业基因编辑和小鼠胚胎操作的实验室training几年时间，并不是像CRISPR在细胞敲除基因一样，training 几周就好。同时我们和同领域科学家也在不停优化方法，让更多人更容易的做出来。

质疑我们文章的20个实验室，绝大多数都是core facility的人，并不是专业做小鼠基因编辑的实验室，他们几乎没有先重复我们文章中的位点，而他们找3个中心重复我们实验的时候，和我们的实验条件差别很大，比如注射浓度居然相差20倍。同时，他们之中没有任何一个人发邮件跟我探讨实验细节和关键点。

我能够理解他们不能重复我实验的心情，但是生物有许多实验都需要很多积累和平台。我至今还是无法理解，已经有其他实验室重复出了我文章中的结果，我自己的学生和Rudolf的其他工作人员也都能重复出来，许多其他实验室也能够用这种方法做出来，这也能算造假吗？非得我把每个人都手把手教会，让他们都能重复出我的结果才行吗？

2. 关于我phD的文章，可以直接联系我导师李劲松老师，或者周琪老师，他们后续有许多工作都重复了我的实验结果，这些都可以在网上找到发表的文章。如果您或者其他人觉得他们都不可信，那我无话可说。这个实验对系统的要求就更高了，许多人没有这个平台和技术，所以这技术很难向CRISPR那样推广，但并不能说明这文章的不可靠。有些实验并不是一个博后或者学生就能轻易重复出来的，不知他们是否有到我实验室或者李老师等实验室直接交流或者询问？

3. 关于我最近的Cell文章，才刚刚在线，我们会积极自己做更多的摸索和拓展，同时协助其他实验室重复，等过段时间就自然知晓。不可能随意发到Twitter或者mitbbs的信息我都得一一回应，况且国内并不能登陆看到，大部分都是别人转给我的，而且我无法登陆回应。发出质疑好的方式是邮件发给我或者editor，我都会做一一回应，我不喜欢这种informal的形式。

以下是对postdoc Cell文章的回应：

Gurumurthy et al. [1]recently reported that a method developed by Yang et al. to generate floxed allele (designated as “two donor method” by Gurumurthy et al.) [2]had poor reproducibility. They claimed that three centers could not reproduce our results on generating conditional alleles of the *Mecp2*locus and that the “two-donor method” had very low success rate on other loci.

Here, we provide our responses to these claims:

1. Our results on *Mecp2*locus published by Yang et al have been reproduced by independent experiments in the Jaenisch (8-10% correct alleles), Yang (8% correct alleles) and Hatada’s groups (2-6% correct alleles) [3], respectively. In addition, multiple peer-reviewed publications [3, 9-12]have successfully used this method to create conditional knockout (CKO) mice (9 out of 11 loci succeeded, 2.5% to 18% efficiency). We noticed that the efficiency of generating CKO mice by CRISPR/Cas9 could vary, which might due to different platform features or experiment conditions.

2. The conditions used by Gurumurthy et al. [1]do not correspond to the conditions used in our paper. The concentrations of CRISPR reagents used in the Gurumurthy et al.’s study [1]on the *Mecp2* locus (10 ng/μl for Cas9 mRNA, 10 ng/μl for sgRNA and 10 ng/μl for oligos) were much lower (10 fold lower RNA and 20 fold lower oligo donor concentration) than those used in the Yang et al.’s experiments (Cas9 100 ng/μl, sgRNA 50

ng/μl and 100 ng/μl for each oligo) [2]and Yang et al.'s previous [4]and following publications [5-8]. It is well known that the concentrations of CRISPR reagents are well correlated with the genome editing efficiency.

3. We utilized piezo-driven zygote injection method in our original paper, which allows for injecting CRISPR components at much higher concentration. The difference between this method and pronuclear injection method used by Gurumurthy et al. might also contribute to the difference of successful rates.

In general, with any genome editing method or strategy being used, the efficiencies at different genomic loci are often highly variable. In the 2013 proof of concept paper, we showed the feasibility of generating floxed allele at *Mecp2*locus using CRISPR. To assume the efficiency we demonstrated at*Mecp2*locus will be directly translated to the success rate at other genomic loci seems premature.

We agree with the Gurumurthy et al's comment that the "one-donor method" offers higher success rate for generating floxed alleles in general, while the efficiency of "one-donor method" is also variable depending on the genomic loci and donor plasmid design. Before the publication of Gurumurthy et al., we also noted this, and developed a "one-donor method", termed "Tild-CRISPR" method [8], and demonstrated the feasibility and high efficiency in generating CKO mice.

With the fast improvement of genome editing technologies, we and many others constantly optimize our protocols. We welcome all discussions about the choice of optimal strategy for particular applications, however, we think the reproducibility of any published work can only be validated by using the exact same experimental methods and technical parameters.

以下是我和Genome Biology沟通的邮件。

Great, thanks, I will proceed with sending this to review then.

From: 杨辉 <huiyang@ion.ac.cn>
Sent: Wednesday, April 29, 2020 10:41 AM
To: Yixin Yao <yixin.yao@biomedcentral.com>
Subject: Re: RE: correspondence

Dear Yixin,

Thanks for your efforts. We are OK with the edits.

Best,
Hui

-----原始邮件-----
发件人:"Yixin Yao" <yixin.yao@biomedcentral.com>
发送时间:2020-04-29 09:43:57 (星期三)
收件人: "杨辉" <huiyang@ion.ac.cn>
抄送:
主题: RE: correspondence

Dear Hui,

Barb and I had a discussion, and we made a few edits. Could you please take a look at the attached edits and let

us know if you feel they are OK? We will send it to one of the original reviewers once we got confirmation from you, and send it to Guru after confirmation from reviewer.

Thanks,
Yixin

From: 杨辉 <huiyang@ion.ac.cn>
Sent: Monday, April 27, 2020 12:26 PM
To: Yixin Yao <yixin.yao@biomedcentral.com>
Subject: Re: correspondence

Dear Yixin,

Here is our response. Please let me know if any questions.

Best,
Hui

-----原始邮件-----
发件人:"Yixin Yao" <yixin.yao@biomedcentral.com>
发送时间:2019-10-29 13:05:01 (星期二)
收件人: "huiyang@ion.ac.cn" <huiyang@ion.ac.cn>
抄送: "Barbara Cheifet" <barbara.cheifet@genomebiology.com>
主题: correspondence

Dear Hui,

Thank you for contacting us before sending the correspondence regarding Reproducibility of CRISPR-Cas9 methods for generation of conditional mouse alleles: a multi-center evaluation
I have now had a chance to discuss it with my colleagues at *Genome Biology*, we are willing to consider the correspondence and we will send it to review before sending it to the corresponding authors of Reproducibility of CRISPR-Cas9 methods for generation of conditional mouse alleles: a multi-center evaluation. who will be able to respond. We are happy for you to contact the corresponding authors offline, so they will know what's coming in the discussion. We hope the correspondences will provide an informative and helpful forum for researchers in the field.

With best wishes,
Yixin

Yixin Yao PhD
Senior Editor, *Genome Biology*

989 Changle Road
Shanghai, China 200031

E yixin.yao@biomedcentral.com
@GenomeBiology
http://genomebiology.biomedcentral.com

ensuring the integrity of the research we publish, and championing the benefits of open research. BMC is part of Springer Nature, giving us greater opportunities to help authors connect and advance discoveries across the world

-----原始邮件-----
发件人:"mpoo@ion.ac.cn" <mpoo@ion.ac.cn>
发送时间:2020-05-01 15:27:30 (星期五)
收件人: huiyang <huiyang@ion.ac.cn>
抄送:
主题: Yigong

---

mpoo@ion.ac.cn

From: Shi, Yigong
Date: 2020-05-01 00:33
To: mpoo@ion.ac.cn
CC: Yi Rao
Subject: Fw: forward to Yigong

Dear Mu-ming,
I was approached by one of the Tsinghua students who is now an Assistant Professor at a well-known university. He told me how much time he had wasted trying to follow a method reported by YANG Hui while in the Jaenisch lab. He stated that most scientists in his field have problems with YANG Hui's data and integrity. The nature of his comments and the discussion below (albeit casual and informal) prompted me to forward this information to you.
Although we don't yet have a solid proof of scientific misconduct, YANG Hui does appear to have a pattern of questionable behavior. He is the wrong type of role model for young scientists! Unfortunately, he is gaining popularity and having an increasingly powerful impact on young students.
Best,
Yigong

Please discard my name/email from this chain when forwarding.
For 1 (ION) and 2 (Whitehead), I totally agree with these comments below'
For 3 (Shanghai Institute of Biochemistry), I am not expert, so I am not going to endorse those comments.

1 For the most recent work at Cell-
Here are open comments from Seth Blackshaw criticizing the flaws (if not fabrication) of the data.

发信人: mousebreeder (Miney), 信区: Biology
标 题: Re: 各位对今天杨辉的Cell文章怎么看？
发信站: BBS 未名空间站 (Sun Apr 12 11:27:22 2020, 美东)
Seth Blackshaw from Johns Hopkins made some comments on these papers, which can be found on twitter.

I agree with him that the origin of the presumably regenerated ganglion cells or cones was not well established in either paper since the promotor

in the virus vector could mistarget. That needs to be convincingly demonstrated by genetic means as he suggested. However, I don't agree with him that the reprogramming could have been caused by non-specific effects of the virus vector; the chance for that to happen is zero.

I will make some additional comments just on the Cell paper since the bioXiv paper is too preliminary. Other than the expression data missing, to establish that Muller cells were indeed reprogrammed into ganglion cells, they need to show what happened to Muller cells during the transition. That would include Muller cells in the process of migrating from INL to GCL and beginning to lose characteristics of Muller cells and gain characteristics of Ganglion cells in terms of morphology and marker gene expression. A more comprehensive and detailed analysis of the reprogrammed ganglion cells in terms of dendritic projection and morphology, axon projection, subtype marker expression, and electric physiology is also needed.

Among all this, the easiest experiment probably is, instead of just showing a few cells on retinal sections with a couple of markers, to demonstrate by flat-mount imaging a field of regenerated ganglion cells extending their axons to the optic disk at the different time points of reprogramming.

All in all, the authors made extraordinary claims, which must be substantiated by extraordinary evidence. The above questions are all very obvious. I don't know how the paper passed Cell's review process without them being addressed.
>>>
昨天仔细读了这篇文章
数据量很大，结果非常神奇，机制一概没有

如果顺着这篇文章的思路，证据完整、完美（除了axon bundle的交叉部分没有看懂，不知道是不是单眼注射）
但是这篇文章的结果违背了我做了十几年发育生物学的训练和对其理解
一个基因的敲降，可以能将Glia转分化，然后这个转分化的神经能和导弹一样连接到大脑皮层，在意识层面产生新的视觉？
而且文中明确这种被转化的新神经与大脑的连接并不依赖旧有神经的消失
简直.....
我试图认可结果，寻找其他解释，因为我不是做小鼠视网膜神经的，无法判断数据质量。而按照文章所说，证据太强了，没有其他可能。
http://www.mitbbs.com/article_t/Biology/32106661.html

<image001(05-01-15-26-03).png>

2 For the postdoc work - (there were serious issues, the paper that got her job after 10 months of postdoc with Rudy Jaensich)
https://www.biorxiv.org/content/10.1101/393231v2
17 international labs jointly disclosed that they could not repeat this work, needless to comment on the rest of the world, which probably wasted $$$/time on the same technique.

https://www.the-scientist.com/news-opinion/study-challenges-crispr-method-for-making-conditional-knockout-mice--64875
>>>
发信人: mousebreeder (Miney), 信区: Biology
标 题: Re: 各位对今天杨辉的Cell文章怎么看？
发信站: BBS 未名空间站 (Sun Apr 12 12:55:55 2020, 美东)

I just realize that Yang is the first author of the Cell paper from the Jaenisch lab showing the generation of knockin mice using CRISPR with an efficiency nobody else could reproduce. He has since published quite a few more papers using CRISPR. I was not successful using one of his methods (Tild-CRISPR). I would not have tried it if I knew it was the same guy.

He has 29 people in his lab. Hope he is making good use of the resource he is enjoying.

发信人: mousebreeder (Miney), 信区: Biology
标 题: Re: "韩春雨"的祖师爷--杨辉
发信站: BBS 未名空间站 (Fri Apr 17 16:34:52 2020, 美东)

So many labs and transgenic facilities followed that Cell paper and wasted a lot of money, effort, and time trying to make conditional mice. What I am disappointed with this is that in the end, he is going to be all fine. But if he keeps doing this kind of crappy work, which I suspect he will as indicated by this new Cell paper, he could get caught eventually and suffer the consequences.

发信人: crispr2016 (), 信区: Biology
标 题: "韩春雨"的祖师爷--杨辉
发信站: BBS 未名空间站 (Fri Apr 17 14:08:29 2020, 美东)

杨辉于2012-2013年在白头研究所的Rudolf Jaenisch实验室总共做了10个月的博士后, 在这期间, 杨辉以第一作者或共同第一作者的身份总共发表两篇Cell文章。这两篇文章都是第一次成功并且完美的将CRISPR质粒注射进入合子中， 一步到位的构建突变小鼠。

Yang H, Wang H, Shivalila CS, Cheng AW, Shi L, Jaenisch R. One-step generation of mice carrying reporter and conditional alleles by CRISPR/Cas-mediated genome engineering. Cell. 154: 1370-9. PMID 23992847 DOI: 10.1016/j.cell.2013.08.022

Wang H, Yang H, Shivalila CS, Dawlaty MM, Cheng AW, Zhang F, Jaenisch R. One-step generation of mice carrying mutations in multiple genes by CRISPR/Cas-mediated genome engineering. Cell. 153: 910-8. PMID 23643243 DOI: 10.1016/j.cell.2013.04.025

然而, 该技术发表5年之后全世界有将近17家实验室公开谴责该方法涉嫌造假。

https://www.the-scientist.com/news-opinion/study-challenges-crispr-method-for-making-conditional-knockout-mice--64875

Researchers from 17 labs report low efficacy rates for the popular technique.
Sukanya Charuchandra
Sep 28, 2018

Aconsortium of 17 laboratories worldwide has presented results contradicting a highly cited study that described a technique to create conditional knockout mice using CRISPR. The preprint, published on bioRxiv on September 1, shows a much lower efficiency rate for the technique compared to the original report.

The results of the new study indicate the limitations of the original study, whose success appears to be relegated to deleting a specific gene within a hybrid mouse strain. The lead author of the first report, cited nearly 1,000 times by Google Scholar’s count, stands by the strength of his method.

Before the original study, published in 2013 by geneticist Rudolf Jaenisch at the Whitehead Institute of Biomedical Research and colleagues, embryonic stem cells were used to prepare conditional knockout mice—animals with a gene engineered to be turned off on command that are missing a gene—a process that could take years and had only a 1 percent efficacy rate. The CRISPR technique was presented as one-stop-shop to obtaining conditional knockout mice with a 16 percent success rate. By injecting zygotes with the CRISPR machinery, Jaenisch’s team successfully sandwiched the to-be-deleted gene between two LoxP sites (a step called floxing) that allow the gene to

be conditionally regulated.

“The original Jaenisch paper was a landmark,” says geneticist John Schimenti, director of Cornell University’s Stem Cell and Transgenic Core Facility, who was not involved in either study. “It certainly demonstrated that you can get a high efficiency and high efficiency mutagenesis at specific loci.”

Conditional knockout mice are extremely important in biomedical research as they let scientists delete essential genes in specific tissues in the organism and at particular times during development. While the Jaenisch method was promising, research groups that have tried to generate mice using the technique have not been as successful.

“Everybody who’s tried to make floxed alleles by the method they originally proposed is generally met with failure,” says Schimenti, who has observed the “same exact issues” in Cornell’s transgenic facility as those noted in the preprint.

The Jaenisch method often results in off-target mutations, deletions, or a failure to insert both LoxP sites in the correct orientation, notes Schimenti. “This is generally recognized in the community, it’s been very difficult to recapitulate anything close to the numbers that Jaenisch’s group reported,” he says.

Talks between a close-knit research community at conferences and elsewhere about the challenges other labs were having with the technique led Gaetan Burgio, who runs the transgenesis facility at the Australian National University, and his colleagues to try and determine what was going wrong.

To begin with, three groups replicated the original experiment targeting the same gene in a different strain of mice and had zero success. Next, 17 labs , including the original three, independently repeated the experiment on a total of 56 genes and two intergenic regions in the mouse genome across five different strains of mice. The combined dataset from all the labs included 17,887 microinjected or electroporated mouse zygotes and a resultant 1,718 live mice, of which only 15 possessed both of the inserted LoxP sites needed for conditional control. Across all the mice that were tested, off-target deletions or mutations were observed in lieu of the correct insertion of the LoxP sites.

Compared to the original study’s 16 percent efficiency rate of obtaining conditional knockout alleles in mice, Burgio and others had a success rate of merely 0.87 percent. “The success rate of the method . . . is equivalent to the classical methods with embryonic stem cells,” says Burgio.

The replication team aimed to figure out the possible factors responsible for successful conditional knockout mice and found that the simultaneous insertion of two LoxP sites was critical for the success of the technique.

Jaenisch considers the difference between the mouse strains used in the two studies to be a sticking point and an underlying reason for the high variation between the two studies. “I have to discount these data as being serious,” says Jaenisch, who questions the quality of the recent study.

Schimenti agrees that the genetic background should have been taken into consideration when replicating the original study. “I think it’s kind of a flaw in the bioRxiv study—if they were testing the Jaenisch results, they should have used the exact same types of animals.” However, both Burgio and Schimenti raise the point that the strain of mice used in the Jaenisch paper is uncommon compared to the mice used in the new study.

Schimenti also suggests the possibility that the original 16 percent success rate may have been representative of the single locus in the specific strain of mice used in that study. “I think it’s clear that this is a very problematic technique,” says Schimenti. “There needs to be a workaround. ”

3. There were some additional accusation of his Graudate work on stem cell cloning, which I

have no insights

Hui Yang
Principal Investigator
Laboratory of Disease Models in Non-Human Primates
Institute of Neuroscience,
Shanghai Chinese Academy of Sciences
Room A0517, The New Life Science Building,
320 Yueyang Road, Shanghai, P.R.China, 200031

<Response to Gurumurthy et al-0501.docx>

From: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Sent time: 05/09/2020 12:10:43 PM
To: Fu, Xiang-Dong
Subject: Re: Yigong

Thanks for sharing the information. As you can see the message just sent to us from NSR, MMP continues to get the trust of Chunli, so we may have to wait for a new president for CAS to raise the issue directly, but your open letter would be different.

For a separate matter, can you give me a few names who may help us to discuss the situation in GZ? Right now, Prof. Boqin Qiang, Gualiang Xu, Yeguang Chen, Anming Meng will join you, Tao Xu and I for the discussion. I wrote to Mingjie Zhang this morning to ask him to do the same since he helped me last December for the initial assessment of the lab. Who else will be helpful for this purpose? Shall we ask Linzhao Cheng who works in the stem cell area and also heads the branch at USTC? I want to come up with a list and then ask each one to commit to a specific time next week for a Zoom meeting.

Best regards, XF

> On May 9, 2020, at 12:41 PM, Fu, Xiang-Dong <xdfu@health.ucsd.edu> wrote:
>
> Dear Yigong,
>
> Thanks for forwarding this string of emails to me. Now, as you know, our paper has been accepted by Nature. Once the paper appears in print, people will tell how much difference between our work and Yang Hui's Cell paper. As you and Yi have noticed, many experts have expressed concerns on their work. To me, most of their data can be explained by leaked Cre expression driven by the minimal GFAP promoter in their AAV vector. Gong Chen was the first to use this approach and he has hard time publishing his work because of the same concern from the field. Gong noticed that they used 1000X more AAV-GFAP-Cre than his study, and according to his experience, the leakage would be dramatic. By the way, we tried their gene editing strategy to generate conditional ko mice with zero success, while we are highly successful in introducing point mutation one at time using the same approach.
>
> This brought the issue of how they obtained the "anticipated" behavioral benefits. As pointed out by Zhigong He, the chemical-induced disease model is highly variable and mice show a significant degree in recovering by themselves. In our experiments, we had to monitor the establishment of stable phenotype before reprogramming and following behavioral changes in time course experiments with one set of mice for up to 2 years. In comparison, they did not have time to repeat their animal experiments even once (their paper was submitted to Nature 6 months after hearing my talk at ION, rejected and then to Cell). Thus, the most plausible explanation is their cherry picking of the data to fit the conclusions. This is precisely the core problem of data manipulation, which is beyond the gray zone as Mu-Ming tried to shrug under the rug. In my mind, Yang Hui has shown a consistent pattern of scientific dishonesty.
>
> After fully cooling down, I intend to write an open letter to use this specific case to reflect the current lack of scientific ethics eduction to the current generation of young scientists. I am afraid that Mu-Ming is contributing, and in many cases especially when involved people in ION, nurturing short-cut approaches to hot topics, quickly pouching a hole, and then moving to the next target, rather than attacking a fundamental problem by making systematic efforts. He probably thinks nothing wrong with it, which would be a great strategy to use the manpower and resources to beat original scientists. This is clearly a wrong way to do science, as once the outcome is already known, what is the point to investigate? Once my letter is drafted, I will circulate among our small circle before deciding on the next step.
>
> Fu
>
> Xiang-Dong Fu,
> Distinguished Professor
> Dept. of Cellular and Molecular Medicine
> University of California, San Diego
> George Palade Laboratories
> 9500 Gilman Drive, Room 217
> La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

On May 9, 2020, at 2:17 AM, shi-lab@tsinghua.edu.cn wrote:

Hi Fu,
I wrote to Mu-ming about Hui YANG's scientific integrity. Mu-ming forwarded my email to him. He sent the following reply to me. I did not reply to his email.
His explanation is pale compared to the scale of the problem he faces.
Best,
Yigong

发件人: 杨辉 <huiyang@ion.ac.cn>
发送时间: 2020年5月1日 17:13
收件人: mpoo@ion.ac.cn
抄送: shi-lab@mail.tsinghua.edu.cn; yrao@pku.edu.cn
主题: Re: Yigong

施老师，您好，

1. 关于我postdoc的文章，质疑文章一在线我已于editor取得联系，也与Rudolf Jaenisch交流过，同时做了一些实验再次验证我们数据和结论没有任何问题。详细见附件，有很多已经发表的文献可以重复我们的数据或者方法。与editor私下交流，也确实有一些reviewer也可以重复我们的实验，这个您可以和editor去确认，邮箱见下面附文。Yixin Yao <yixin.yao@biomedcentral.com>
您也可以找您信赖的人评价一下我们回应的文章，看看是否有问题。

我们这一方法许多人无法重复确实可以理解，实验平台和各方面技能都有一定要求，要把我们这一系统做好，需要在专业基因编辑和小鼠胚胎操作的实验室training几年时间，并不是像CRISPR在细胞敲除基因一样，training 几周就好。同时我们和同领域科学家也在不停优化方法，让更多人更容易的做出来。

质疑我们文章的20个实验室，绝大多数都是core facility的人，并不是专业做小鼠基因编辑的实验室，他们几乎没有先重复我们文章中的位点，而他们找3个中心重复我们实验的时候，和我们的实验条件差别很大，比如注射浓度居然相差20倍。同时，他们之中没有任何一个人发邮件跟我探讨实验细节和关键点。

我能够理解他们不能重复我实验的心情，但是生物有许多实验都需要很多积累和平台。我至今还是无法理解，已经有其他实验室重复出了我文章中的结果，我自己的学生和Rudolf的其他工作人员也都能重复出来，许多其他实验室也能够用这种方法做出来，这也能算造假吗？非得我把每个人都手把手教会，让他们都能重复出我的结果才行吗？

2. 关于我phD的文章，可以直接联系我导师李劲松老师，或者周琪老师，他们后续有许多工作都重复了我的实验结果，这些都可以在网上找到发表的文章。如果您或者其他人觉得他们都不可信，那我无话可说。这个实验对系统的要求就更高了，许多人没有这个平台和技术，所以这技术很难向CRISPR那样推广，但并不能说明这文章的不可靠。有些实验并不是一个博后或者学生就能轻易重复出来的，不知他们是否有到我实验室或者李老师等实验室直接交流或者询问？

3. 关于我最近的Cell文章，才刚刚在线，我们会积极自己做更多的摸索和拓展，同时协助其他实验室重复，等过段时间就自然知晓。不可能随意发到Twitter或者mitbbs的信息我都得一一回应，况且国内并不能登陆看到，大部分都是别人转给我的，而且我无法登陆回应。发出质疑好的方式是邮件发给我或者editor，我都会做一一回应，我不喜欢这种informal的形式。

以下是对postdoc Cell文章的回应：

Gurumurthy et al. [1]recently reported that a method developed by Yang et al. to generate floxed allele (designated as "two donor method" by Gurumurthy et al.) [2]had poor reproducibility. They claimed that three centers could not reproduce our results on generating conditional alleles of the *Mecp2*locus and that the "two-donor method"

had very low success rate on other loci.

Here, we provide our responses to these claims:

1. Our results on *Mecp2*locus published by Yang et al have been reproduced by independent experiments in the Jaenisch (8-10% correct alleles), Yang (8% correct alleles) and Hatada's groups (2-6% correct alleles) [3], respectively. In addition, multiple peer-reviewed publications [3, 9-12]have successfully used this method to create conditional knockout (CKO) mice (9 out of 11 loci succeeded, 2.5% to 18% efficiency). We noticed that the efficiency of generating CKO mice by CRISPR/Cas9 could vary, which might due to different platform features or experiment conditions.

2. The conditions used by Gurumurthy et al. [1]do not correspond to the conditions used in our paper. The concentrations of CRISPR reagents used in the Gurumurthy et al.'s study [1]on the *Mecp2* locus (10 ng/μl for Cas9 mRNA, 10 ng/μl for sgRNA and 10 ng/μl for oligos) were much lower (10 fold lower RNA and 20 fold lower oligo donor concentration) than those used in the Yang et al.'s experiments (Cas9 100 ng/μl, sgRNA 50 ng/μl and 100 ng/μl for each oligo) [2]and Yang et al.'s previous [4]and following publications [5-8]. It is well known that the concentrations of CRISPR reagents are well correlated with the genome editing efficiency.

3. We utilized piezo-driven zygote injection method in our original paper, which allows for injecting CRISPR components at much higher concentration. The difference between this method and pronuclear injection method used by Gurumurthy et al. might also contribute to the difference of successful rates.

In general, with any genome editing method or strategy being used, the efficiencies at different genomic loci are often highly variable. In the 2013 proof of concept paper, we showed the feasibility of generating floxed allele at *Mecp2*locus using CRISPR. To assume the efficiency we demonstrated at*Mecp2*locus will be directly translated to the success rate at other genomic loci seems premature.

We agree with the Gurumurthy et al's comment that the "one-donor method" offers higher success rate for generating floxed alleles in general, while the efficiency of "one-donor method" is also variable depending on the genomic loci and donor plasmid design. Before the publication of Gurumurthy et al., we also noted this, and developed a "one-donor method", termed "Tild-CRISPR" method [8], and demonstrated the feasibility and high efficiency in generating CKO mice.

With the fast improvement of genome editing technologies, we and many others constantly optimize our protocols. We welcome all discussions about the choice of optimal strategy for particular applications, however, we think the reproducibility of any published work can only be validated by using the exact same experimental methods and technical parameters.

以下是我和Genome Biology沟通的邮件。

Great, thanks, I will proceed with sending this to review then.

From: 杨辉 <huiyang@ion.ac.cn>
Sent: Wednesday, April 29, 2020 10:41 AM
To: Yixin Yao <yixin.yao@biomedcentral.com>

Subject: Re: RE: correspondence

Dear Yixin,

Thanks for your efforts. We are OK with the edits.

Best,
Hui

-----原始邮件-----
发件人:"Yixin Yao" <yixin.yao@biomedcentral.com>
发送时间:2020-04-29 09:43:57 (星期三)
收件人: "杨辉" <huiyang@ion.ac.cn>
抄送:
主题: RE: correspondence

Dear Hui,

Barb and I had a discussion, and we made a few edits. Could you please take a look at the attached edits and let us know if you feel they are OK? We will send it to one of the original reviewers once we got confirmation from you, and send it to Guru after confirmation from reviewer.

Thanks,
Yixin

From: 杨辉 <huiyang@ion.ac.cn>
Sent: Monday, April 27, 2020 12:26 PM
To: Yixin Yao <yixin.yao@biomedcentral.com>
Subject: Re: correspondence

Dear Yixin,

Here is our response. Please let me know if any questions.

Best,
Hui

-----原始邮件-----
发件人:"Yixin Yao" <yixin.yao@biomedcentral.com>
发送时间:2019-10-29 13:05:01 (星期二)
收件人: "huiyang@ion.ac.cn" <huiyang@ion.ac.cn>
抄送: "Barbara Cheifet" <barbara.cheifet@genomebiology.com>
主题: correspondence

Dear Hui,

Thank you for contacting us before sending the correspondence regarding Reproducibility of CRISPR-Cas9 methods for generation of conditional mouse alleles: a multi-center evaluation
I have now had a chance to discuss it with my colleagues at *Genome Biology*, we are willing to consider the correspondence and we will send it to review before sending it to the corresponding authors of Reproducibility of CRISPR-Cas9 methods for generation of conditional mouse alleles: a multi-center evaluation. who will be able to respond. We are happy for you to contact the corresponding authors offline, so they will know what's coming in the discussion. We hope the correspondences will provide an informative and helpful forum for researchers in the field.

With best wishes,
Yixin

Yixin Yao PhD

Senior Editor, *Genome Biology*

989 Changle Road
Shanghai, China 200031

E yixin.yao@biomedcentral.com
@GenomeBiology
http://genomebiology.biomedcentral.com

-----原始邮件-----
发件人:"mpoo@ion.ac.cn" <mpoo@ion.ac.cn>
发送时间:2020-05-01 15:27:30 (星期五)
收件人: huiyang <huiyang@ion.ac.cn>
抄送:
主题: Yigong

---

mpoo@ion.ac.cn

From: Shi, Yigong
Date: 2020-05-01 00:33
To: mpoo@ion.ac.cn
CC: Yi Rao
Subject: Fw: forward to Yigong

Dear Mu-ming,
I was approached by one of the Tsinghua students who is now an Assistant Professor at a well-known university. He told me how much time he had wasted trying to follow a method reported by YANG Hui while in the Jaenisch lab. He stated that most scientists in his field have problems with YANG Hui's data and integrity. The nature of his comments and the discussion below (albeit casual and informal) prompted me to forward this information to you.
Although we don't yet have a solid proof of scientific misconduct, YANG Hui does appear to have a pattern of questionable behavior. He is the wrong type of role model for young scientists! Unfortunately, he is gaining popularity and having an increasingly powerful impact on young students.
Best,
Yigong

Please discard my name/email from this chain when forwarding.
For 1 (ION) and 2 (Whitehead), I totally agree with these comments below'
For 3 (Shanghai Institute of Biochemistry), I am not expert, so I am not going to endorse those comments.

1 For the most recent work at Cell-
Here are open comments from Seth Blackshaw criticizing the flaws (if not fabrication) of the data.

发信人: mousebreeder (Miney), 信区: Biology
标 题: Re: 各位对今天杨辉的Cell文章怎么看？
发信站: BBS 未名空间站 (Sun Apr 12 11:27:22 2020, 美东)
Seth Blackshaw from Johns Hopkins made some comments on these papers, which can be found on twitter.

I agree with him that the origin of the presumably regenerated ganglion cells or cones was not well established in either paper since the promotor in the virus vector could mistarget. That needs to be convincingly demonstrated by genetic means as he suggested. However, I don't agree with him that the reprogramming could have been caused by non-specific effects of the virus vector; the chance for that to happen is zero.

I will make some additional comments just on the Cell paper since the bioXiv paper is too preliminary. Other than the expression data missing, to establish that Muller cells were indeed reprogrammed into ganglion cells, they need to show what happened to Muller cells during the transition. That would include Muller cells in the process of migrating from INL to GCL and beginning to lose characteristics of Muller cells and gain characteristics of Ganglion cells in terms of morphology and marker gene expression. A more comprehensive and detailed analysis of the reprogrammed ganglion cells in terms of dendritic projection and morphology, axon projection, subtype marker expression, and electric physiology is also needed.

Among all this, the easiest experiment probably is, instead of just showing a few cells on retinal sections with a couple of markers, to demonstrate by flat-mount imaging a field of regenerated ganglion cells extending their axons to the optic disk at the different time points of reprogramming.

All in all, the authors made extraordinary claims, which must be substantiated by extraordinary evidence. The above questions are all very obvious. I don't know how the paper passed Cell's review process without them being addressed.
>>>
昨天仔细读了这篇文章
数据量很大，结果非常神奇，机制一概没有

如果顺着这篇文章的思路，证据完整、完美（除了axon bundle的交叉部分没有看懂，不知道是不是单眼注射）
但是这篇文章的结果违背了我做了十几年发育生物学的训练和对其理解
一个基因的敲降，可以能将Glia转分化，然后这个转分化的神经能和导弹一样连接到大脑皮层，在意识层面产生新的视觉？
而且文中明确这种被转化的新神经与大脑的连接并不依赖旧有神经的消失
简直.....
我试图认可结果，寻找其他解释，因为我不是做小鼠视网膜神经的，无法判断数据质量。而按照文章所说，证据太强了，没有其他可能。
http://www.mitbbs.com/article_t/Biology/32106661.html

<image001(05-01-15-26-03).png>

2 For the postdoc work - (there were serious issues, the paper that got her job after 10 months of postdoc with Rudy Jaensich)
https://www.biorxiv.org/content/10.1101/393231v2
17 international labs jointly disclosed that they could not repeat this work, needless to comment on the rest of the world, which probably wasted $$$/time on the same technique.

https://www.the-scientist.com/news-opinion/study-challenges-crispr-method-for-making-conditional-knockout-mice--64875
>>>
发信人: mousebreeder (Miney), 信区: Biology
标 题: Re: 各位对今天杨辉的Cell文章怎么看？
发信站: BBS 未名空间站 (Sun Apr 12 12:55:55 2020, 美东)

I just realize that Yang is the first author of the Cell paper from the Jaenisch lab showing the generation of knockin mice using CRISPR with an efficiency nobody else could reproduce. He has since published quite a few more papers using CRISPR. I was not successful using one of his methods (Tild-CRISPR). I would not have tried it if I knew it was the same guy.

He has 29 people in his lab. Hope he is making good use of the resource he is enjoying.

发信人: mousebreeder (Miney), 信区: Biology
标 题: Re: "韩春雨"的祖师爷--杨辉
发信站: BBS 未名空间站 (Fri Apr 17 16:34:52 2020, 美东)

So many labs and transgenic facilities followed that Cell paper and wasted a lot of money, effort, and time trying to make conditional mice. What I am disappointed with this is that in the end, he is going to be all fine. But if he keeps doing this kind of crappy work, which I suspect he will as indicated by this new Cell paper, he could get caught eventually and suffer the consequences.

发信人: crispr2016 (), 信区: Biology
标 题: "韩春雨"的祖师爷--杨辉
发信站: BBS 未名空间站 (Fri Apr 17 14:08:29 2020, 美东)

杨辉于2012-2013年在白头研究所的Rudolf Jaenisch实验室总共做了10个月的博士后，在这期间，杨辉以第一作者或共同第一作者的身份总共发表两篇Cell文章。这两篇文章都是第一次成功并且完美的将CRISPR质粒注射进入合子中， 一步到位的构建突变小鼠。

Yang H, Wang H, Shivalila CS, Cheng AW, Shi L, Jaenisch R. One-step generation of mice carrying reporter and conditional alleles by CRISPR/Cas-mediated genome engineering. Cell. 154: 1370-9. PMID 23992847 DOI: 10.1016/j.cell.2013.08.022

Wang H, Yang H, Shivalila CS, Dawlaty MM, Cheng AW, Zhang F, Jaenisch R. One-step generation of mice carrying mutations in multiple genes by CRISPR/Cas-mediated genome engineering. Cell. 153: 910-8. PMID 23643243 DOI: 10.1016/j.cell.2013.04.025

然而，该技术发表5年之后全世界有将近17家实验室公开谴责该方法涉嫌造假。

https://www.the-scientist.com/news-opinion/study-challenges-crispr-method-for-making-conditional-knockout-mice--64875

Researchers from 17 labs report low efficacy rates for the popular technique.

Sukanya Charuchandra

Sep 28, 2018

Aconsortium of 17 laboratories worldwide has presented results contradicting a highly cited study that described a technique to create conditional knockout mice using CRISPR. The preprint, published on bioRxiv on September 1, shows a much lower efficiency rate for the technique compared to the original report.

The results of the new study indicate the limitations of the original study, whose success appears to be relegated to deleting a specific gene within a hybrid mouse strain. The lead author of the first report, cited nearly 1,000 times by Google Scholar's count, stands by the strength of his method.

Before the original study, published in 2013 by geneticist Rudolf Jaenisch at the Whitehead Institute of Biomedical Research and colleagues, embryonic stem cells were used to prepare conditional knockout mice—animals with a gene engineered to be turned off on command that are missing a gene—a process that could take years and had only a 1 percent efficacy rate. The CRISPR technique was presented as one-stop-shop to obtaining conditional knockout mice with a 16 percent success rate. By injecting zygotes with the CRISPR machinery, Jaenisch's team successfully sandwiched the to-be-deleted gene between two LoxP sites (a step called floxing) that allow the gene to be conditionally regulated.

"The original Jaenisch paper was a landmark," says geneticist John Schimenti, director of Cornell University's Stem Cell and Transgenic Core Facility, who was not involved in either study. "It certainly demonstrated that you can get a high efficiency and high efficiency mutagenesis at specific loci."

Conditional knockout mice are extremely important in biomedical research as they let scientists delete essential genes in specific tissues in the organism and at particular times during development. While the Jaenisch method was promising, research groups that have tried to generate mice using the technique have not been as successful.

"Everybody who's tried to make floxed alleles by the method they originally proposed is generally met with failure," says Schimenti, who has observed the "same exact issues" in Cornell's transgenic facility as those noted in the preprint.

The Jaenisch method often results in off-target mutations, deletions, or a failure to insert both LoxP sites in the correct orientation, notes Schimenti. "This is generally recognized in the community, it's been very difficult to recapitulate anything close to the numbers that Jaenisch's group reported," he says.

Talks between a close-knit research community at conferences and elsewhere about the challenges other labs were having with the technique led Gaetan Burgio, who runs the transgenesis facility at the Australian National University, and his colleagues to try and determine what was going wrong.

To begin with, three groups replicated the original experiment targeting the same gene in a different strain of mice and had zero success. Next, 17 labs , including the original three, independently repeated the experiment on a total of 56 genes and two intergenic regions in the mouse genome across five different strains of mice. The combined dataset from all the labs included 17,887 microinjected or electroporated mouse zygotes and a resultant 1,718 live mice, of which only 15 possessed both of the inserted LoxP sites needed for conditional control. Across all the mice that were tested, off-target deletions or mutations were observed in lieu of the correct insertion of the LoxP sites.

Compared to the original study's 16 percent efficiency rate of obtaining conditional knockout alleles in mice, Burgio and others had a success rate of merely 0.87 percent. "The success rate of the method . . . is equivalent to the classical methods with embryonic stem cells," says Burgio.

> The replication team aimed to figure out the possible factors responsible for successful conditional knockout mice and found that the simultaneous insertion of two LoxP sites was critical for the success of the technique.
>
> Jaenisch considers the difference between the mouse strains used in the two studies to be a sticking point and an underlying reason for the high variation between the two studies. “I have to discount these data as being serious,” says Jaenisch, who questions the quality of the recent study.
>
> Schimenti agrees that the genetic background should have been taken into consideration when replicating the original study. “I think it’s kind of a flaw in the bioRxiv study—if they were testing the Jaenisch results, they should have used the exact same types of animals.” However, both Burgio and Schimenti raise the point that the strain of mice used in the Jaenisch paper is uncommon compared to the mice used in the new study.
>
> Schimenti also suggests the possibility that the original 16 percent success rate may have been representative of the single locus in the specific strain of mice used in that study. “I think it’s clear that this is a very problematic technique,” says Schimenti. “There needs to be a workaround.
> ”

3. There were some additional accusation of his Graudate work on stem cell cloning, which I have no insights

---

Hui Yang
Principal Investigator
Laboratory of Disease Models in Non-Human Primates
Institute of Neuroscience,
Shanghai Chinese Academy of Sciences
Room A0517, The New Life Science Building,
320 Yueyang Road, Shanghai, P.R.China, 200031

<Response to Gurumurthy et al-0501.docx>

From:	Fu, Xiang-Dong
Sent time:	05/09/2020 12:47:20 PM
To:	Xiao-Fan Wang, Ph D. <xiao.fan.wang@duke.edu>
Subject:	Re: Yigong
Attachments:	Dear Leaders of CAS.docx

Hi Xiaofan,

The email from Yigong prompted me to think about the letter I intend to write. Here is my first draft. If possible, please take a look to advise if I am in the right track.
On your request to think about the strategic planning for GZ, I feel that all current setting is still among basic scientists, who like me have little ideas on how to translate basic science discoveries to practical applications if this is the goal of the centers in GZ. Otherwise, it will become another party to gain resources for whatever they are doing. In this regard, you may consider Xiaodong Wang. Perhaps, Hongqui Deng is also a good candidate. Outside China, Chuan He and perhaps En Li would be worth considering. What China needs is a group of scientists successful in both science and industry.

Fu

Xiang-Dong Fu,
Distinguished Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

> On May 9, 2020, at 12:10 PM, Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu> wrote:
>
> Thanks for sharing the information. As you can see the message just sent to us from NSR, MMP continues to get the trust of Chunli, so we may have to wait for a new president for CAS to raise the issue directly, but your open letter would be different.
>
> For a separate matter, can you give me a few names who may help us to discuss the situation in GZ? Right now, Prof. Boqin Qiang, Gualiang Xu, Yeguang Chen, Anming Meng will join you, Tao Xu and I for the discussion. I wrote to Mingjie Zhang this morning to ask him to do the same since he helped me last December for the initial assessment of the lab. Who else will be helpful for this purpose? Shall we ask Linzhao Cheng who works in the stem cell area and also heads the branch at USTC? I want to come up with a list and then ask each one to commit to a specific time next week for a Zoom meeting.
>
> Best regards, XF
>
> > On May 9, 2020, at 12:41 PM, Fu, Xiang-Dong <xdfu@health.ucsd.edu> wrote:
> >
> > Dear Yigong,
> >
> > Thanks for forwarding this string of emails to me. Now, as you know, our paper has been accepted by Nature. Once the paper appears in print, people will tell how much difference between our work and Yang Hui's Cell paper. As you and Yi have noticed, many experts have expressed concerns on their work. To me, most of their data can be explained by leaked Cre expression driven by the minimal

GFAP promoter in their AAV vector. Gong Chen was the first to use this approach and he has hard time publishing his work because of the same concern from the field. Gong noticed that they used 1000X more AAV-GFAP-Cre than his study, and according to his experience, the leakage would be dramatic. By the way, we tried their gene editing strategy to generate conditional ko mice with zero success, while we are highly successful in introducing point mutation one at time using the same approach.

This brought the issue of how they obtained the "anticipated" behavioral benefits. As pointed out by Zhigong He, the chemical-induced disease model is highly variable and mice show a significant degree in recovering by themselves. In our experiments, we had to monitor the establishment of stable phenotype before reprogramming and following behavioral changes in time course experiments with one set of mice for up to 2 years. In comparison, they did not have time to repeat their animal experiments even once (their paper was submitted to Nature 6 months after hearing my talk at ION, rejected and then to Cell). Thus, the most plausible explanation is their cherry picking of the data to fit the conclusions. This is precisely the core problem of data manipulation, which is beyond the gray zone as Mu-Ming tried to shrug under the rug. In my mind, Yang Hui has shown a consistent pattern of scientific dishonesty.

After fully cooling down, I intend to write an open letter to use this specific case to reflect the current lack of scientific ethics eduction to the current generation of young scientists. I am afraid that Mu-Ming is contributing, and in many cases especially when involved people in ION, nurturing short-cut approaches to hot topics, quickly pouching a hole, and then moving to the next target, rather than attacking a fundamental problem by making systematic efforts. He probably thinks nothing wrong with it, which would be a great strategy to use the manpower and resources to beat original scientists. This is clearly a wrong way to do science, as once the outcome is already known, what is the point to investigate? Once my letter is drafted, I will circulate among our small circle before deciding on the next step.

Fu

Xiang-Dong Fu,
Distinguished Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

> On May 9, 2020, at 2:17 AM, shi-lab@tsinghua.edu.cn wrote:
>
> Hi Fu,
> I wrote to Mu-ming about Hui YANG's scientific integrity. Mu-ming forwarded my email to him. He sent the following reply to me. I did not reply to his email. His explanation is pale compared to the scale of the problem he faces.
> Best,
> Yigong
>
> **发件人:** 杨辉 <huiyang@ion.ac.cn>
> **发送时间:** 2020年5月1日 17:13
> **收件人:** mpoo@ion.ac.cn
> **抄送:** shi-lab@mail.tsinghua.edu.cn; yrao@pku.edu.cn

主题: Re: Yigong

施老师，您好，

1. 关于我postdoc的文章，质疑文章一在线我已于editor取得联系，也与Rudolf Jaenisch交流过，同时做了一些实验再次验证我们数据和结论没有任何问题。详细见附件，有很多已经发表的文献可以重复我们的数据或者方法。与editor私下交流，也确实有一些reviewer也可以重复我们的实验，这个您可以和editor去确认，邮箱见下面附文。Yixin Yao <yixin.yao@biomedcentral.com>
您也可以找您信赖的人评价一下我们回应的文章，看看是否有问题。

我们这一方法许多人无法重复确实可以理解，实验平台和各方面技能都有一定要求，要把我们这一系统做好，需要在专业基因编辑和小鼠胚胎操作的实验室training几年时间，并不是像CRISPR在细胞敲除基因一样，training 几周就好。同时我们和同领域科学家也在不停优化方法，让更多人更容易的做出来。

质疑我们文章的20个实验室，绝大多数都是core facility的人，并不是专业做小鼠基因编辑的实验室，他们几乎没有先重复我们文章中的位点，而他们找3个中心重复我们实验的时候，和我们的实验条件差别很大，比如注射浓度居然相差20倍。同时，他们之中没有任何一个人发邮件跟我探讨实验细节和关键点。

我能够理解他们不能重复我实验的心情，但是生物有许多实验都需要很多积累和平台。我至今还是无法理解，已经有其他实验室重复出了我文章中的结果，我自己的学生和Rudolf的其他工作人员也都能重复出来，许多其他实验室也能够用这种方法做出来，这也能算造假吗？非得我把每个人都手把手教会，让他们都能重复出我的结果才行吗？

2. 关于我phD的文章，可以直接联系我导师李劲松老师，或者周琪老师，他们后续有许多工作都重复了我的实验结果，这些都可以在网上找到发表的文章。如果您或者其他人觉得他们都不可信，那我无话可说。这个实验对系统的要求就更高了，许多人没有这个平台和技术，所以这技术很难向CRISPR那样推广，但并不能说明这文章的不可靠。有些实验并不是一个博后或者学生就能轻易重复出来的，不知他们是否有到我实验室或者李老师等实验室直接交流或者询问？

3. 关于我最近的Cell文章，才刚刚在线，我们会积极自己做更多的摸索和拓展，同时协助其他实验室重复，等过段时间就自然知晓。不可能随意发到Twitter或者mitbbs的信息我都得一一回应，况且国内并不能登陆看到，大部分都是别人转给我的，而且我无法登陆回应。发出质疑好的方式是邮件发给我或者editor，我都会做一一回应，我不喜欢这种informal的形式。

以下是对postdoc Cell文章的回应：

Gurumurthy et al. [1]recently reported that a method developed by Yang et al. to generate floxed allele (designated as “two donor method” by Gurumurthy et al.) [2]had poor reproducibility. They claimed that three centers could not reproduce our results on generating conditional alleles of the *Mecp2*locus and that the “two-donor method” had very low success rate on other loci.

Here, we provide our responses to these claims:

1. Our results on *Mecp2*locus published by Yang et al have been reproduced by independent experiments in the Jaenisch (8-10% correct alleles), Yang (8% correct alleles) and Hatada’s groups (2-6% correct alleles) [3], respectively. In addition, multiple peer-reviewed publications [3, 9-12]have successfully used this method to create conditional knockout (CKO) mice (9 out of 11 loci succeeded, 2.5% to 18% efficiency). We noticed that the efficiency of generating CKO mice by CRISPR/Cas9 could vary, which might due to different platform features or experiment conditions.

2. The conditions used by Gurumurthy et al. [1]do not correspond to the conditions used in our paper. The concentrations of CRISPR reagents used in the Gurumurthy et al.’s study [1]on the *Mecp2* locus (10 ng/μl for Cas9 mRNA, 10 ng/μl for sgRNA and 10 ng/μl for oligos) were much lower (10 fold lower RNA and 20 fold lower oligo donor

concentration) than those used in the Yang et al.'s experiments (Cas9 100 ng/μl, sgRNA 50 ng/μl and 100 ng/μl for each oligo) [2]and Yang et al.'s previous [4]and following publications [5-8]. It is well known that the concentrations of CRISPR reagents are well correlated with the genome editing efficiency.

3. We utilized piezo-driven zygote injection method in our original paper, which allows for injecting CRISPR components at much higher concentration. The difference between this method and pronuclear injection method used by Gurumurthy et al. might also contribute to the difference of successful rates.

In general, with any genome editing method or strategy being used, the efficiencies at different genomic loci are often highly variable. In the 2013 proof of concept paper, we showed the feasibility of generating floxed allele at *Mecp2*locus using CRISPR. To assume the efficiency we demonstrated at*Mecp2*locus will be directly translated to the success rate at other genomic loci seems premature.

We agree with the Gurumurthy et al's comment that the "one-donor method" offers higher success rate for generating floxed alleles in general, while the efficiency of "one-donor method" is also variable depending on the genomic loci and donor plasmid design. Before the publication of Gurumurthy et al., we also noted this, and developed a "one-donor method", termed "Tild-CRISPR" method [8], and demonstrated the feasibility and high efficiency in generating CKO mice.

With the fast improvement of genome editing technologies, we and many others constantly optimize our protocols. We welcome all discussions about the choice of optimal strategy for particular applications, however, we think the reproducibility of any published work can only be validated by using the exact same experimental methods and technical parameters.

以下是我和Genome Biology沟通的邮件。

Great, thanks, I will proceed with sending this to review then.

From: 杨辉 <huiyang@ion.ac.cn>
Sent: Wednesday, April 29, 2020 10:41 AM
To: Yixin Yao <yixin.yao@biomedcentral.com>
Subject: Re: RE: correspondence

Dear Yixin,

Thanks for your efforts. We are OK with the edits.

Best,
Hui

> -----原始邮件-----
> **发件人:**"Yixin Yao" <yixin.yao@biomedcentral.com>

发送时间:2020-04-29 09:43:57 (星期三)
收件人:"杨辉" <huiyang@ion.ac.cn>
抄送:
主题: RE: correspondence

Dear Hui,

Barb and I had a discussion, and we made a few edits. Could you please take a look at the attached edits and let us know if you feel they are OK? We will send it to one of the original reviewers once we got confirmation from you, and send it to Guru after confirmation from reviewer.

Thanks,
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From: 杨辉 <huiyang@ion.ac.cn>
Sent: Monday, April 27, 2020 12:26 PM
To: Yixin Yao <yixin.yao@biomedcentral.com>
Subject: Re: correspondence

Dear Yixin,

Here is our response. Please let me know if any questions.

Best,
Hui

-----原始邮件-----
发件人:"Yixin Yao" <yixin.yao@biomedcentral.com>
发送时间:2019-10-29 13:05:01 (星期二)
收件人: "huiyang@ion.ac.cn" <huiyang@ion.ac.cn>
抄送: "Barbara Cheifet" <barbara.cheifet@genomebiology.com>
主题: correspondence

Dear Hui,

Thank you for contacting us before sending the correspondence regarding Reproducibility of CRISPR-Cas9 methods for generation of conditional mouse alleles: a multi-center evaluation
I have now had a chance to discuss it with my colleagues at *Genome Biology*, we are willing to consider the correspondence and we will send it to review before sending it to the corresponding authors of Reproducibility of CRISPR-Cas9 methods for generation of conditional mouse alleles: a multi-center evaluation. who will be able to respond. We are happy for you to contact the corresponding authors offline, so they will know what's coming in the discussion. We hope the correspondences will provide an informative and helpful forum for researchers in the field.

With best wishes,
Yixin

Yixin Yao PhD
Senior Editor, *Genome Biology*

989 Changle Road
Shanghai, China 200031

E yixin.yao@biomedcentral.com
@GenomeBiology
http://genomebiology.biomedcentral.com

-----原始邮件-----
发件人:"mpoo@ion.ac.cn" <mpoo@ion.ac.cn>
发送时间:2020-05-01 15:27:30 (星期五)
收件人: huiyang <huiyang@ion.ac.cn>
抄送:
主题: Yigong

---

mpoo@ion.ac.cn

From: Shi, Yigong
Date: 2020-05-01 00:33
To: mpoo@ion.ac.cn
CC: Yi Rao
Subject: Fw: forward to Yigong

Dear Mu-ming,
I was approached by one of the Tsinghua students who is now an Assistant Professor at a well-known university. He told me how much time he had wasted trying to follow a method reported by YANG Hui while in the Jaenisch lab. He stated that most scientists in his field have problems with YANG Hui's data and integrity. The nature of his comments and the discussion below (albeit casual and informal) prompted me to forward this information to you.
Although we don't yet have a solid proof of scientific misconduct, YANG Hui does appear to have a pattern of questionable behavior. He is the wrong type of role model for young scientists! Unfortunately, he is gaining popularity and having an increasingly powerful impact on young students.
Best,
Yigong

Please discard my name/email from this chain when forwarding.
For 1 (ION) and 2 (Whitehead), I totally agree with these comments below'
For 3 (Shanghai Institute of Biochemistry), I am not expert, so I am not

going to endorse those comments.

1 For the most recent work at Cell-
Here are open comments from Seth Blackshaw criticizing the flaws (if not fabrication) of the data.

发信人: mousebreeder (Miney), 信区: Biology
标 题: Re: 各位对今天杨辉的Cell文章怎么看？
发信站: BBS 未名空间站 (Sun Apr 12 11:27:22 2020, 美东)
Seth Blackshaw from Johns Hopkins made some comments on these papers, which
can be found on twitter.

I agree with him that the origin of the presumably regenerated ganglion cells or cones was not well established in either paper since the promotor in the virus vector could mistarget. That needs to be convincingly demonstrated by genetic means as he suggested. However, I don't agree with
him that the reprogramming could have been caused by non-specific effects of
the virus vector; the chance for that to happen is zero.

I will make some additional comments just on the Cell paper since the bioXiv
paper is too preliminary. Other than the expression data missing, to establish that Muller cells were indeed reprogrammed into ganglion cells, they need to show what happened to Muller cells during the transition. That
would include Muller cells in the process of migrating from INL to GCL and beginning to lose characteristics of Muller cells and gain characteristics of Ganglion cells in terms of morphology and marker gene expression. A more
comprehensive and detailed analysis of the reprogrammed ganglion cells in
terms of dendritic projection and morphology, axon projection, subtype marker expression, and electric physiology is also needed.

Among all this, the easiest experiment probably is, instead of just showing a few cells on retinal sections with a couple of markers, to demonstrate by flat-mount imaging a field of regenerated ganglion cells extending their axons to the optic disk at the different time points of reprogramming.

All in all, the authors made extraordinary claims, which must be substantiated by extraordinary evidence. The above questions are all very obvious. I don't know how the paper passed Cell's review process without them being addressed.
>>>
昨天仔细读了这篇文章
数据量很大，结果非常神奇，机制一概没有

如果顺着这篇文章的思路，证据完整、完美（除了axon bundle的交叉部分没有看懂，
不知道是不是单眼注射）
但是这篇文章的结果违背了我做了十几年发育生物学的训练和对其理解
一个基因的敲降，可以能将Glia转分化，然后这个转分化的神经能和导弹一样连接到大
脑皮层，在意识层面产生新的视觉？
而且文中明确这种被转化的新神经与大脑的连接并不依赖旧有神经的消失
简直.....
我试图认可结果，寻找其他解释，因为我不是做小鼠视网膜神经的，无法判断数据质量
。而按照文章所说，证据太强了，没有其他可能。
http://www.mitbbs.com/article_t/Biology/32106661.html

<image001(05-01-15-26-03).png>

2 For the postdoc work - (there were serious issues, the paper that got her job after 10 months of postdoc with Rudy Jaensich)
https://www.biorxiv.org/content/10.1101/393231v2
17 international labs jointly disclosed that they could not repeat this work, needless to comment on the rest of the world, which probably wasted $$$/time on the same technique.

https://www.the-scientist.com/news-opinion/study-challenges-crispr-method-for-making-conditional-knockout-mice--64875
>>>
发信人: mousebreeder (Miney), 信区: Biology
标 题: Re: 各位对今天杨辉的Cell文章怎么看？
发信站: BBS 未名空间站 (Sun Apr 12 12:55:55 2020, 美东)

I just realize that Yang is the first author of the Cell paper from the Jaenisch lab showing the generation of knockin mice using CRISPR with an efficiency nobody else could reproduce. He has since published quite a few more papers using CRISPR. I was not successful using one of his methods (Tild-CRISPR). I would not have tried it if I knew it was the same guy.

He has 29 people in his lab. Hope he is making good use of the resource he is enjoying.

发信人: mousebreeder (Miney), 信区: Biology
标 题: Re: "韩春雨"的祖师爷--杨辉
发信站: BBS 未名空间站 (Fri Apr 17 16:34:52 2020, 美东)

So many labs and transgenic facilities followed that Cell paper and wasted a lot of money, effort, and time trying to make conditional mice. What I am disappointed with this is that in the end, he is going to be all fine. But if he keeps doing this kind of crappy work, which I suspect he will as indicated by this new Cell paper, he could get caught eventually and suffer the consequences.

发信人: crispr2016 (), 信区: Biology
标 题: "韩春雨"的祖师爷--杨辉
发信站: BBS 未名空间站 (Fri Apr 17 14:08:29 2020, 美东)

杨辉于2012-2013年在白头研究所的Rudolf Jaenisch实验室总共做了10个月的博士后,
在这期间, 杨辉以第一作者或共同第一作者的身份总共发表两篇Cell文章。这两篇文章
都是第一次成功并且完美的将CRISPR质粒注射进入合子中， 一步到位的构建突变小鼠。

Yang H, Wang H, Shivalila CS, Cheng AW, Shi L, Jaenisch R. One-step generation of mice carrying reporter and conditional alleles by CRISPR/Cas-
mediated genome engineering. Cell. 154: 1370-9. PMID 23992847 DOI: 10.1016/j
.cell.2013.08.022

Wang H, Yang H, Shivalila CS, Dawlaty MM, Cheng AW, Zhang F, Jaenisch R. One
-step generation of mice carrying mutations in multiple genes by CRISPR/Cas-
mediated genome engineering. Cell. 153: 910-8. PMID 23643243 DOI: 10.1016/j.
cell.2013.04.025

然而，该技术发表5年之后全世界有将近17家实验室公开谴责该方法涉嫌造假。

https://www.the-scientist.com/news-opinion/study-challenges-crispr-method-
for-making-conditional-knockout-mice--64875

Researchers from 17 labs report low efficacy rates for the popular technique.
Sukanya Charuchandra
Sep 28, 2018

Aconsortium of 17 laboratories worldwide has presented results contradicting
a highly cited study that described a technique to create conditional knockout mice using CRISPR. The preprint, published on bioRxiv on September
1, shows a much lower efficiency rate for the technique compared to the original report.

The results of the new study indicate the limitations of the original study, whose success appears to be relegated to deleting a specific gene within a hybrid mouse strain. The lead author of the first report, cited nearly 1,000 times by Google Scholar's count, stands by the strength of his method.

Before the original study, published in 2013 by geneticist Rudolf Jaenisch at the Whitehead Institute of Biomedical Research and colleagues, embryonic
stem cells were used to prepare conditional knockout mice—animals with a gene engineered to be turned off on command that are missing a gene—a process that could take years and had only a 1 percent efficacy rate. The CRISPR technique was presented as one-stop-shop to obtaining conditional
knockout mice with a 16 percent success rate. By injecting zygotes with the CRISPR machinery, Jaenisch's team successfully sandwiched the to-be-deleted
gene between two LoxP sites (a step called floxing) that allow the gene to be conditionally regulated.

"The original Jaenisch paper was a landmark," says geneticist John Schimenti, director of Cornell University's Stem Cell and Transgenic Core Facility, who was not involved in either study. "It certainly demonstrated that you can get a high efficiency and high efficiency mutagenesis at specific loci."

Conditional knockout mice are extremely important in biomedical research as
they let scientists delete essential genes in specific tissues in the organism and at particular times during development. While the Jaenisch method was promising, research groups that have tried to generate mice using
the technique have not been as successful.

"Everybody who's tried to make floxed alleles by the method they originally proposed is generally met with failure," says Schimenti, who has observed the "same exact issues" in Cornell's transgenic facility as those noted in the preprint.

The Jaenisch method often results in off-target mutations, deletions, or a failure to insert both LoxP sites in the correct orientation, notes Schimenti. "This is generally recognized in the community, it's been very

difficult to recapitulate anything close to the numbers that Jaenisch's group reported," he says.

Talks between a close-knit research community at conferences and elsewhere
about the challenges other labs were having with the technique led Gaetan Burgio, who runs the transgenesis facility at the Australian National University, and his colleagues to try and determine what was going wrong.

To begin with, three groups replicated the original experiment targeting the same gene in a different strain of mice and had zero success. Next, 17 labs
, including the original three, independently repeated the experiment on a total of 56 genes and two intergenic regions in the mouse genome across five
different strains of mice. The combined dataset from all the labs included 17,887 microinjected or electroporated mouse zygotes and a resultant 1,718
live mice, of which only 15 possessed both of the inserted LoxP sites needed
for conditional control. Across all the mice that were tested, off-target deletions or mutations were observed in lieu of the correct insertion of the LoxP sites.

Compared to the original study's 16 percent efficiency rate of obtaining conditional knockout alleles in mice, Burgio and others had a success rate of merely 0.87 percent. "The success rate of the method . . . is equivalent to the classical methods with embryonic stem cells," says Burgio.

The replication team aimed to figure out the possible factors responsible for successful conditional knockout mice and found that the simultaneous insertion of two LoxP sites was critical for the success of the technique.

Jaenisch considers the difference between the mouse strains used in the two
studies to be a sticking point and an underlying reason for the high variation between the two studies. "I have to discount these data as being serious," says Jaenisch, who questions the quality of the recent study.

Schimenti agrees that the genetic background should have been taken into
consideration when replicating the original study. "I think it's kind of a flaw in the bioRxiv study—if they were testing the Jaenisch results, they should have used the exact same types of animals." However, both Burgio and
Schimenti raise the point that the strain of mice used in the Jaenisch paper is uncommon compared to the mice used in the new study.

Schimenti also suggests the possibility that the original 16 percent success rate may have been representative of the single locus in the specific strain of mice used in that study. "I think it's clear that this is a very problematic technique," says Schimenti. "There needs to be a workaround. "

3. There were some additional accusation of his Graudate work on stem cell cloning, which I have no insights

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Hui Yang
Principal Investigator
Laboratory of Disease Models in Non-Human Primates
Institute of Neuroscience,
Shanghai Chinese Academy of Sciences
Room A0517, The New Life Science Building,

320 Yueyang Road, Shanghai, P.R.China, 200031

<Response to Gurumurthy et al-0501.docx>

Dear Leaders of CAS, MOST, and CNSF,

I choose to write this open letter to bring your attention to an investigator Yang Hui at the Institute of Neuroscience (ION) with serious concern on his scientific integrity and potential misconduct. The intension of this letter is to use this specific case to raise a general concern on the issue of scientific ethics.

The facts:

We have been systematically pursuing a potential master regulator (PTB, an RNA binding protein) in neurogenesis. After we published our initial work on the PTB-regulated loop as the basis for its depletion-induced neuronal reprogramming in 2013, we moved on to explore this strategy to convert non-neuronal cells (astrocytes) to functional neurons directly in the brain as a strategy to generate new neurons in a disease setting. This represents an emerging approach to treating neurodegenerative diseases by replenishing lost neurons.

After intensive work for 6 years (plus 3 years in review), we have made an astonishing discovery that a single injection of anti-PTB agent is sufficient to reconstitute the lost nigrostriatal pathway in a Parkinson's disease model, thereby completely eradicating the disease phenotype. I was invited to give a seminar on this topic by Dr. Mu-Ming Poo, director of ION, in June 14, 2017. During my seminar, I also mentioned our collaborative efforts and success in the retina system. After my talk, Yang Hui immediately jumped in to launch similar studies, and in about 6 months, they sent their paper for publication, eventually appeared in Cell (April 18 online, April 30 in print), and once the paper was published, ION held a news conference to claim their original discovery.

I immediately wrote to Dr. Poo to indicate that the Cell paper basically stole our experimental approach, ideas, and positive results (admitted that they implemented our strategy in slightly different biological contexts). Dr. Poo replied to indicate that if my accusation were true, it would suggest a form of scientific misconduct that would trigger a serious investigation, but he believed that the problem belonged to what he called "gray zone", as Yang Hui initiated the work based on our 2013 publication. I thus requested the evidence for this. A few days later, Dr. Poo forwarded the response from Yang Hui to me, showing that they initiated most of the work in May 17 and 18, 2017 (thus before my seminar). I knew this was a lie, as I have evidence to demonstrate that he did not know PTB before my seminar and even not remember the name of the gene in July 8, 2017. I requested Mu-Ming to certify Yang Hui's evidence, but never obtain any response ever since.

The scientific issues:

After publication of the Cell paper, many experts in the field questioned the data quality, as there is no evidence for induced cell migration, gradual changes in morphology and gene expression, and progressive acquisition of electrophysiological properties of newly converted cells. My own exanimation of their data led to the suspension that most of

immunological evidence presented might result from leaked GFAF-Cre expression, which is well known in the field.

The question then is how they obtained the correct behavioral benefits. All experts in the field know that the induced disease phenotype in their models can be quite variable. In our own hands, we had to monitor the establishment of stable phenotype before reprogramming, follow behavioral changes in an elaborated time course experiment with one set of mice for up to 2 years, and document both positive and negative outcomes from all mice analyzed. In comparison, it appears that they did not have time to repeat their animal experiments even once, as I know that they sent their paper to Nature about 6 months after hearing my talk at ION. It was rejected for lack of evidence to support their conclusions. The fact that the work passed review at Cell does not necessarily mean that they have corrected the deficiencies in the paper.

This then raised a more serious concern on how they were able to obtain their data they wanted. To me, a plausible explanation would be cherry picking of their data based on the conclusion they wish to reach, and in this case, on our positive outcomes. This needs to be investigated by an independent committee to examine original data in their notebooks. Apparently, this appears to be a reoccurring pattern for Yang Hui, as the scientific community has extensively questioned his postdoctoral work on a highly efficient insertion mutagenesis method. This problem of data manipulation is clearly beyond the gray zone as called by Dr. Poo and it is more difficult to catch than the common data duplication problem in various published papers.

The general implications:

What is norm for original research and scientific exchange? Scientists are supposed to conceive original ideas in their areas of interest. Scientific meetings are meant to promote exchange of ideas and sharing insights and data, starting with published findings as the basis. Scientists often have related ideas and competition is thus unavoidable, but in most cases, scientists choose to coordinate or collaborate during the publication process. Obviously, such ideal situation is not always the case, and there are a lot of examples for "bad" behaviors in the scientific community, which is not unique in China. However, scientific research has become a "job" in the modern time, which is often tied to material and spiritual gain. While not unique in China, the problem has become extreme where people tend not to share unpublished results in meetings and seminars. Consequently, scientists do not exchange ideas even within the same universities or institutions or departments. Then, what is the purpose for meetings and seminars to serve?

One problem for the current culture is that scientists do not feel anything improper or wrong by grabbing other's ideas or results and trying to repeat them quickly to claim their own discoveries. Thus, many "discoveries" are resource-driven, not years of hard work in pursuing scientific excellence. As Dr. Poo put it, there is a large gray zone in this regard, but when it goes to an extreme, what it does is to convey a general strategy to quickly become successful, thus contributing to a bad culture in the scientific community. This is apparently what is going on in China, more frequently than the rest of the world.

Is this something that needs the attention of leading scientists and funding agencies? In my opinion, this is an important problem to address if Chinese scientists are to be fully integrated into the internationally community and gain respect from their peers by making original discoveries. There are numerous bright spots in science and scientists in China, especially in the more recent era of China emerging as a global scientific and economic power. However, such success does not justify the tolerance of the converse. When it comes to intellectual properties, this issue becomes even more urgent when China is to become a leader in the world.

Cultural change towards the right direction is a long match. In this process, senior leaders have obligatory roles to play and role models have immense influence on the young generation of scientists. In the current case, Yang Hui has been awarded for a lot of prestigious prices and awards. Given his reputation and track record, one would wonder he would serve as a role model for his peers. Dr. Poo has been going around to give lectures on scientific integrity. I in fact have tremendous regard of him for his contribution to science in China and to neuroscience in general, but given the current situation, I become less clear about whether he applies the same standard to the investigators under his direct supervision at ION. Based on my personal interactions with Dr. Poo, he clearly knows what is going in this particular case, as I shared our unpublished results during my seminar and I informed him where we were in the review process when I visited him in the summer of 2018. At this precise time point, he has been working behind the theme to help Yang Hui resubmit their paper to Cell. He clearly had the opportunity to direct this potential conflict of interest issue to the right track, but unfortunately, he chose to remain completely silent. After the publication of the Cell paper, Dr. Poo engineered a press release, claiming another major milestone from ION under his leadership, as it will tie to resources and power late. I could not imagine well how Dr. Poo felt when putting this into the general prospective of the scientific ethics problem he has been serving as a spokesman for.

In conclusion, I choose to communicate my thoughts in an open letter format to induce discussion on the scientific ethics issue. It is thus my hope that this letter will have some positive influence on establishing a better culture in the Chinese scientific community.

From:	Xiao-Fan Wang, Ph D. <xiao.fan.wang@duke.edu>
Sent time:	05/09/2020 07:13:02 PM
To:	Fu, Xiang-Dong
Subject:	Re: Yigong
Attachments:	Dear Leaders of CAS.docx

I have made some minor edits and you can ask MJ to translate it into Chinese before sending to more people (better by individual emails, at most two people, so to avoid leaking out as Yi Rao's letter). XF

> On May 9, 2020, at 3:47 PM, Fu, Xiang-Dong <xdfu@health.ucsd.edu> wrote:
>
> <Dear Leaders of CAS.docx>

Dear Leaders of CAS, MOST, and CNSF,

I choose to write this formal letter to bring your attention to a critical issue related to problems associated with scientific ethics among some scientists in China. This action was triggered by the conduct of a Principal Investigator Dr. Yang Hui at the Institute of Neuroscience (ION) of CAS with a serious concern on his scientific integrity and potential misconduct. The intension of this letter is to use this specific case to raise a general concern on the issue of scientific ethics.

The facts:

In the past nine years, we have been systematically pursuing the functional characterization of a potential master regulator (PTB, an RNA binding protein) in neurogenesis. After we published our initial work on the PTB-regulated signaling loop as the basis for its depletion-induced neuronal reprogramming in 2013, we moved on to explore the application of this discovery to convert non-neuronal cells (astrocytes) to functional neurons directly in the brain as a strategy to generate new neurons in a disease setting. This represents an emerging approach to treating neurodegenerative diseases by replenishing lost neurons.

After intensive work for 6 years (plus additional 3 years in the review process of a major manuscript describing the findings), we have made an astonishing discovery that a single injection of anti-PTB agent is sufficient to reconstitute the lost nigrostriatal pathway in a Parkinson's Disease (PD) model, thereby completely eradicating the disease phenotype. I was invited to give a seminar on this topic by Dr. Mu-Ming Poo, Director of ION, on June 14, 2017. During my seminar, I also mentioned our collaborative efforts with another group and success of our strategy in the retina system. Based on several pieces of evidence that I now possess, Dr. Yang immediately jumped in after hearing my talk to launch similar studies, and in about 6 months, they sent their paper for publication, eventually appeared last month in Cell (April 18 online, April 30 in print). Once the paper was published, ION held a news conference to claim their original discovery.

After the publication of Yang's paper, I immediately wrote to Dr. Poo to indicate that the Cell paper basically stole our ideas, experimental approach, and positive results (admitted that they implemented our strategy in slightly different biological contexts). Dr. Poo replied to indicate that if my accusation were true, it would suggest a form of scientific misconduct that would trigger a serious investigation, but he believed that the problem belonged to what he called "gray zone", as Dr. Yang initiated the work based on our 2013 publication. I thus requested the evidence for this claim in my reply to Dr. Poo. A few days later, Dr. Poo forwarded the response from Dr. Yang to me, claiming that they initiated most of the work around May 17 and 18, 2017 (thus just before my seminar on June 14). I knew this to be a lie, as I have hard evidence to demonstrate that he did not even know what the gene PTB was before my seminar and then could not remember the name of the gene on July 8, 2017 when he asked a small group of scientists to provide an explanation. Because I had the hard evidence, I requested Dr. Poo to certify if Dr. Yang could provide hard evidence on when exactly he initiated the experiments, such as

ordering the DNA primers to make the constructs for the experiment, but I never obtained any response from either Dr. Yang or Dr. Poo after my request.

The scientific issues:

After publication of the Cell paper, many experts in the neurobiology field questioned the quality and reliability of the data, since there was no solid evidence for induced cell migration, gradual changes in cell morphology and gene expression, and progressive acquisition of electrophysiological properties of newly converted neuronal cells. My own examination of their data led to the suspension that most of immunological evidence presented in the paper might have resulted from leaked GFAF-Cre expression, which is a well known phenomenon in the field.

The question then is how they obtained the correct behavioral benefits presented in the paper. All experts in the field know that the induced disease phenotype in their models can be quite variable. In our own hands, we had to monitor the establishment of stable phenotype before reprogramming for cell conversion, follow behavioral changes of the animals in an elaborated time course experiment with one set of mice for up to 2 years, and documented both positive and negative outcomes from all mice analyzed. In comparison, it appears that Dr. Yang's group did not have the time to repeat their animal experiments even once, as I know now that they sent their paper to Nature about 6 months after hearing my talk at ION. The paper was rejected by Nature for lack of solid experimental evidence to support their conclusions. The fact that the work eventually passed review at Cell did not necessarily mean that they have corrected the deficiencies of their data presented in the paper.

These facts then raised a more serious concern on how they were able to obtain their data that they desired based on the knowledge of positive results from my laboratory. To me, a plausible explanation would be cherry picking of their data based on the conclusion they wished to reach, and in this case, on our positive outcomes. This issue needs to be investigated by an independent committee, ideally formed by scientists outside of ION, to examine original data in their notebooks. Apparently, this appears to be a reoccurring pattern for Dr. Yang, as the scientific community has extensively questioned his postdoctoral work on a highly efficient insertion mutagenesis method. This problem of potential data manipulation is clearly beyond the "gray zone" as called by Dr. Poo but it is more difficult to catch than the common problem of data duplication or manipulation in various published papers.

The general implications:

From these experiences, I want to raise this question: What is the norm for original research and scientific exchange? Scientists are supposed to conceive original ideas in their areas of interest. Scientific meetings are meant to promote exchange of ideas and sharing insights and data, starting with published findings as the basis. Scientists often have related ideas and competition is thus unavoidable, but in most cases, scientists choose to coordinate or collaborate during the publication process. Obviously, such ideal

situation is not always the case, and there are a lot of examples for "bad" behaviors in the scientific community, which is not unique for China. However, scientific research has become a "job" in the modern time, which is often tied to material and spiritual gains. While not unique in China, the problem has become extreme recently where people tend not to share unpublished results in meetings and seminars. Consequently, scientists do not exchange ideas even within the same universities or institutions or departments. Then, what is the purpose for scientific meetings and seminars to serve?

One problem for the current culture is that scientists do not feel anything improper or wrong by grabbing other's ideas or results and trying to repeat them quickly to claim as their own discoveries. Thus, many "discoveries" are resource-driven, not years of hard work in pursuing scientific excellence. As Dr. Poo puts it, there is a large "gray zone" in this regard, but when the behavior goes to an extreme, what it does is to convey a general strategy to quickly become successful, thus contributing to a bad culture in the scientific community. This is apparently what is going on in China, more frequently than the rest of the world. Is this something that needs the attention of leading scientists and funding agencies? In my opinion, this is an important problem to address if Chinese scientists are to be fully integrated into the internationally community and gain respect from their peers by making original discoveries. I truly believe that there are numerous bright spots in science and scientists in China, especially in the more recent era of China emerging as a global scientific and economic power. However, such success does not justify the misbehavior and tolerance of the converse. When it comes to intellectual properties, this issue becomes even more urgent when China is to become a leader in science and technology development in the world.

Cultural change towards the right direction is a long match. In this process, I believe that senior leaders have obligatory roles to play and role models have immense influence on the young generation of scientists. In the current case, Dr. Yang has been awarded for a number of prestigious prizes and awards. Given his reputation and track record, one would wonder if he would serve as a role model for his peers. Dr. Poo has been going around to give lectures on scientific integrity. I in fact have had tremendous regard of him for his contribution to science in China and to neuroscience in general, but given the current situation, I have become less convinced whether he applies the same standard to the investigators under his direct supervision at ION. Based on my personal interactions with Dr. Poo, he clearly knows what was going in this particular case, as I shared our unpublished results during my seminar and informed him where we were in the review process of our manuscript when I visited him again in the summer of 2018. At this precise time point, he was working behind the theme to help Dr. Yang to resubmit their paper to Cell. He clearly had the opportunity to correct the mistake and direct this potential conflict of interest issue to the right track, but unfortunately, he chose to remain completely silent. After publication of the Cell paper, Dr. Poo engineered a press release, claiming another major milestone from ION under his leadership, as the achievement would tie to future allocation of resources. I could not imagine how Dr. Poo would fell it we putting this specific case into the general prospective of the scientific ethics problem that he has been serving as a spokesman for better conduct in the scientific community.

In conclusion, I choose to communicate my thoughts in this formal letter format to induce discussion on the scientific ethics issue. It is thus my hope that this letter will have some positive influence on establishing a better culture in the Chinese scientific community.

From: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Sent time: 05/24/2020 06:21:42 PM
To: Fu, Xiang-Dong
Subject: Re: Help to proofread the letter in Chinese

I have made some minor modifications and it is ready to go.

Best regards, XF

> On May 24, 2020, at 7:41 PM, Fu, Xiang-Dong <xdfu@health.ucsd.edu> wrote:
>
> Hi Xiaofan,
>
> Multiple people have helped me to translate our letter in English into Chinese. Can you help take a final proofread? Thanks.
>
> Fu
>
> Xiang-Dong Fu,
> Distinguished Professor
> Dept. of Cellular and Molecular Medicine
> University of California, San Diego
> George Palade Laboratories
> 9500 Gilman Drive, Room 217
> La Jolla, CA 92093-0651
>
> Phone: 858-534-4937
> Email: xdfu@health.ucsd.edu
>
> <公开信-4(1).docx>

From: Xiao-Fan Wang, Ph D. <xiao.fan.wang@duke.edu>
Sent time: 05/24/2020 06:22:07 PM
To: Fu, Xiang-Dong
Subject: Re: Help to proofread the letter in Chinese
Attachments: 公开信-4(1).docx

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forgot to attach it. XF

> On May 24, 2020, at 7:41 PM, Fu, Xiang-Dong <xdfu@health.ucsd.edu> wrote:
>
> Hi Xiaofan,
>
> Multiple people have helped me to translate our letter in English into Chinese. Can you help take a final proofread? Thanks.
>
> Fu
>
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> <公开信-4(1).docx>

尊敬的中科院、科技部、基金委领导：

我是付向东，目前就职于加州大学圣地亚哥分校、担任细胞和分子医学系教授。在此写信实名举报中科院神经所研究员杨辉剽窃和涉嫌造假等学术道德不端行为，也希望借这一事件恳请国家科技管理高层关注和重视当前国内学术界日益凸显和严重的科学诚信和学术道德问题，以维护中国科学界的声誉。

事件原委：

在过去十多年间，我们团队致力于阐析细胞命运决定关键因子 PTBP1 在神经发生和神经元发育中的功能与作用机制，并于 2013 年首次报道了 PTBP1 介导的基因调控网络可高效转分化非神经元细胞为神经元（详见 Cell 152：82-86， 2013）；同时，我们还着手探索了 PTBP1 调控的转分化神经元在神经退行性疾病治疗中的应用。经过 9 年多的不懈努力（包括 6 年的实验工作及近 3 年审稿过程中的补充实验工作），我们在帕金森综合征疾病小鼠模型中，成功地实现了一次性注射抗 PTBP1 因子就可重建帕金森综合症黑质纹状体回路，并完全消除了模型动物的帕金森综合征症状。

2018 年 6 月 14 号，受蒲慕明所长特邀学术报告，我在中科院神经所报告了我们这项未发表，治疗帕金森综合征的研究成果，详细介绍了此项研究工作的科学思路、全部实验设计和研究结果；同时，我还分享了将抗 PTBP1 因子成功应用到视网膜疾病治疗的一项合作研究工作。杨辉和神经所百余名科研人员参加了我的学术报告，报告之后，杨辉和几位研究员与我共进晚餐，杨辉在晚餐时向我咨询了许多实验细节问题。

让我始料未及的是，杨辉在全面了解了我们的研究思路和成功的实验结果后，立即着手换一种实验方式敲降 PTBP1，重复我们的研究工作，得到了相似的实验结果，并在短短 6 个月后便将他们的论文投稿，最终今年在《细胞》杂志发表（4 月 8 号上线，4 月 30 号出版）。更让人不可置信的是，在杨辉论文发表后，蒲慕明所长领导的神经所还召开了新闻发布会，宣称此项工作是他们研究所的“原始发现”和“重大突破”，不知那天参加过我学术报告会的各位神经所的研究员和研究生对此该作何感想？而杨辉本人则在微信朋友圈恬不知耻地宣称，这是他迄今最满意最有成就感的一项工作！剽窃来的工作竟然也有如此的成就感？实在是令人不齿又匪夷所思！

得知杨辉的《细胞》论文即将在线发表后，我立即联系了蒲慕明所长，指出这篇论文是剽窃了我在神经所报告的，尚未发表的工作，虽然选了略有不同的脑区进行敲降 PTBP1，但剽窃事实一目了然。蒲慕明所长答复，如果情况属实，杨辉的行为属于学术不端（scientific misconduct），应该认真调查和严肃处理；但他同时声称杨辉的工作有可能是基于我们实验室 2013 年发表的论文，属于所谓“灰色地带”。杨辉也随即声明他们的研究工作始于 2018 年 5 月 17－18 号，“正巧”在我去神经所做报告之前（2018 年 6 月 14 号）。但事实上，在我去神经所学术报告之前，杨辉居然连 PTBP1 为何物都不知道，2018 年 7 月 8 号他还在一个同行微信群里询问 PTBP1 基因的具体名称，这充分说明“研究工作始于 2018 年 5 月 17－18 号”是彻

头彻尾的谎言。之后，我请蒲慕明所长让杨辉提供订购 PTBP1 相关 DNA 引物的时间及证据，这应该是开始实验的最先步骤。然而，我至今没收到他们的任何回复。

论文的科学数据问题：

杨辉的这篇《细胞》论文在 4 月份在线发表后，许多神经生物学领域的专家随即对其数据的质量和可靠性提出了一系列质疑，指出论文并没有确凿的证据证明诱导新产生的神经元细胞所必经的细胞迁移、渐近的细胞形态和基因表达转变以及新获得的神经电生理特性等等。通俗地说，由于没有细胞转分化过程的系列实验数据的支持，很难说他们的结论真实可靠，不能排除他们看到的阳性结果是出于实验室常见的实验假象。我在阅读他们的论文之后认为，支持他们结论的大多数所谓证据，很有可能是由于 GFAF-Cre 在内源神经元中的泄漏表达所致，这种泄漏表达是领域中众所周知的现象。

神经生物学专家都知道，诱导型疾病动物模型的表型存在非常大的差异和不稳定性。以我们的研究为例，在进行细胞重新编程之前，首先需要建立稳定的疾病表型动物模型，然后再诱导细胞转分化，同时进行严密观察和实时跟踪，并留下一组动物进行长达 2 年观察，分析所有阳性和阴性结果，以便得到真实可靠的结论。因为这个原因，我们花了整整 9 年，进行多次重复并用多种方法反复验证后才完成这项研究工作。与之相反，杨辉小组在短短六个月内就完成了从课题启动到论文撰写，据悉他们在 2019 年初就将研究论文提交给《自然》，但因缺乏充分实验证据支持论文结论而被拒稿，虽然这项工作最终在《细胞》杂志发表，但并不代表他们数据真实可靠。他们是如何能够在如此短时间内获得动物实验数据？从时间上推论，他们都没有足够时间重复动物实验，极有可能是有目的地挑选了对其有利的实验数据，甚至还不能排除伪造实验数据的可能性。这让我联想到杨辉在博士后阶段仅经过数月就发表了的“高效插入基因突变方法”研究论文（详见 Cell 154：1370-1379，2013），已被领域内科学家广泛质疑，有 20 多个独立实验室联合报道不能重复他的实验结果（详见 Genome Biology 20:171, 2019）。这里我们不禁要问，杨辉究竟是自古英雄出少年, 还是从来就惯于剽窃，甚至有造假嫌疑的作弊高手？

就本次 PTBP1 相关的《细胞》论文工作，究竟他们的研究是何时开始？数据是如何收集的？等等一系列疑问，我认为应该成立一个由神经所以外的科学家组成的独立调查委员会，进行严肃认真地调查，因为这次事件已超过了蒲慕明所长所指的科学研究中“灰色地带”问题。

对科学道德问题的思考：

我希望通过这次事件引起国内学术界认真思考：我们应该如何保护原创性研究、惩处剽窃行为和维护健康的科研环境？学术交流和研讨，旨在促进科学思想交流，分享最新见解和研究成果（包括未发表数据），以促进科学研究。然而，现实中总有一些急功近利者，他们摒弃原始创造的科学理念，走捷径、抄近路，剽窃他人学术成果，完全没有道德底线。虽然这并不是中国特有现象，但这个问题在当下国内学术界正变得越来越严重。由于剽窃事件频发，很多科学家在学术会议和同行交流

中都只报告已发表或被杂志接受工作，不再愿意分享最新科学思想和未发表数据。甚至，不少同一研究机构的科学家之间都不相互交流和分享未发表的研究成果，以免自己耕耘多年的学术成果被同事剽窃。我们不禁要问，这样的科学氛围健康吗？科学会议和学术交流的目的何在？

更为严重的是，当今科学界充斥着 “成者为王、败者为寇”的怪现象。有不少人将科学研究变成了谋取功名的工具，他们并不注重原创性科学发现，而是通过走捷径、快速获取科研成果，赚得名利双收。这些人并不认为剽窃他人科学思想有何不妥或不道德，他们经常从学术会议或交流研讨中得到他人有价值的研究思路和策略，立即动用自己的人力和物力资源，快速重复他人研究工作并抢先发表，并宣称是自己的原始发现。这些“发现”往往是资源和利益驱动的，并非为追求科学卓越而付诸努力的结果。这些人甚至理直气壮地宣称自己的行为只不过是处于 “灰色地带”。当下的确有一些人对于此道得心应手，剽窃他人学术思想和未发表成果，高效产出 “原始发现”，并因此成为“明星”科学家，获得更多资源。然而，科学是没有捷径可走的，原创学术研究需要长时间的耕耘和付出。而简单重复已知的结果，快速发表论文，这还算科学研究吗？长此以往，中国的科学研究将何去何从？

资深科学家和明星科学家对学术界及年轻科学家具有巨大的影响和榜样作用。以此次事件为例，作为一个“80”后明星科学家，杨辉已诸多荣誉载身，获得过许多重要奖项。然而，鉴于他的不少学术“成就”都基于“灰色地带”，他将给年轻科学家及学生树立一个什么样的榜样？同样，资深科学家蒲慕明所长在这次事件中又扮演什么样的角色？我一直非赏钦佩蒲慕明所长对中国科学特别是神经学科学的贡献，尤其是他最近关于《科学诚信和创新性》的 3 小时讲座，讲得特别详细和到位。然而，遭遇这次事件后，我不禁要问，蒲慕明所长对他领导的神经所是否采用了同样的学术道德标准？蒲慕明所长十分清楚我们这个研究工作及进展，但同时又在背后纵容杨辉剽窃并代他撰写论文，说明他的“科学诚信”是双重标准！2019 年暑期，我曾再次访问蒲慕明所长，并跟他交流了我们工作的最新进展。作为正常的学术交流，他应该告知我，杨辉正在进行与我们工作相关的实验，他却只字未提。如果杨辉的实验并非剽窃，他又有什么理由替其隐瞒呢？他可以佯装并不知道杨辉的工作，但我在事后得知，当时他正在帮助杨辉修改论文，改投到《细胞》。他完全有机会纠正杨辉的错误、避免这个冲突发生，但他选择了隐瞒和沉默。作为中国科学伦理代言人，蒲慕明所长的所作所为是否符合科学诚信和学术道德规范？我感到当利益与他或者他所领导的研究所发生冲突时，他所代言的科学诚信和创新似乎都不复存在，所有不端行为都可归类于“灰色地带”。试问，杨辉这种肆意剽窃他人成果还有什么科学诚信可言？这种在预知实验结果条件下拼凑数据甚至伪造数据还有什么创新可言？

中国国内层出不穷的学术不端事件应引起学术界高层领导、领军科学家及研究经费资助机构的关注和深思。如果不及时遏制和惩戒这些学术不端行为，将助长不良科研文化孳生、误导青年学生以此为成功阶梯，最终将破坏学术文化并阻碍原创科学研究的发展。毋需置疑，随着中国崛起为全球科学和经济强国，中国科学和科学家已带给国际学术界越来越多的亮点，但是这些亮点并不能抵消或掩盖学术不端

行为造成的污点。当今中国科学正向世界科学技术发展领导者迈进，尊重知识产权将尤为重要和紧迫。

综上所述，我以实名举报的方式，一、请求成立一个由神经所以外的科学家组成的独立调查委员会， 严肃认真地调查杨辉的学术不端及数据的真实性；二、表达我的一些感受,抛砖引玉，希望能够引发国内学术界对科学道德、科学诚信的讨论。希望大家能用反思、纠错、引导的力量，在中国建立一个更健全、完善、诚信的科研环境。

From: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Sent time: 05/25/2020 11:20:24 AM
To: Fu, Xiang-Dong
Subject: info

I looked at the websites for the three places where you may want to submit your letter if going through the normal process. It appears that any letter will be first screened by relevant offices within CAS, MOST or CNSF, and I do not know if your letter would reach the relevant people, since such matters will be handled through layers of bureaucracy. On the other hand, you can send it to their personal boxes, and in some cases, their secretary will handle it and inform them right away. For MOST, the VM who handles this type of matters is **李萌**, but I do not have his email only phone number, so you may want to ask XianEn for Li's email. If you think that this is the way to go, I can give you the rest emails (CAS should have Bai and Jianguo Hou since he handles this type of matters; Jinghai Li and Yiyu Chen from CNSF). XF

From:	Fu, Xiang-Dong
Sent time:	06/14/2020 04:34:51 PM
To:	赵为 <zhaow@most.cn>
Cc:	Xiao-Fan Wang, Ph D. <xiao.fan.wang@duke.edu>
Subject:	Re: introduction
Attachments:	举报信.pdf

Dear Wei,

Our mutual friend Dr. Xiaofan Wang suggests me to send you the attached letter to charge serious scientific misconduct committed by Yang Hui from the Shanghai Institute of Neuroscience. I would be greatly appreciated if you could also forward the letter to VM Meng Li. I write this letter with the intension to induce discussion on the scientific ethics issue in order to establish a better culture for promoting scientific exchange and original innovative research.

Thanks for your attention to this letter.

Best regards,
Fu

Xiang-Dong Fu,
Distinguished Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
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Phone: 858-534-4937
Email: xdfu@ucsd.edu

> On Jun 7, 2020, at 5:27 PM, Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu> wrote:
>
> Hi Wei:
>
> As I mentioned to you last time during our conversation, Dr. Xiangdong Fu from UC San Diego would like to submit a formal letter to VM Meng Li. I hope you can receive it from Dr. Fu and send to VM Li as I only have his cell phone number but not email address. I have copied Dr. Fu for this message, so he can communicate with you directly.
>
> Best regards, XF

尊敬的中科院、科技部、基金委领导：

我是付向东，目前就职于加州大学圣地亚哥分校、担任细胞和分子医学系教授。在此写信实名举报中科院神经所研究员杨辉剽窃和涉嫌造假等学术道德不端行为，同时希望借这一事件恳请国家科技管理高层关注和重视当前国内学术界日益凸显和严重的科学诚信和学术道德问题，以维护中国科学界的声誉。

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2018 年 6 月 14 号，受蒲慕明所长特邀学术报告，我在中科院神经所报告了我们这项未发表的、治疗帕金森综合征的研究成果，详细介绍了此项研究工作的科学思路、全部实验设计和研究结果；同时，我还分享了将抗 PTBP1 因子成功应用到视网膜疾病治疗的一项合作研究工作。杨辉和神经所百余名科研人员参加了我的学术报告。报告之后，杨辉和几位研究员与我共进晚餐，在晚餐期间杨辉向我咨询了许多关于实验细节问题。

让我始料未及的是，杨辉在全面了解了我们的研究思路和成功的实验结果后，立即着手换一种实验技术敲降 PTBP1，重复我们的研究工作，得到了相似的实验结果，并在短短 6 个月后便将他们的论文投稿，最终在今年的《细胞》杂志发表（4 月 8 号上线，4 月 30 号出版）。更让人难以置信的是，在杨辉论文发表后，蒲慕明所长领导的神经所还召开了新闻发布会，宣称此项工作是他们研究所的“原始发现”和“重大突破”，不知那天参加过我学术报告会的各位神经所研究员和研究生对此该作何感想？而杨辉本人则在微信朋友圈恬不知耻地宣称，这是他迄今最满意、最有成就感的一项工作!剽窃来的工作竟然也有成就感？实在是令人不齿又匪夷所思！

得知杨辉的《细胞》论文即将在线发表后，我立即联系了蒲慕明所长，指出这篇论文剽窃了我在神经所报告的、尚未发表的工作，虽然选择略有不同的脑区进行敲降 PTBP1，但剽窃事实一目了然。蒲慕明所长答复，如果情况属实，杨辉的行为属于学术不端（scientific misconduct），应该认真调查和严肃处理；但他同时声称杨辉的工作有可能是基于我们实验室 2013 年发表的论文，属于所谓“灰色地带”。杨辉也随即声明他们的研究工作始于 2018 年 5 月 17－18 号，“正巧”在我去神经所做报告之前（2018 年 6 月 14 号）。但事实上，我有证据在我去神经所学术报告之前，杨辉居然连 PTBP1 为何物都不知道，这充分说明“研究工作始于 2018 年 5 月 17－18 号”是彻头彻尾的谎言。随即，我请蒲慕明所长让杨辉提供订购 PTBP1 相关

DNA 引物的时间及证据，这应该是开始实验的最先步骤。然而，至今没收到他们的任何回复。如此简单的证据为何拿不出来，这不做实他的谎言和剽窃行为吗？如果他继续捏造假证据，事件的性质就从剽窃进一步恶化成为欺诈行为。

论文的科学数据问题：

杨辉的这篇《细胞》论文在 4 月份在线发表后，许多神经生物学领域的专家随即对其数据的质量和可靠性提出了一系列质疑，指出论文并没有确凿的证据证明诱导新产生的神经元细胞所必经的细胞迁移、渐近的细胞形态和基因表达转变以及新获得的神经电生理特性等等。通俗地说，由于没有细胞转分化过程的系列实验数据的支持，很难说他们的结论真实可靠，不能排除他们看到的阳性结果是出于实验室常见的实验假象。我在阅读他们的论文之后认为，支持他们结论的大多数所谓证据，很有可能是由于 GFAF-Cre 在内源神经元中的泄漏表达所致，这种泄漏表达是领域中众所周知的现象。

神经生物学专家都知道，诱导型疾病动物模型的表型通常存在较大的差异和不稳定性。以我们的研究为例，在进行细胞重新编程之前，首先需要建立稳定的疾病表型动物模型，然后再诱导细胞转分化，同时进行严密观察和实时跟踪，并留下一组动物进行长达 2 年观察，分析所有阳性和阴性结果，以便得到真实可靠的结论。因为这个原因，我们花了整整 9 年时间，进行了多次重复并采用多种方法反复验证后才完成这项研究工作。与之相反，杨辉小组在短短六个月内就完成了从课题启动到论文撰写，据悉他们在 2019 年初就将研究论文提交给《自然》，但因缺乏充分实验证据支持论文结论而被拒稿，虽然这项工作最终在《细胞》杂志发表，但并不代表他们数据真实可靠。他们是如何能够在如此短时间内获得动物实验数据？从时间上推论，他们甚至没有足够时间重复动物实验。唯一的解释是他们极有可能是有目的地挑选对其有利的实验数据，甚至还不能排除伪造实验数据的可能性。这让我联想到杨辉在博士后阶段发表的“高效插入基因突变方法”研究论文（详见 Cell 154：1370-1379， 2013），遭到领域内科学家广泛质疑，有 20 多个独立实验室联合报道不能重复他的实验结果（详见 Genome Biology 20:171, 2019）。对于其他科学家的质疑，杨辉除了辩称自己比别人高明，强调实验条件略有不同外，没有任何合理解释，至今我们再也没有看到他重复自己结果的实验证据。这里我们不禁要问，杨辉究竟是自古英雄出少年,还是从来就是惯于剽窃，甚至有造假嫌疑的作弊高手？

就本次 PTBP1 相关的《细胞》论文工作而言，究竟他们的研究是何时开始？数据是如何得到的？等等一系列疑问，我认为应该成立一个由神经所以外的科学家组成的独立调查委员会，进行严肃认真的调查，因为这次事件已超过了蒲慕明所长所指的科学研究中“灰色地带”问题。

对科学道德问题的思考：

我希望通过这次事件引起国内学术界认真思考:我们应该如何保护原创性研究、惩处剽窃行为和维护健康的科研环境？学术交流和研讨，旨在促进科学思想交流、分享最新见解和研究成果（包括未发表数据），以促进科学研究进步。然而，现实

中总有一些急功近利者，他们摒弃原始创造的科学理念，走捷径、抄近路，剽窃他人学术成果，完全没有道德底线。虽然这并不是中国特有现象，但这个问题在当下国内学术界正变得越来越严重。由于剽窃事件频发，很多科学家在学术会议和同行交流中都只报告已发表或被杂志接受工作，不再愿意分享最新科学思想和未发表数据。甚至不少同一研究机构的科学家之间，都不愿相互交流和分享未发表的研究成果，以免自己耕耘多年的学术成果被人剽窃。我们不禁要问，这样的科学氛围健康吗？科学会议和学术交流的目的何在？

更为严重的是，当今学术界充斥着 “成者为王、败者为寇”的怪现象。有不少人将科学研究变成了谋取功名的工具，他们并不注重原创性科学发现，而是通过走捷径、快速获取科研成果，赚得名利双收。这些人并不认为剽窃他人科学思想有何不妥或不道德，他们经常从学术会议或交流研讨中，得到他人有价值的研究思路和策略，立即动用自己的人力和物力资源，快速重复他人研究工作并抢先发表，并宣称是自己的原始发现。这些“发现”往往是资源和利益驱动的，并非为追求科学卓越而付诸努力的结果。这些人甚至理直气壮地宣称，自己的行为只不过是属于“灰色地带”。当下的确有一些人对于此道得心应手，剽窃他人学术思想和未发表成果，高效产出 “原始发现”，并因此成为“明星”科学家，获得了更多资源。然而，科学是没有捷径可走的，原创学术研究需要长时间的耕耘和付出。简单重复已知的结果、快速发表论文，这还算科学研究吗？长此以往，中国的科学研究将何去何从？

资深科学家和明星科学家对学术界及年轻科学家具有巨大的影响和榜样作用。以此次事件为例，作为一个“80”后明星科学家，杨辉已诸多荣誉载身，获得过许多重要科技人才奖项。然而，鉴于他的不少学术“成就”都基于“灰色地带”，他将给年轻科学家及学生树立一个什么样的榜样？同样，资深科学家蒲慕明所长在这次事件中又扮演什么样的角色？我一直非常钦佩蒲慕明所长对中国科学特别是神经学科学的贡献，尤其是他最近关于《科学诚信和创新性》的 3 小时讲座，讲得特别到位。然而，遭遇这次事件后，我不禁要问，蒲慕明所长对他领导的神经所是否采用了同样的学术道德标准？蒲慕明所长十分清楚我们这个研究工作以及进展，但同时又在背后纵容杨辉剽窃并代他撰写论文，他的“科学诚信”难道是双重标准？我曾在 2019 年暑期再次访问蒲慕明所长，并跟他交流了我们 PTBP1 相关工作的最新进展。作为正常的相互学术交流，他应该告知我，杨辉正在进行与我们工作相关的实验，他却只字未提。如果杨辉的研究并非剽窃，他又有什么理由替其隐瞒呢？也许他佯装并不知道杨辉的工作，但我在事后得知，他帮助撰写了杨辉在神经所发表的几乎所有论文。我访问他的那个时间，他正在帮助杨辉修改即将改投到《细胞》的论文。他完全有机会纠正杨辉的错误、避免这个冲突发生，但他选择了隐瞒和沉默。作为中国科学伦理代言人，蒲慕明所长的所作所为是否符合科学诚信和学术道德规范？我感到当利益与他或者他所领导的研究所发生冲突时，他所代言的科学诚信和创新似乎都不复存在，所有不端行为都可归属于“灰色地带”。试问，杨辉这种肆意剽窃他人成果还有什么科学诚信可言？这种在预知实验结果条件下拼凑数据甚至伪造数据还有什么创新可言？

中国国内层出不穷的学术不端事件应引起学术界高层领导、领军科学家及研究经费资助机构的关注和深思。如果不及时遏制和惩戒这些学术不端行为，将助长不良科研文化孳生、误导青年学生以此为成功阶梯，最终将破坏学术文化并阻碍原创科学研究的发展。毋需置疑，随着中国崛起为全球科学和经济强国，中国科学和科学家已带给国际学术界越来越多的亮点，但是这些亮点并不能抵消或掩盖学术不端行为造成的污点。当今中国科学正向世界科学技术发展领导者迈进，尊重知识产权将尤为重要和紧迫。

综上所述，我以实名举报的方式：一、请求成立一个由神经所以外的科学家组成的独立调查委员会， 严肃认真地调查杨辉的学术不端以及数据的真实性；二、表达我的一些感受,抛砖引玉,希望能够引发国内学术界对科学道德、科学诚信的讨论。希望我们能反思、纠错和引导，在中国建立一个更健全、完善、诚信的科研环境。

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Sent time: 07/16/2020 11:16:32 PM

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The manuscript should be revised for many grammatical errors and incorrect/missing information, could you help me at your convenience?

A slightly different brain region was selected to knock down PTBP1, but the plagiarism was obvious.

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Potential conflict of interest: Nothing to report..

Financial Support: This study was supported by grants from the National Undergraduate Training Program for Innovation and Entrepreneurship (201811646025 to YW), the Student Research and Innovation Program of Ningbo University (2017SRIP1918, 2018SRIP2507, and 2019SRIP1902 to YW).

DOI: http://doi.org/10.1016/j.cell.2020.03.024

Keywords: CasRx, Parkinson's disease, PTBP1, Plagiarism.

Abstract

On April 8, 2020 in the journal cell, June 24, 2020, published online in the journal nature: two papers with different methods on low molecular (PTBP1), the same success within the mouse will have function of glial cells into neurons-the "regenerative therapy" is used in the treatment of neurodegenerative diseases, which is an important milestone. On July 2, 2020, Xiang-Dong Fu real-name reported that Yang hui alleged plagiarism his work, and fraud and other academic moral misconduct tip-off is widely spread, which referred to him as the role of technical appraisement PTBP1 invested time and work more than 9 years, including six years of experimental work, and nearly 3 years added experimental work in the process of reviewing.

Parkinson's disease (PD) is the second most neurodegenerative disease that causes harm to the elderly, second only to Alzheimer's disease (AD). Worldwide, PD kills hundreds of thousands of people every year. Although we already know that the direct cause of PD is the degradation of dopaminergic neurons in the substantia nigra, we have not been able to prevent or reverse the nerves of PD patients degraded. On June 24, 2020, Professor Fu led a team to publish a cover article in the current Nature entitled “Reversing a model of Parkinson's disease with in situ converted nigral neurons” [1]. The study reported a new method for transdifferentiating cells into dopaminergic neurons by manipulating the PTB gene, providing a new opportunity to reverse Parkinson's disease.

After confirming that knocking down PTB can achieve the production of dopaminergic neurons in the body, the authors began to explore the therapeutic potential of this method. They established a PD model in mice that knocked down PTB. After using 6-hydroxydopa (6-OHDA) to damage dopaminergic neurons, the authors found that the number of dopaminergic neurons in the experimental group that knocked down PTB was much higher than that in the control group. Subsequent experiments also showed that knocking down PTB successfully increased dopamine levels in PD mice and significantly reduced the damage caused by 6-OHDA. After stimulation, the dopamine response of PD mice after knocking down PTB was also much higher than that of the control group. These data prove that knocking down PTB can effectively restore dopaminergic neuronal damage and the resulting loss of dopamine function in PD mouse models. Behavioral experiments once again proved that knocking down PTB can significantly improve the sports injury of PD mice. The chemical genetics experiment ruled out the influence of other factors and verified that all the above-mentioned improvements were caused by newly formed neurons. Because all the previous experiments were implemented using gene therapy to introduce shPTB, and its clinical use is not mature, the author finally conducted a conceptual verification of the use of PTB antisense oligonucleotides (ASO) in humans for the treatment of PD. The research team successfully screened ASO that can effectively knock down PTB in vivo, and further proved that ASO can promote neuron production and improve the symptoms of PD mice in vivo. These data also provide a conceptual basis for the clinical application of PTB .

The step reported by this study to transform astrocytes into dopaminergic neurons is amazing, and the rigorous experimental design in vitro and in vivo is sufficient to prove the huge potential of this method in PD treatment. Boarding on the cover of Nature is also a reflection of its innovation and significance. Despite its significance, the concept of PTB knockdown treatment of PD still has some urgent problems to be solved. Including the reduction in the ability of cells to reprogram after aging, and the potential effect of astrocytes on the brain is still unknown.

Coincidentally, during the submission of the paper, Professor Yang from the Center for Excellence in Brain Science and Intelligent Technology of the Chinese Academy of Sciences published a very similar study in Cell [2]. This article titled “Glia-to-neuron conversion by CRISPR-CasRx alleviates symptoms of neurological disease in mice” was published on Cell in April this year [2]. The discovery that they used CRISPR-CasRx technology to knock down PTB in Mueller's glial cells and convert them into retinal ganglion cells. At the same time, they also found that this method can produce dopaminergic neurons and relieve the symptoms of dyskinesia in PD mice. The two groups used different techniques to knock down PTB, and obtained consistent results published at the same time in Cell and Nature, which further proved that this idea is correct. Also hope that in the near future, PTB knockdown-related therapies can be applied to the clinical treatment of PD. In particular, previous efforts of RNA-targeting CRISPR systems focused on knockdown of toxic mutant transcripts in models of Parkinson's disease,

whereas this study presents the novel aspect of using these tools for in vivo therapeutic cell fate conversion, which is quite interesting and could be a broadly applicable approach. The concept of converting already present precursor cells to neurons that are capable of integrating and extending axons is extremely valuable.

Professor Fu's team found that knocking down the RNA-binding protein PTB (PTB1) in astrocytes can directly transform them into functional neurons. This one-step conversion method can induce the generation of new dopamine functional neurons in the mouse model of Parkinson's disease, rebuild damaged neural circuits, restore dopamine levels in the striatum, and effectively treat Parkinsonism-related dyskinesia. At the same time, it was found that by using antisense oligonucleotides to temporarily inhibit PTB, astrocytes can also be converted into neurons, and a similar reversal of the disease phenotype can be achieved. This research provides a promising treatment for Parkinson's disease and other neurodegenerative diseases, and has received extensive attention in the field of neuroscience. It is worthy of being selected as the cover article of Nature.

Nevertheless, professor Fu has accused wrong doing and scientific misconduct of professor Yang. Firstly, professor Yang expressed false accusations about plagiarism. Recently, professor Yang re-issued a statement: 1. Acknowledged to borrow professor Fu's work; 2. Acknowledged that he had not communicated with professor Fu on the progress of repeating the experiment before publication; 3. Currently communicating with Cell to add thank professor Fu for his contribution and Apologize. The most important reason of professor Yang re-issued a statement is that Aaron D. Gitler, a reviewer of Nature magazine and a professor of basic medicine at Stanford University, is a reviewer of two Nature papers submitted by professor Fu and Yang Hui. He introduced that in November 2018, he had reviewed the papers of Fu Xiangdong's team, at that time it was suggested to add more experiments [1]. Four months later, the paper of Yang Hui's team was submitted to Nature, which was similar to the conclusion of Fu Xiangdong's paper [1, 2]. Gitler said that in general “Taking away the ideas of others without telling the person who provided them is "ungregarable or unfriendly. " ”[2].

Why does Fu Xiangdong think Yang Hui's team's paper is "plagiarized work"? In the letter, Fu said he went to the Shanghai Institute of Neurology to give a speech on June 14, 2018, at the invitation of Poo Muming, director of the Institute of Neurology of the Chinese Academy of Sciences. "I reported our unpublished research on Parkinson's disease at the Institute of Neurology of the Chinese Academy of Sciences. I described the scientific thinking, experimental design and research results of this research in detail. I also Shared a collaborative research on the successful application of anti-PTBP1 factor in the treatment of retinal diseases." That night, Yang and several researchers had dinner with Fu, during which He consulted Fu about the details of the experiment, according to the complaint." To my surprise, Yang hui in the full understanding of our research ideas and successful

experiment results, immediately set out to change a kind of experimental technology to knock down PTBP1, repeat our research work, obtained similar results, and in a short span of six months after will contribute their papers, and eventually published in this journal cell." Fu said in the letter.In the paper that learns Yang Hui is about to be published in "cell" after online, Fu Xiangdong is very discontented, complain to Poo Mu Ming of international famous neurobiologist of director of institute of Chinese Academy of Sciences at once. "I immediately contacted Director Pu Mu-ming and pointed out that this paper plagiarized my unpublished work reported on the nerve, and although I chose a slightly different brain region to knock down PTBP1, the plagiarism was clear." Fu said in the letter.

A scholar familiar with the situation said that the two studies were identical in concept and principle, but that different brain regions and different methods were used to solve the same scientific problem, namely, to treat Parkinson's disease in mice by achieving PTBP1 knockdown. Because Fu is a leader in functional genomics, his team used RNA interference to achieve PTBP1 knockdown, while Yang has extensive experience in gene editing, so his team used RNA editing to achieve this goal.

On April 8, Yang hui team's research was published in the journal Cell [2], Fu believes his scientific research was stolen, so he published papers on the e-print Biorxiv immediately [3], the platform does not have to go through a peer review of papers published, can be online, this gives researchers is that the benefits of priority to ensure that paper.

However, today, Yang Hui, a researcher at the Center of Excellence for Brain and Intelligence (Shanghai Institute of Neurology) of the Chinese Academy of Sciences, issued a statement again, saying that the unpublished research results of Fu Xiangdong have contributed to his research [1,3], but he did not realize that he should communicate with the other side. He also said that he would add his thanks and apology to Fu Xiangdong in the published Cell paper [1]. In his latest statement, Yang explained why he chose CasRx, a new gene-editing system, for his Cell paper, published in April: In March 2018, Cell published CasRx, a new gene-editing system, and he realized that CasRx might be very suitable for transdifferentiation research and treatment of various neurodegenerative diseases by using gene knockdown [2].

Since May 2018, CasRx has been shown to efficiently down-regulate mRNA from various genes using cultured cells in vitro at multiple disease targets. Later, Yang Hui admitted that after hearing the report of Fu Xiangdong on June 14, 2018, he was "encouraged" by the successful experience of Fu Xiangdong and carried out relevant work

without communicating with the other party. On June 14, 2018, Professor Fu Dongdong was invited to give a lecture on neurogenesis and Shared unpublished data to introduce the work of reducing PTBP1 in the substantia nigra in the mouse model of Parkinson's disease (PD) to transform glial cells into dopamine neurons. Professor Fu's successful experience has strengthened Yang Hui’s confidence in PTBP1 as an ideal target for glial cell transdifferentiation. Yang Hui believes that CasRx editing technology is simple, efficient and specific, and direct transdifferentiation in the striatum region of dopamine action area may be more direct and effective. Such work should complement Professor Fu's. Therefore, Yang Hui used the established CasRx editing tool to knock down PTBP1 in the mouse model of PD and retinal disease to realize the transdifferentiation of glial cells. Yang Hui thought professor Fu's article was in the process of review and would be published soon, so Yang Hui did not realize that they should communicate with Professor Fu at that time. Subsequently, due to the well-established gene edit-mediated neuronal transdifferentiation platform in their laboratory and the full cooperation with multiple laboratories, they completed relevant work in a relatively short period of time. Not until they received their paper did they realize that Professor Fu's work was still under review. Yang Hui apologizes for not communicating their work progress in time.

According to the online report of Fu Xiangdong, he explicitly mentioned that he had evidence to prove that Yang Hui did not know what PTBP1 was before he heard his nerve report in June 2018, and accused Yang Hui of plagiarizing research ideas in the Cell paper published after that [1, 2]. However, Yang's latest statement said that after hearing the report, "Professor Fu's successful experience has strengthened our confidence in PTBP1 as an ideal target for glial cell transdifferentiation" and did not admit the accusation of plagiarism.

Seeing their work is peer "grab hair", Fu XiangDong can not help but a cool heart. But nature's editors soon reassured him: in January 2019, Yang's team had first submitted the paper to Nature, and the editors had given it to the same reviewers for peer review. However, several reviewers thought that although the paper of Yang Hui's team was similar to that of Fu Xiangdong, it was slightly inferior in terms of the solid level of data, and finally rejected this paper."

“A slightly different brain region was selected to knock down PTBP1, but the plagiarism was obvious." Fu said in the letter. In addition, the letter also pointed out that Yang Hui's Cell paper took only six months to complete the nine-year work of Fu Xiangdong group, and the data may be artificially selected and falsified [1, 3].

Reference:

1. Qian, H., et al., Reversing a model of Parkinson's disease with in situ converted nigral neurons. Nature, 2020. 582(7813): p. 550-556.

2. Zhou, H., et al., Glia-to-Neuron Conversion by CRISPR-CasRx Alleviates Symptoms of Neurological Disease in Mice. Cell, 2020. 181(3): p. 590-603.e16.

3. Qian, H., et al., Therapeutic Reversal of Chemically Induced Parkinson Disease by Converting Astrocytes into Nigral Neurons. bioRxiv. 2020.04.06.028084; doi: https://doi.org/10.1101/2020.04.06.028084

Dear Editor-in-Chief,

Enclosed manuscript entitled "**A slightly different brain region was selected to knock down PTBP1, but the plagiarism was obvious.**" is for the consideration of publication as a comment.

My manuscript is original research. It has not been previously published and has not been submitted for publication elsewhere while under consideration. There are none conflicts of interest.

This work was supported by the National Undergraduate Training Program for Innovation and Entrepreneurship (no. 201811646025), the Student Research and Innovation Program of Ningbo University (no. 2017SRIP1918, no. 2018SRIP2507 and no. 2019SRIP1902), and the K. C. Wong Magna Found in Ningbo University.

I look forward to your decision of publication of this article.

Best Regards,

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There are no conflicts of interest in this paper

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A slightly different brain region was selected to knock down PTBP1, but the plagiarism was obvious.

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Potential conflict of interest Nothing to report..

Financial Support: This study was supported by grants from the National Undergraduate Training Program for Innovation and Entrepreneurship (201811646025 to YW), the Student Research and Innovation Program of Ningbo University (2017SRIP1918, 2018SRIP2507, and 2019SRIP1902 to YW).

DOI: http://doi.org/10.1016/j.cell.2020.03.024

Keywords: CasRx, Parkinson's disease, PTBP1, Plagiarism.

Abstract

On April 8, 2020 in the journal cell, June 24, 2020, published online in the journal nature: two papers with different methods on low molecular (PTBP1), the same success within the mouse will have function of glial cells into neurons the "regenerative therapy" is used in the treatment of neurodegenerative diseases, which is an important milestone. On July 2, 2020, Xiang Dong Fu real name reported that Yang hui alleged plagiarism his work, and fraud and other academic moral misconduct tip off is widely spread, which referred to him as the role of technical appraisement PTBP1 invested time and work more than 9 years, including six years of experimental work, and nearly 3 years added experimental work in the process of reviewing.

Parkinson's disease (PD) is the second most neurodegenerative disease that causes harm to the elderly, second only to Alzheimer's disease (AD). Worldwide, PD ld is hundreds of thousands of people every year. Although we already know that the direct cause of PD is the degradation of dopaminergic neurons in the substantia nigra, we have not been able to prevent or reverse the nerves of PD patients degraded. On June 24, 2020, Professor Fu led a team to pub lish a cover article in the current Nature entitled "Reversing a model of Parkinson's disease with in situ converted nigral neurons" [1]. The study reported a new method for transdifferentiating cells into dopaminergic neurons by manipulating the PTB gene, providing a new opportunity to reverse Parkinson's disease.

After confirming that knocking down PTB can achieve the production of dopaminergic neurons in the body, the authors began to explore the therapeutic potential of this method. They estab lished a PD model in mice that knocked down PTB. After using 6-hydroxydopa (6-OHDA) to damage dopaminergic neurons, the authors found that the number of dopaminergic neurons in the experimental group that knocked down PTB was much higher than that in the control group. Subsequent experiments also showed that knocking down PTB successfully increased dopamine levels in PD mice and significantly reduced the damage caused by 6-OHDA. After s imulation, the dopamine response of PD mice after knocking down PTB was also much higher than that of the control group. These data prove that knocking down PTB can effectively restore dopaminergic neuronal damage and the resu ting loss of dopamine function in PD mouse models. Behavioral experiments once again proved that knocking down PTB can sign ficantly improve the sports injury of PD mice. The chemical genetics experiment ruled out the influence of other factors and verified that a l the above-mentioned improvements were caused by newly formed neurons. Because all the previous experiments were implemented using gene therapy to introduce shPTB, and its clinical use is not mature, the author finally conducted a conceptual verification of the use of PTB an isense oligonucleotides (ASO) in humans for the treatment of PD. The research team successfully screened ASO hat can effectively knock down PTB in vivo, and further proved that ASO can promote neuron production and improve the symptoms of PD mice in vivo. These data also provide a conceptual basis for the clinical application of PTB .

The step reported by this study to transform astrocytes into dopaminergic neurons is amazing, and the rigorous experimental design in v tro and in vivo is sufficient to prove the huge potential of this method in PD treatment. Boarding on the cover of Nature is also a reflection of its innovation and significance. Despite its significance, the concept of PTB knockdown treatment of PD still has some urgent problems to be solved. Including the reduction in the abil ty of cells to reprogram after aging, and the potential effect of astrocytes on the brain is still unknown.

Coincidentally, during the submission of the paper, Professor Yang from the Center for Excellence in Brain Science and Intelligent Technology of the Chinese Academy of Sciences published a very sim lar study in Ce l [2]. This article titled "G la-to-neuron conversion by CRISPR-CasRx alleviates symptoms of neurological disease in mice" was published on Ce l in Apr l this year [2]. The discovery that they used CRISPR-CasRx technology to knock down PTB in Mueller's g lial cells and convert them into retinal ganglion ce ls. At the same time, they also found that this method can produce dopaminergic neurons and relieve the symptoms of dyskinesia in PD mice. The two groups used different techniques to knock down PTB, and obtained consistent results published at the same time in Cell and Nature, which further proved that this idea is correct. Also hope that in the near future, PTB knockdown-related therapies can be applied to the clinical treatment of PD. In particular, previous efforts of RNA-targeting CRISPR systems focused on knockdown of toxic mutant transcripts in models of Parkinson's disease, whereas this study presents the novel aspect of using these tools for in vivo herapeutic cell fate conversion, which is quite interesting and could be a broadly applicable approach. The concept of converting already present precursor cells to neurons that are capable of integrating and extending axons is extremely valuable.

Professor Fu's team found that knocking down the RNA-binding protein PTB (PTB1) in astrocytes can directly transform them into functional neurons. This one-step conversion method can induce the generation of new dopamine functional neurons in the mouse model of Parkinson's disease, rebuild damaged neural circu ts, restore dopamine levels in the striatum, and effectively treat Parkinsonism-related dyskinesia. At the same time, t was found that by using antisense o ligonucleotides to temporarily inh b t PTB, astrocytes can also be converted into neurons, and a similar reversal of the disease phenotype can be achieved. This research provides a promising treatment for Parkinson's disease and other neurodegenerative diseases, and has received extensive attention in the leld of neuroscience. It is worthy of being selected as the cover article of Nature.

Nevertheless, professor Fu has accused wrong doing and scientific misconduct of professor Yang. Firstly, professor Yang expressed false accusations about plagiarism. Recently, professor Yang re-issued a statement 1. Acknowledged to borrow professor Fu's work; 2. Acknowledged that he had not communicated with professor Fu on the progress of repeating the experiment before publication; 3. Currently communicating w th Cell to add thank professor Fu for his contribution and Apologize. The most important reason of professor Yang re-issued a statement is that Aaron D. Gitler, a reviewer of Nature magazine and a professor of basic medicine at Stanford University, is a reviewer of two Nature papers submitted by professor Fu and Yang Hui. He introduced that in November 2018, he had reviewed the papers of Fu Xiangdong's team, at that time it was suggested to add more experiments [1]. Four months later, the paper of Yang Hui's team was submitted to Nature, which was similar to the conclusion of Fu Xiangdong's paper [1, 2]. Gitler said that in general "Taking away the ideas of others without tel ing the person who provided them is "ungregarable or unfriendly. " "[2].

Why does Fu Xiangdong hink Yang Hui's team's paper is "plagiarized work"? In the letter, Fu said he went to the Shanghai Institute of Neurology to give a speech on June 14, 2018, at the invitation of Poo Muming, director of the Institute of Neurology of the Chinese Academy of Sciences. "I reported our unpublished research on Parkinson's disease at the Institute of Neurology of the Chinese Academy of Sciences. I described the scientific thinking, experimental design and research results of this research in detail. I also Shared a collaborative research on the successful application of anti-PTBP1 factor in the treatment of retinal diseases." That night, Yang and several researchers had dinner w th Fu, during which He consulted Fu about the details of the experiment, according to the complaint." To my surprise, Yang hui in the full understanding of our research ideas and successful experiment results, immediately set out to change a kind of experimental technology to knock down PTBP1, repeat our research work, obtained similar results, and in a short span of six months after will contribute their papers, and eventually published in this journal cell." Fu said in the letter.In he paper that learns Yang Hui is about to be published in "cell" after online, Fu Xiangdong is very discontented, complain to Pu Mu Ming of international famous neurobiologist of director of institute of Chinese Academy of Sciences at once. "I immediately contacted Director Pu Mu-ming and pointed out that this paper plagiarized my unpub ished work reported on the nerve, and although I chose a slightly d fferent brain region to knock down PTBP1, the plagiarism was clear." Fu said in he letter.

A scholar familiar with the situation said that the two studies were identical in concept and principle, but that different brain regions and different methods were used to solve the same scientific problem, namely, to treat Parkinson's disease in mice by achieving PTBP1 knockdown. Because Fu is a leader in functional genomics, his team used RNA interference to achieve PTBP1 knockdown, wh le Yang has extensive experience in gene editing, so his team used RNA editing to achieve this goal.

On April 8, Yang hui team's research was pub ished in the journal Ce l [2], Fu believes his scientific research was stolen, so he pub ished papers on the e-print Biorxiv immediately [3], the platform does not have to go through a peer review of papers published, can be on ine, this gives researchers is that the benef ts of priority to ensure that paper.

However, today, Yang Hui, a researcher at the Center of Exce lence for Brain and Inte ligence (Shanghai Institute of Neurology) of the Chinese Academy of Sciences, issued a statement again, saying that the unpublished research results of Fu Xiangdong have contributed to his research [1,3], but he did not realize that he should communicate with the other side. He also said that he would add his thanks and apology to Fu Xiangdong in the pub ished Cell paper [1]. In his latest statement, Yang explained why he chose CasRx, a new gene-editing system, for his Cell paper, published in April In March 2018, Cell published CasRx, a new gene-ed ting system, and he realized that CasRx might be very su table for transd fferentiation research and treatment of various neurodegenerative diseases by using gene knockdown [2].

Since May 2018, CasRx has been shown to efficiently down-regulate mRNA from various genes using cultured ce ls in v tro at multiple disease targets. Later, Yang Hui admitted that after hearing the report of Fu Xiangdong on June 14, 2018, he was "encouraged" by the successful experience of Fu Xiangdong and carried out relevant work without communicating with the other party. On June 14, 2018, Professor Fu Dongdong was inv ted to give a lecture on neurogenesis and Shared unpub ished data to introduce the work of reducing PTBP1 in the substantia nigra in the mouse model of Parkinson's disease (PD) to transform glial cells into dopamine neurons. Professor Fu's successful experience has strengthened Yang Hui's confidence in PTBP1 as an ideal target for g ial cell transd fferentiation. Yang Hui be ieves that CasRx editing technology is simple, efficient and specific, and direct transdifferentiation in the striatum region of dopamine action area may be more direct and effective. Such work should complement Professor Fu's. Therefore, Yang Hui used the established CasRx editing tool to knock down PTBP1 in the mouse model of PD and retinal disease to realize the transdifferentiation of g ial cells. Yang Hui thought professor Fu's article was in the process of review and would be pub ished soon, so Yang Hui did not realize that they should communicate with Professor Fu at that time. Subsequently, due to the well-established gene ed t-mediated neuronal transdifferentiation platform in their laboratory and the fu l cooperation with mu tiple laboratories, they completed relevant work in a relatively short period of time. Not until they received their paper did they realize that Professor Fu's work was still under review. Yang Hui apologizes for not communicating their work progress in time.

According to the online report of Fu Xiangdong, he exp icitly mentioned that he had evidence to prove that Yang Hui did not know what PTBP1 was before he heard his nerve report in June 2018, and accused Yang Hui of plagiarizing research ideas in the Ce l paper pub ished after that [1, 2]. However, Yang's latest statement said that after hearing the report, "Professor Fu's successful experience has strengthened our confidence in PTBP1 as an ideal target for glial cell transdifferentiation" and did not adm t the accusation of plagiarism.

Seeing their work is peer "grab hair", Fu XiangDong can not help but a cool heart. But nature's editors soon reassured him in January 2019, Yang's team had first submitted the paper to Nature, and the editors had given it to the same reviewers for peer review. However, several reviewers thought hat a though the paper of Yang Hui's team was similar to that of Fu Xiangdong, it was slightly inferior in terms of the solid level of data, and finally rejected this paper."

“A slightly different brain region was selected to knock down PTBP1, but the plagiarism was obvious." Fu said in the letter. In addition, the letter also pointed out that Yang Hui's Cell paper took only six months to complete the nine-year work of Fu Xiangdong group, and the data may be art ficially selected and falsified [1, 3].

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1. Qian, H., et al., Reversing a model of Parkinson’s disease with in situ converted nigral neurons. Nature, 2020. 582(7813) p. 550-556.

2. Zhou, H., et al., G ia-to-Neuron Conversion by CRISPR-CasRx Alleviates Symptoms of Neurological Disease in Mice. Cell, 2020. 181(3) p. 590-603.e16.

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Potential conflict of interest: Nothing to report..

Financial Support: Th s study was supported by grants from the National Undergraduate Training Program for Innovation and Entrepreneurship (2018116 6025 to YW), the Student Research and Innovat on Program of Ningbo University (2017SRIP1918, 2018SR P2507, and 2019SRIP1902 to YW).

DOI: http://doi org/10 1016/j cell 2020 03 024

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Abstract

On April 8 2020 in the journal cell une 24 2020 published online n the journal nature: two papers with different methods on low molecular (P BP1) the same success within the mouse will have function of glial cells into neurons the "regenerative therapy" is used in the treatment of neurodegenerative diseases which is an important milestone On uly 2 2020 Xiang Dong Fu real name reported that Yang hui al eged plagiarism his work and fraud and other academic moral misconduct tip off is widely spread which referred to him as the role of technical appraisement P BP1 invested time and work more than 9 years inc uding six years of experimental work and nearly 3 years added experimental work in the process of reviewing

Parkinson's disease (PD) s the second most neurodegenerative disease that causes harm o the e derly, second only to Alzheimer's disease (AD). Wor dw de, PD kil s hundreds of thousands of people every year. Although we already know that the direct cause of PD is the degradat on of dopaminergic neurons in the substant a nigra, we have not been able to prevent or reverse the nerves of PD patients degraded. On June 2 , 2020, Professor Fu led a team to publ sh a cover article in the current Nature entit ed Reversing a model of Parkinson s disease with in s tu converted n gral neurons [1]. The study reported a new method for transdifferentiating ce ls into dopaminergic neurons by manipulating the PTB gene, providing a new opportun ty to reverse Parkinson s disease.

After confirming that knocking down PTB can achieve the production of dopaminergic neurons in the body, the authors began to exp ore the therapeutic potent al of th s method. They established a PD model in mice that knocked down PTB. A ter using 6-hydroxydopa (6-OHDA) to damage dopaminergic neurons, the authors ound that the number of dopaminerg c neurons in the experimen al group that knocked down PTB was much higher than that in the control group. Subsequent experiments a so showed that knocking down PTB successfully increased dopamine levels in PD mice and s gnificantly reduced the damage caused by 6-OHDA. After stimulat on, the dopamine response of PD mice after knocking down PTB was also much higher than that of the control group. These data prove that knocking down PTB can effectively restore dopaminergic neuronal damage and the resulting oss of dopamine function in PD mouse models. Behavioral experiments once again proved that knocking down PTB can significantly improve the sports injury of PD m ce. The chem cal genetics experiment ruled out the influence of other factors and verified that all the above-ment oned improvements were caused by newly formed neurons. Because all the previous experiments were imp emented using gene therapy to introduce shPTB, and ts c inical use is not mature, the author finally conducted a conceptual verif cat on of the use of PTB ant sense oligonuc eotides (ASO) in humans for the treatment of PD. The research team successfully screened ASO that can effectively knock down PTB in vivo, and further proved that ASO can promote neuron production and improve the symptoms of PD mice in vivo. These data a so provide a conceptual basis for the clinical application of PTB .

The s ep reported by this study to transform astrocytes into dopaminergic neurons s amazing, and the rigorous experimental design in vitro and in vivo is suffic ent to prove the huge potential of this method in PD treatment. Boarding on the cover of Nature is also a reflect on of ts innovation and signif cance. Despite its signif cance, the concept of PTB knockdown treatment of PD still has some urgent problems to be solved. Including the reduction in the ab lity of ce ls to reprogram after aging, and the potential effect of astrocytes on the brain is still unknown.

Coinc dentally, during the subm ss on of the paper, Professor Yang from the Center for Excel ence in Brain Sc ence and Inte ligent Technology of the Chinese Academy of Sciences published a very simi ar study in Cell [2]. This article tit ed G ia-to-neuron conversion by CR SPR-CasRx alleviates symptoms of neurological d sease in mice was published on Ce l in April this year [2]. The discovery that they used CRISPR-CasRx technology to knock down PTB in Mue ler's glial ce ls and convert them into retinal ganglion cel s. At the same time, they also found that this method can produce dopaminergic neurons and rel eve the symptoms of dyskinesia in PD m ce. The two groups used d fferent techniques to knock down PTB, and obtained consistent resu ts pub ished at the same time in Cell and Nature, which further proved that this idea is correct. Also hope that in the near future, PTB knockdown-related therapies can be app ied to the c inical treatment of PD. In part cular, previous efforts of RNA-targe ing CRISPR systems focused on knockdown of toxic mutant transcrip s in models of Parkinson s d sease, whereas th s study presents the novel aspect of using these too s for in vivo therapeut c cell fate conversion, which is quite interesting and could be a broadly app icab e approach. The concept of converting already present precursor cells to neurons that are capab e of integrating and extending axons s extremely valuable.

Professor Fu's team found that knocking down the RNA-binding protein PTB (PTB1) in astrocytes can directly transform them into functional neurons. This one-step conversion method can induce the generat on of new dopamine functional neurons in the mouse model of Parkinson s disease, rebuild damaged neural circu ts, restore dopamine levels in the str atum, and effectively treat Parkinsonism-related dyskinesia. At the same time, it was found that by using ant sense oligonuc eotides to temporarily inhibit PTB, astrocytes can also be converted into neurons, and a similar reversal of the disease phenotype can be ach eved. This research provides a promising treatment for Parkinson s disease and other neurodegenerative d seases, and has received extensive attention in the field of neuroscience. It is worthy of being selected as the cover article of Nature.

Nevertheless, professor Fu has accused wrong doing and scientific misconduct of professor Yang. Firstly, professor Yang expressed false accusat ons about plagiarism. Recently, professor Yang re-issued a statement: 1. Acknow edged to borrow professor Fu's work; 2. Acknow edged that he had not commun cated with professor Fu on the progress of repeating the experiment before publ cation; 3. Currently communica ing with Cell to add thank professor Fu for his contribut on and Apologize. The most important reason of professor Yang re-issued a statement is that Aaron D. Gi ler, a reviewer of Nature magazine and a professor of basic medicine at Stanford University, s a reviewer of two Nature papers submitted by professor Fu and Yang Hui. He introduced that in November 2018, he had reviewed the papers of Fu Xiangdong s team, at that time t was suggested to add more experiments [1]. Four months later, the paper of Yang Hui's team was submitted to Nature, which was sim lar to the conclus on of Fu X angdong's paper [1, 2]. Git er sa d that in general Taking away the deas of others without telling the person who provided them is ungregarab e or unfriendly. [2].

Why does Fu Xiangdong think Yang Hui's team s paper is p agiarized work ? In the letter, Fu sa d he went to the Shanghai Institute of Neuro ogy to give a speech on June 1 , 2018, at the invitat on of Poo Muming, director of the Institute of Neurology of the Chinese Academy of Sciences. I reported our unpub ished research on Parkinson s disease at the Institute of Neurology of the Chinese Academy of Sciences. I described the scientific thinking, experimental design and research resu ts of th s research in detail. I also Shared a collaborative research on the successful appl cation of anti-PTBP1 factor in the treatment of retinal diseases. That night, Yang and several researchers had dinner with Fu, during which He consulted Fu about the details of the experiment, according to the complaint. To my surprise, Yang hui in the full understanding of our research ideas and successful experiment results, immediately set out to change a kind of experimental technology to knock down PTBP1, repeat our research work, obtained simi ar results, and in a short span of six months after wi l contribute their papers, and eventually pub ished in th s journal ce l. Fu said in the letter.In the paper that learns Yang Hui s about to be published in cell a ter online, Fu Xiangdong is very discontented, complain to Poo Mu Ming of international famous neurobio ogist of director of institute of Chinese Academy of Sc ences at once. I immed ately contacted Director Pu Mu-ming and pointed out that this paper plagiarized my unpubl shed work reported on the nerve, and a though I chose a sl ghtly different brain reg on to knock down PTBP1, the plag arism was clear. Fu said in the etter.

A scholar fam liar with the situation said that the two studies were ident cal in concept and principle, but that different brain reg ons and different methods were used to solve the same sc entif c prob em, namely, o treat Parkinson s disease in m ce by ach eving PTBP1 knockdown. Because Fu is a leader in functional genomics, his team used RNA in erference to achieve PTBP1 knockdown, while Yang has extensive experience in gene editing, so his team used RNA ed ting to ach eve this goal.

On April 8, Yang hui team's research was published in the journal Cell [2], Fu be ieves his sc entific research was stolen, so he pub ished papers on the e-print Biorxiv immediately [3], the platform does not have to go through a peer review of papers pub ished, can be online, this gives researchers s that the benef ts of pr ority to ensure that paper.

However, today, Yang Hui, a researcher at the Center of Excel ence or Brain and Intell gence (Shanghai Inst tute of Neuro ogy) of the Chinese Academy of Sciences, issued a statement again, saying that the unpub ished research results of Fu Xiangdong have contributed to his research [1,3], but he did not real ze that he should commun cate with the other s de. He also said that he would add his thanks and apology to Fu Xiangdong in the published Cell paper [1]. In his latest statement, Yang explained why he chose CasRx, a new gene-ed ing system, for his Cell paper, publ shed in April: In March 2018, Cell publ shed CasRx, a new gene-editing system, and he real zed that CasRx m ght be very suitable for transdifferent ation research and treatment of various neurodegenerative d seases by using gene knockdown [2].

Since May 2018, CasRx has been shown to efficiently down-regu ate mRNA from var ous genes using cultured cel s in vitro at multiple d sease targets. Later, Yang Hui admitted that after hearing the report of Fu X angdong on June 1 , 2018, he was encouraged by the successful experience of Fu Xiangdong and carried out relevant work without commun cating with the other party. On June 1 , 2018, Professor Fu Dongdong was invited to give a lecture on neurogenes s and Shared unpub ished data to introduce the work of reducing PTBP1 in the substant a nigra in the mouse model of Parkinson's d sease (PD) to transform g ial cells into dopamine neurons. Professor Fu s successful experience has strengthened Yang Hui's conf dence in PTBP1 as an ideal target for g ial cell transdi ferentiat on. Yang Hui believes that CasRx editing technology is simple, eff cient and specif c, and direct transdifferentiation in the striatum region of dopamine action area may be more direct and effective. Such work should complement Professor Fu's. Therefore, Yang Hui used the estab ished CasRx editing tool to knock down PTBP1 in the mouse model of PD and retinal d sease to rea ize the transdifferent ation of glial ce ls. Yang Hui thought professor Fu's artic e was in the process of review and wou d be published soon, so Yang Hui did not real ze that they should communicate with Professor Fu at that time. Subsequently, due to the well-establ shed gene edit-mediated neuronal transd fferentia ion p atform in their laboratory and the full cooperation w th mu tiple aborator es, they completed relevant work in a relatively short period of time. Not until they received their paper did they realize that Professor Fu's work was st ll under review. Yang Hui apologizes for not communicating their work progress in time.

According to the on ine report of Fu Xiangdong, he explicitly ment oned that he had evidence to prove that Yang Hui did not know what PTBP1 was before he heard his nerve report in June 2018, and accused Yang Hui of plagiarizing research deas in the Cell paper published after that [1, 2]. However, Yang's atest statement sa d that a ter hearing the report, Professor Fu's successful exper ence has strengthened our con idence in PTBP1 as an ideal arget for gl al cell transdifferen iation and did not adm t the accusa ion of plagiar sm.

Seeing their work is peer grab hair , Fu XiangDong can not help but a cool heart. But nature's editors soon reassured him: in January 2019, Yang's team had first submitted the paper to Nature, and the editors had given t to the same reviewers for peer rev ew. However, several reviewers thought that although the paper of Yang Hui's team was sim lar to that of Fu Xiangdong, it was s ightly infer or in terms of the sol d level of data, and finally rejected th s paper.

A slightly different brain reg on was selected to knock down PTBP1, but the p agiarism was obvious. Fu sa d in the letter. In addit on, the letter a so pointed out that Yang Hui s Cell paper took only six months to complete the nine-year work of Fu X angdong group, and the data may be artif cia ly selected and fa sif ed [1, 3].

Reference:

1. Qian, H., et al., Reversing a model of Parkinson's d sease w th in situ converted nigral neurons. Nature, 2020. 582(7813): p. 550-556.

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3. Qian, H., et al., Therapeutic Reversal of Chemically Induced Parkinson Disease by Converting Astrocytes into Nigral Neurons. bioRxiv. 2020.0 .06.02808 ; doi: https://doi.org/10.1101 2020.0 .06.02808

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Dear teachers:

The manuscript should be revised and published, if some scholars could publish some plagiarism manuscripts without being accused and published, whether we as students could copy new ideas from others ? Why Yang Hui as a scholar from the Center for Excellence in Brain Science and Intelligent Technology of the Chinese Academy of Sciences who has published plagiarism manuscripts on Cell could work in normal by now? Could you help me at your convenience?

A slightly different brain region was selected to knock down PTBP1, but the plagiarism was obvious.

Yezhao Wang1,2

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Potential conflict of interest: Nothing to report..

Financial Support: This study was supported by grants from the National Undergraduate Training Program for Innovation and Entrepreneurship (201811646025 to YW), the Student Research and Innovation Program of Ningbo University (2017SRIP1918, 2018SRIP2507, and 2019SRIP1902 to YW).

DOI: http://doi org/10 1016/j cell 2020 03 024

Keywords: CasRx, Parkinson's disease, PTBP1, Plagiarism.

Abstract

On April 8, 2020 in the journal cell, June 24, 2020, published online in the journal nature: two papers with different methods on low molecular (PTBP1), the same success within the mouse will have function of glial cells into neurons-the "regenerative therapy" is used in the treatment of neurodegenerative diseases, which is an important milestone. On July 2, 2020, Xiang-Dong Fu real-name reported that Yang hui alleged plagiarism his work, and fraud and other academic moral misconduct tip-off is widely spread, which referred to him as the role of technical appraisement PTBP1 invested time and work more than 9 years, including six years of experimental work, and nearly 3 years added experimental work in the process of reviewing.

Parkinson's disease (PD) is the second most neurodegenerative disease that causes harm to the elderly, second only to Alzheimer's disease (AD). Worldwide, PD kills hundreds of thousands of people every year. Although we already know that the direct cause of PD is the degradation of dopaminergic neurons in the substantia nigra, we have not been able to prevent or reverse the nerves of PD patients degraded. On June 24, 2020, Professor Fu led a team to publish a cover article in the current Nature entitled “Reversing a model of Parkinson's disease with in situ converted nigral neurons” [1]. The study reported a new method for transdifferentiating cells into dopaminergic neurons by manipulating the PTB gene, providing a new opportunity to reverse Parkinson's disease.

After confirming that knocking down PTB can achieve the production of dopaminergic neurons in the body, the authors began to explore the therapeutic potential of this method. They established a PD model in mice that knocked down PTB. After using 6-hydroxydopa (6-OHDA) to damage dopaminergic neurons, the authors found that the number of dopaminergic neurons in the experimental group that knocked down PTB was much higher than that in the control group. Subsequent experiments also showed that knocking down PTB successfully increased dopamine levels in PD mice and significantly reduced the damage caused by 6-OHDA. After stimulation, the dopamine response of PD mice after knocking down PTB was also much higher than that of the control group. These data prove that knocking down PTB can effectively restore dopaminergic neuronal damage and the resulting loss of dopamine function in PD mouse models. Behavioral experiments once again proved that knocking down PTB can significantly improve the sports injury of PD mice. The chemical genetics experiment ruled out the influence of other factors and verified that all the above-mentioned improvements were caused by newly formed neurons. Because all the previous experiments were implemented using gene therapy to introduce shPTB, and its clinical use is not mature, the author finally conducted a conceptual verification of the use of PTB antisense oligonucleotides (ASO) in humans for the treatment of PD. The research team successfully screened ASO that can effectively knock down PTB in vivo, and further proved that ASO can promote neuron production and improve the symptoms of PD mice in vivo. These data also provide a conceptual basis for the clinical application of PTB .

The step reported by this study to transform astrocytes into dopaminergic neurons is amazing, and the rigorous experimental design in vitro and in vivo is sufficient to prove the huge potential of this method in PD treatment. Boarding on the cover of Nature is also a reflection of its innovation and significance. Despite its significance, the concept of PTB knockdown treatment of PD still has some urgent problems to be solved. Including the reduction in the ability of cells to reprogram after aging, and the potential effect of astrocytes on the brain is still unknown.

Coincidentally, during the submission of the paper, Professor Yang from the Center for Excellence in Brain Science and Intelligent Technology of the Chinese Academy of Sciences published a very similar study in Cell [2]. This article titled “Glia-to-neuron conversion by CRISPR-CasRx alleviates symptoms of neurological disease in mice” was published on Cell in April this year [2]. The discovery that they used CRISPR-CasRx technology to knock down PTB in Mueller's glial cells and convert them into retinal ganglion cells. At the same time, they also found that this method can produce dopaminergic neurons and relieve the symptoms of dyskinesia in PD mice. The two groups used different techniques to knock down PTB, and obtained consistent results published at the same time in Cell and Nature, which further proved that this idea is correct. Also hope that in the near future, PTB knockdown-related therapies can be applied to the clinical treatment of PD. In particular, previous efforts of RNA-targeting CRISPR systems focused on knockdown of toxic mutant transcripts in models of Parkinson's disease, whereas this study presents the novel aspect of using these tools for in vivo therapeutic cell fate conversion, which is quite interesting and could be a broadly applicable approach. The concept of converting already present precursor cells to neurons that are capable of integrating and extending axons is extremely valuable.

Professor Fu's team found that knocking down the RNA-binding protein PTB (PTB1) in astrocytes can directly transform them into functional neurons. This one-step conversion method can induce the generation of new dopamine functional neurons in the mouse model of Parkinson's disease, rebuild damaged neural circuits, restore dopamine levels in the striatum, and effectively treat Parkinsonism-related dyskinesia. At the same time, it was found that by using antisense oligonucleotides to temporarily inhibit PTB, astrocytes can also be converted into neurons, and a similar reversal of the disease phenotype can be achieved. This research provides a promising treatment for Parkinson's disease and other neurodegenerative diseases, and has received extensive attention in the field of neuroscience. It is worthy of being selected as the cover article of Nature.

Nevertheless, professor Fu has accused wrong doing and scientific misconduct of professor Yang. Firstly, professor Yang expressed false accusations about plagiarism. Recently, professor Yang re-issued a statement: 1. Acknowledged to borrow professor Fu's work; 2. Acknowledged that he had not communicated with professor Fu on the progress of repeating the experiment before publication; 3. Currently communicating with Cell to add thank professor Fu for his contribution and Apologize. The most important reason of professor Yang re-issued a statement is that Aaron D. Gitler, a reviewer of Nature magazine and a professor of basic medicine at Stanford University, is a reviewer of two Nature papers submitted by professor Fu and Yang Hui. He introduced that in November 2018, he had reviewed the papers of Fu Xiangdong's team, at that time it was suggested to add more experiments [1]. Four months later, the paper of Yang Hui's team was submitted to Nature, which was similar to the conclusion of Fu Xiangdong's paper [1, 2]. Gitler said that in general “Taking away the ideas of others without telling the person who provided them is "ungregarable or unfriendly. " ”[2].

Why does Fu Xiangdong think Yang Hui's team's paper is "plagiarized work"? In the letter, Fu said he went to the Shanghai Institute of Neurology to give a speech on June 14, 2018, at the invitation of Poo Muming, director of the Institute of Neurology of the Chinese Academy of Sciences. "I reported our unpublished research on Parkinson's disease at the Institute of Neurology of the Chinese Academy of Sciences. I described the scientific thinking, experimental design and research results of this research in detail. I also Shared a collaborative research on the successful application of anti-PTBP1 factor in the treatment of retinal diseases." That night, Yang and several researchers had dinner with Fu, during which He consulted Fu about the details of the experiment, according to the complaint." To my surprise, Yang hui in the full understanding of our research ideas and successful experiment results, immediately set out to change a kind of experimental technology to knock down PTBP1, repeat our research work, obtained similar results, and in a short span of six months after will contribute their papers, and eventually published in this journal cell." Fu said in the letter.In the paper that learns Yang Hui is about to be published in "cell" after online, Fu Xiangdong is very discontented, complain to Pu Mu Ming of international famous neurobiologist of director of institute of Chinese Academy of Sciences at once. "I immediately contacted Director Pu Mu-ming and pointed out that this paper plagiarized my unpublished work reported on the nerve, and although I chose a slightly different brain region to knock down PTBP1, the plagiarism was clear." Fu said in the letter.

A scholar familiar with the situation said that the two studies were identical in concept and principle, but that different brain regions and different methods were used to solve the same scientific problem, namely, to treat Parkinson's disease in mice by achieving PTBP1 knockdown. Because Fu is a leader in functional genomics, his team used RNA interference to achieve PTBP1 knockdown, while Yang has extensive experience in gene editing, so his team used RNA editing to achieve this goal.

On April 8, Yang hui team's research was published in the journal Cell [2], Fu believes his scientific research was stolen, so he published papers on the e-print Biorxiv immediately [3], the platform does not have to go through a peer review of papers published, can be online, this gives researchers is that the benefits of priority to ensure that paper.

However, today, Yang Hui, a researcher at the Center of Excellence for Brain and Intelligence (Shanghai Institute of Neurology) of the Chinese Academy of Sciences, issued a statement again, saying that the unpublished research results of Fu Xiangdong have contributed to his research [1,3], but he did not realize that he should communicate with the other side. He also said that he would add his thanks and apology to Fu Xiangdong in the published Cell paper [1]. In his latest statement, Yang explained why he chose CasRx, a new gene-editing system, for his Cell paper, published in April: In March 2018, Cell published CasRx, a new gene-editing system, and he realized that CasRx might be very suitable for transdifferentiation research and treatment of various neurodegenerative diseases by using gene knockdown [2].

Since May 2018, CasRx has been shown to efficiently down-regulate mRNA from various genes using cultured cells in vitro at multiple disease targets. Later, Yang Hui admitted that after hearing the report of Fu Xiangdong on June 14, 2018, he was "encouraged" by the successful experience of Fu Xiangdong and carried out relevant work without communicating with the other party. On June 14, 2018, Professor Fu Dongdong was invited to give a lecture on neurogenesis and Shared unpublished data to introduce the work of reducing PTBP1 in the substantia nigra in the mouse model of Parkinson's disease (PD) to transform glial cells into dopamine neurons. Professor Fu's successful experience has strengthened Yang Hui’s confidence in PTBP1 as an ideal target for glial cell transdifferentiation. Yang Hui believes that CasRx editing technology is simple, efficient and specific, and direct transdifferentiation in the striatum region of dopamine action area may be more direct and effective. Such work should complement Professor Fu's. Therefore, Yang Hui used the established CasRx editing tool to knock down PTBP1 in the mouse model of PD and retinal disease to realize the transdifferentiation of glial cells. Yang Hui thought professor Fu's article was in the process of review and would be published soon, so Yang Hui did not realize that they should communicate with Professor Fu at that time. Subsequently, due to the well-established gene edit-mediated neuronal transdifferentiation platform in their laboratory and the full cooperation with multiple laboratories, they completed relevant work in a relatively short period of time. Not until they received their paper did they realize that Professor Fu's work was still under review. Yang Hui apologizes for not communicating their work progress in time.

According to the online report of Fu Xiangdong, he explicitly mentioned that he had evidence to prove that Yang Hui did not know what PTBP1 was before he heard his nerve report in June 2018, and accused Yang Hui of plagiarizing research ideas in the Cell paper published after that [1, 2]. However, Yang's latest statement said that after hearing the report, "Professor Fu's successful experience has strengthened our confidence in PTBP1 as an ideal target for glial cell transdifferentiation" and did not admit the accusation of plagiarism.

Seeing their work is peer "grab hair", Fu XiangDong can not help but a cool heart. But nature's editors soon reassured him: in January 2019, Yang's team had first submitted the paper to Nature, and the editors had given it to the same reviewers for peer review. However, several reviewers thought that although the paper of Yang Hui's team was similar to that of Fu Xiangdong, it was slightly inferior in terms of the solid level of data, and finally rejected this paper."

“A slightly different brain region was selected to knock down PTBP1, but the plagiarism was obvious." Fu said in the letter. In addition, the letter also pointed out that Yang Hui's Cell paper took only six months to complete the nine-year work of Fu Xiangdong group, and the data may be artificially selected and falsified [1, 3].

Reference:

1. Qian, H., et al., Reversing a model of Parkinson’s disease with in situ converted nigral neurons. Nature, 2020. 582(7813): p. 550-556.

2. Zhou, H., et al., Glia-to-Neuron Conversion by CRISPR-CasRx Alleviates Symptoms of Neurological Disease in Mice. Cell, 2020. 181(3): p. 590-603.e16.

3. Qian, H., et al., Therapeutic Reversal of Chemically Induced Parkinson Disease by Converting Astrocytes into Nigral Neurons. bioRxiv. 2020.04.06.028084; doi: https://doi.org/10.1101/2020.04.06.028084

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A slightly different brain region was selected to knock down PTBP1, but the plagiarism was obvious.

Yezhao Wang1,2

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Potential conflict of interest: Nothing to report..

Financial Support: This study was supported by grants from the National Undergraduate Training Program for Innovation and Entrepreneurship (201811646025 to YW), the Student Research and Innovation Program of Ningbo University (2017SRIP1918, 2018SRIP2507, and 2019SRIP1902 to YW).

DOI: http://doi.org/10.1016/j.cell.2020.03.024

Keywords: CasRx, Parkinson's disease, PTBP1, Plagiarism.

Abstract

On April 8, 2020 in the journal cell, June 24, 2020, published online in the journal nature: two papers with different methods on low molecular (PTBP1), the same success within the mouse will have function of glial cells into neurons-the "regenerative therapy" is used in the treatment of neurodegenerative diseases, which is an important milestone. On July 2, 2020, Xiang-Dong Fu real-name reported that Yang hui alleged plagiarism his work, and fraud and other academic moral misconduct tip-off is widely spread, which referred to him as the role of technical appraisement PTBP1 invested time and work more than 9 years, including six years of experimental work, and nearly 3 years added experimental work in the process of reviewing.

Parkinson's disease (PD) is the second most neurodegenerative disease that causes harm to the elderly, second only to Alzheimer's disease (AD). Worldwide, PD kills hundreds of thousands of people every year. Although we already know that the direct cause of PD is the degradation of dopaminergic neurons in the substantia nigra, we have not been able to prevent or reverse the nerves of PD patients degraded. On June 24, 2020, Professor Fu led a team to publish a cover article in the current Nature entitled “Reversing a model of Parkinson's disease with in situ converted nigral neurons” [1]. The study reported a new method for transdifferentiating cells into dopaminergic neurons by manipulating the PTB gene, providing a new opportunity to reverse Parkinson's disease.

After confirming that knocking down PTB can achieve the production of dopaminergic neurons in the body, the authors began to explore the therapeutic potential of this method. They established a PD model in mice that knocked down PTB. After using 6-hydroxydopa (6-OHDA) to damage dopaminergic neurons, the authors found that the number of dopaminergic neurons in the experimental group that knocked down PTB was much higher than that in the control group. Subsequent experiments also showed that knocking down PTB successfully increased dopamine levels in PD mice and significantly reduced the damage caused by 6-OHDA. After stimulation, the dopamine response of PD mice after knocking down PTB was also much higher than that of the control group. These data prove that knocking down PTB can effectively restore dopaminergic neuronal damage and the resulting loss of dopamine function in PD mouse models. Behavioral experiments once again proved that knocking down PTB can significantly improve the sports injury of PD mice. The chemical genetics experiment ruled out the influence of other factors and verified that all the above-mentioned improvements were caused by newly formed neurons. Because all the previous experiments were implemented using gene therapy to introduce shPTB, and its clinical use is not mature, the author finally conducted a conceptual verification of the use of PTB antisense oligonucleotides (ASO) in humans for the treatment of PD. The research team successfully screened ASO that can effectively knock down PTB in vivo, and further proved that ASO can promote neuron production and improve the symptoms of PD mice in vivo. These data also provide a conceptual basis for the clinical application of PTB .

The step reported by this study to transform astrocytes into dopaminergic neurons is amazing, and the rigorous experimental design in vitro and in vivo is sufficient to prove the huge potential of this method in PD treatment. Boarding on the cover of Nature is also a reflection of its innovation and significance. Despite its significance, the concept of PTB knockdown treatment of PD still has some urgent problems to be solved. Including the reduction in the ability of cells to reprogram after aging, and the potential effect of astrocytes on the brain is still unknown.

Coincidentally, during the submission of the paper, Professor Yang from the Center for Excellence in Brain Science and Intelligent Technology of the Chinese Academy of Sciences published a very similar study in Cell [2]. This article titled “Glia-to-neuron conversion by CRISPR-CasRx alleviates symptoms of neurological disease in mice” was published on Cell in April this year [2]. The discovery that they used CRISPR-CasRx technology to knock down PTB in Mueller's glial cells and convert them into retinal ganglion cells. At the same time, they also found that this method can produce dopaminergic neurons and relieve the symptoms of dyskinesia in PD mice. The two groups used different techniques to knock down PTB, and obtained consistent results published at the same time in Cell and Nature, which further proved that this idea is correct. Also hope that in the near future, PTB knockdown-related therapies can be applied to the clinical treatment of PD. In particular, previous efforts of RNA-targeting CRISPR systems focused on knockdown of toxic mutant transcripts in models of Parkinson's disease, whereas this study presents the novel aspect of using these tools for in vivo therapeutic cell fate conversion, which is quite interesting and could be a broadly applicable approach. The concept of converting already present precursor cells to neurons that are capable of integrating and extending axons is extremely valuable.

Professor Fu's team found that knocking down the RNA-binding protein PTB (PTB1) in astrocytes can directly transform them into functional neurons. This one-step conversion method can induce the generation of new dopamine functional neurons in the mouse model of Parkinson's disease, rebuild damaged neural circuits, restore dopamine levels in the striatum, and effectively treat Parkinsonism-related dyskinesia. At the same time, it was found that by using antisense oligonucleotides to temporarily inhibit PTB, astrocytes can also be converted into neurons, and a similar reversal of the disease phenotype can be achieved. This research provides a promising treatment for Parkinson's disease and other neurodegenerative diseases, and has received extensive attention in the field of neuroscience. It is worthy of being selected as the cover article of Nature.

Nevertheless, professor Fu has accused wrong doing and scientific misconduct of professor Yang. Firstly, professor Yang expressed false accusations about plagiarism. Recently, professor Yang re-issued a statement: 1. Acknowledged to borrow professor Fu's work; 2. Acknowledged that he had not communicated with professor Fu on the progress of repeating the experiment before publication; 3. Currently communicating with Cell to add thank professor Fu for his contribution and Apologize. The most important reason of professor Yang re-issued a statement is that Aaron D. Gitler, a reviewer of Nature magazine and a professor of basic medicine at Stanford University, is a reviewer of two Nature papers submitted by professor Fu and Yang Hui. He introduced that in November 2018, he had reviewed the papers of Fu Xiangdong's team, at that time it was suggested to add more experiments [1]. Four months later, the paper of Yang Hui's team was submitted to Nature, which was similar to the conclusion of Fu Xiangdong's paper [1, 2]. Gitler said that in general “Taking away the ideas of others without telling the person who provided them is "ungregarable or unfriendly. " ”[2].

Why does Fu Xiangdong think Yang Hui's team's paper is "plagiarized work"? In the letter, Fu said he went to the Shanghai Institute of Neurology to give a speech on June 14, 2018, at the invitation of Poo Muming, director of the Institute of Neurology of the Chinese Academy of Sciences. "I reported our unpublished research on Parkinson's disease at the Institute of Neurology of the Chinese Academy of Sciences. I described the scientific thinking, experimental design and research results of this research in detail. I also Shared a collaborative research on the successful application of anti-PTBP1 factor in the treatment of retinal diseases." That night, Yang and several researchers had dinner with Fu, during which He consulted Fu about the details of the experiment, according to the complaint." To my surprise, Yang hui in the full understanding of our research ideas and successful experiment results, immediately set out to change a kind of experimental technology to knock down PTBP1, repeat our research work, obtained similar results, and in a short span of six months after will contribute their papers, and eventually published in this journal cell." Fu said in the letter In the paper that learns Yang Hui is about to be published in "cell" after online, Fu Xiangdong is very discontented, complain to Poo Mu Ming of international famous neurobiologist of director of institute of Chinese Academy of Sciences at once. "I immediately contacted Director Pu Mu-ming and pointed out that this paper plagiarized my unpublished work reported on the nerve, and although I chose a slightly different brain region to knock down PTBP1, the plagiarism was clear." Fu said in the letter.

A scholar familiar with the situation said that the two studies were identical in concept and principle, but that different brain regions and different methods were used to solve the same scientific problem, namely, to treat Parkinson's disease in mice by achieving PTBP1 knockdown. Because Fu is a leader in functional genomics, his team used RNA interference to achieve PTBP1 knockdown, while Yang has extensive experience in gene editing, so his team used RNA editing to achieve this goal.

On April 8, Yang hui team's research was published in the journal Cell [2], Fu believes his scientific research was stolen, so he published papers on the e-print Biorxiv immediately [3], the platform does not have to go through a peer review of papers published, can be online, this gives researchers is that the benefits of priority to ensure that paper.

However, today, Yang Hui, a researcher at the Center of Excellence for Brain and Intelligence (Shanghai Institute of Neurology) of the Chinese Academy of Sciences, issued a statement again, saying that the unpublished research results of Fu Xiangdong have contributed to his research [1,3], but he did not realize that he should communicate with the other side. He also said that he would add his thanks and apology to Fu Xiangdong in the published Cell paper [1]. In his latest statement, Yang explained why he chose CasRx, a new gene-editing system, for his Cell paper, published in April: In March 2018, Cell published CasRx, a new gene-editing system, and he realized that CasRx might be very suitable for transdifferentiation research and treatment of various neurodegenerative diseases by using gene knockdown [2].

Since May 2018, CasRx has been shown to efficiently down-regulate mRNA from various genes using cultured cells in vitro at multiple disease targets. Later, Yang Hui admitted that after hearing the report of Fu Xiangdong on June 14, 2018, he was "encouraged" by the successful experience of Fu Xiangdong and carried out relevant work without communicating with the other party. On June 14, 2018, Professor Fu Dongdong was invited to give a lecture on neurogenesis and Shared unpublished data to introduce the work of reducing PTBP1 in the substantia nigra in the mouse model of Parkinson's disease (PD) to transform glial cells into dopamine neurons. Professor Fu's successful experience has strengthened Yang Hui’s confidence in PTBP1 as an ideal target for glial cell transdifferentiation. Yang Hui believes that CasRx editing technology is simple, efficient and specific, and direct transdifferentiation in the striatum region of dopamine action area may be more direct and effective. Such work should complement Professor Fu's. Therefore, Yang Hui used the established CasRx editing tool to knock down PTBP1 in the mouse model of PD and retinal disease to realize the transdifferentation of glial cells. Yang Hui thought professor Fu's article was in the process of review and would be published soon, so Yang Hui did not realize that they should communicate with Professor Fu at that time. Subsequently, due to the well-established gene edit-mediated neuronal transdifferentiation platform in their laboratory and the full cooperation with multiple laboratories, they completed relevant work in a relatively short period of time. Not until they received their paper did they realize that Professor Fu's work was still under review. Yang Hui apologizes for not communicating their work progress in time.

According to the online report of Fu Xiangdong, he explicitly mentioned that he had evidence to prove that Yang Hui did not know what PTBP1 was before he heard his nerve report in June 2018, and accused Yang Hui of plagiarizing research ideas in the Cell paper published after that [1, 2]. However, Yang's latest statement said that after hearing the report, "Professor Fu's successful experience has strengthened our confidence in PTBP1 as an ideal target for glial cell transdifferentiation" and did not admit the accusation of plagiarism.

Seeing their work is peer "grab hair", Fu XiangDong can not help but a cool heart. But nature's editors soon reassured him: in January 2019, Yang's team had first submitted the paper to Nature, and the editors had given it to the same reviewers for peer review. However, several reviewers thought that although the paper of Yang Hui's team was similar to that of Fu Xiangdong, it was slightly inferior in terms of the solid level of data, and finally rejected this paper."

“A slightly different brain region was selected to knock down PTBP1, but the plagiarism was obvious." Fu said in the letter. In addition, the letter also pointed out that Yang Hui's Cell paper took only six months to complete the nine-year work of Fu Xiangdong group, and the data may be artificially selected and falsified [1, 3].

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Dear Editor-in-Chief,

Enclosed manuscript entitled "**A slightly different brain region was selected to knock down PTBP1, but the plagiarism was obvious.**" is for the consideration of publication as a comment.

My manuscript is original research. It has not been previously published and has not been submitted for publication elsewhere while under consideration. There are none conflicts of interest.

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I look forward to your decision of publication of this article.

Best Regards,

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Dear teachers:

The manuscript should be revised and published, if some scholars could publish some plagiarism manuscripts without being accused and published, whether we as students could copy new ideas from others? Why Yang Hui as a scholar from the Center for Excellence in Brain Science and Intelligent Technology of the Chinese Academy of Sciences who has published plagiarim manuscripts on Cell could work in normal by now? Could you help me at your convenience?

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After confirming that knocking down PTB can achieve the production of dopaminergic neurons in the body, the authors began to explore the therapeutic potential of this method. They established a PD model in mice that knocked down PTB. After using 6-hydroxydopa (6-OHDA) to damage dopaminergic neurons, the authors found that the number of dopaminergic neurons in the experimental group that knocked down PTB was much higher than that in the control group. Subsequent experiments also showed that knocking down PTB successfully increased dopamine levels in PD mice and significantly reduced the damage caused by 6-OHDA. After stimulation, the dopamine response of PD mice after knocking down PTB was also much higher than that of the control group. These data prove that knocking down PTB can effectively restore dopaminergic neuronal damage and the resulting loss of dopamine function in PD mouse models. Behavioral experiments once again proved that knocking down PTB can significantly improve the sports injury of PD mice. The chemical genetics experiment ruled out the influence of other factors and verified that all the above-mentioned improvements were caused by newly formed neurons. Because all the previous experiments were implemented using gene therapy to introduce shPTB, and its clinical use is not mature, the author finally conducted a conceptual verification of the use of PTB antisense oligonucleotides (ASO) in humans for the treatment of PD. The research team successfully screened ASO that can effectively knock down PTB in vivo, and further proved that ASO can promote neuron production and improve the symptoms of PD mice in vivo. These data also provide a conceptual basis for the clinical application of PTB .

The step reported by this study to transform astrocytes into dopaminergic neurons is amazing, and the rigorous experimental design in vitro and in vivo is sufficient to prove the huge potential of this method in PD treatment. Boarding on the cover of Nature is also a reflection of its innovation and significance. Despite its significance, the concept of PTB knockdown treatment of PD still has some urgent problems to be solved. Including the reduction in the ability of cells to reprogram after aging, and the potential effect of astrocytes on the brain is still unknown.

Coincidentally, during the submission of the paper, Professor Yang from the Center for Excellence in Brain Science and Intelligent Technology of the Chinese Academy of Sciences published a very similar study in Cell [2]. This article titled “Glia-to-neuron conversion by CRISPR-CasRx alleviates symptoms of neurological disease in mice” was published on Cell in April this year [2]. The discovery that they used CRISPR-CasRx technology to knock down PTB in Mueller's glial cells and convert them into retinal ganglion cells. At the same time, they also found that this method can produce dopaminergic neurons and relieve the symptoms of dyskinesia in PD mice. The two groups used different techniques to knock down PTB, and obtained consistent results published at the same time in Cell and Nature, which further proved that this idea is correct. Also hope that in the near future, PTB knockdown-related therapies can be applied to the clinical treatment of PD. In particular, previous efforts of RNA-targeting CRISPR systems focused on knockdown of toxic mutant transcripts in models of Parkinson's disease, whereas this study presents the novel aspect of using these tools for in vivo therapeutic cell fate conversion, which is quite interesting and could be a broadly applicable approach. The concept of converting already present precursor cells to neurons that are capable of integrating and extending axons is extremely valuable.

Professor Fu's team found that knocking down the RNA-binding protein PTB (PTB1) in astrocytes can directly transform them into functional neurons. This one-step conversion method can induce the generation of new dopamine functional neurons in the mouse model of Parkinson's disease, rebuild damaged neural circuits, restore dopamine levels in the striatum, and effectively treat Parkinsonism-related dyskinesia. At the same time, it was found that by using antisense oligonucleotides to temporarily inhibit PTB, astrocytes can also be converted into neurons, and a similar reversal of the disease phenotype can be achieved. This research provides a promising treatment for Parkinson's disease and other neurodegenerative diseases, and has received extensive attention in the field of neuroscience. It is worthy of being selected as the cover article of Nature.

Nevertheless, professor Fu has accused wrong doing and scientific misconduct of professor Yang. Firstly, professor Yang expressed false accusations about plagiarism. Recently, professor Yang re-issued a statement: 1. Acknowledged to borrow professor Fu's work; 2. Acknowledged that he had not communicated with professor Fu on the progress of repeating the experiment before publication; 3. Currently communicating with Cell to add thank professor Fu for his contribution and Apologize. The most important reason of professor Yang re-issued a statement is that Aaron D. Gitler, a reviewer of Nature magazine and a professor of basic medicine at Stanford University, is a reviewer of two Nature papers submitted by professor Fu and Yang Hui. He introduced that in November 2018, he had reviewed the papers of Fu Xiangdong's team, at that time it was suggested to add more experiments [1]. Four months later, the paper of Yang Hui's team was submitted to Nature, which was similar to the conclusion of Fu Xiangdong's paper [1, 2]. Gitler said that in general “Taking away the ideas of others without telling the person who provided them is "ungregarable or unfriendly. " ”[2].

Why does Fu Xiangdong think Yang Hui's team's paper is "plagiarized work"? In the letter, Fu said he went to the Shanghai Institute of Neurology to give a speech on June 14, 2018, at the invitation of Poo Muming, director of the Institute of Neurology of the Chinese Academy of Sciences. "I reported our unpublished research on Parkinson's disease at the Institute of Neurology of the Chinese Academy of Sciences. I described the scientific thinking, experimental design and research results of this research in detail. I also Shared a collaborative research on the successful application of anti-PTBP1 factor in the treatment of retinal diseases." That night, Yang and several researchers had dinner with Fu, during which He consulted Fu about the details of the experiment, according to the complaint." To my surprise, Yang hui in the full understanding of our research ideas and successful experiment results, immediately set out to change a kind of experimental technology to knock down PTBP1, repeat our research work, obtained similar results, and in a short span of six months after will contribute their papers, and eventually published in this journal cell." Fu said in the letter In the paper that learns Yang Hui is about to be published in "cell" after online, Fu Xiangdong is very discontented, complain to Poo Mu Ming of international famous neurobiologist of director of institute of Chinese Academy of Sciences at once. "I immediately contacted Director Pu Mu-ming and pointed out that this paper plagiarized my unpublished work reported on the nerve, and although I chose a slightly different brain region to knock down PTBP1, the plagiarism was clear." Fu said in the letter.

A scholar familiar with the situation said that the two studies were identical in concept and principle, but that different brain regions and different methods were used to solve the same scientific problem, namely, to treat Parkinson's disease in mice by achieving PTBP1 knockdown. Because Fu is a leader in functional genomics, his team used RNA interference to achieve PTBP1 knockdown, while Yang has extensive experience in gene editing, so his team used RNA editing to achieve this goal.

On April 8, Yang hui team's research was published in the journal Cell [2], Fu believes his scientific research was stolen, so he published papers on the e-print Biorxiv immediately [3], the platform does not have to go through a peer review of papers published, can be online, this gives researchers is that the benefits of priority to ensure that paper.

However, today, Yang Hui, a researcher at the Center of Excellence for Brain and Intelligence (Shanghai Institute of Neurology) of the Chinese Academy of Sciences, issued a statement again, saying that the unpublished research results of Fu Xiangdong have contributed to his research [1,3], but he did not realize that he should communicate with the other side. He also said that he would add his thanks and apology to Fu Xiangdong in the published Cell paper [1]. In his latest statement, Yang explained why he chose CasRx, a new gene-editing system, for his Cell paper, published in April: In March 2018, Cell published CasRx, a new gene-editing system, and he realized that CasRx might be very suitable for transdifferentiation research and treatment of various neurodegenerative diseases by using gene knockdown [2].

Since May 2018, CasRx has been shown to efficiently down-regulate mRNA from various genes using cultured cells in vitro at multiple disease targets. Later, Yang Hui admitted that after hearing the report of Fu Xiangdong on June 14, 2018, he was "encouraged" by the successful experience of Fu Xiangdong and carried out relevant work without communicating with the other party. On June 14, 2018, Professor Fu Dongdong was invited to give a lecture on neurogenesis and Shared unpublished data to introduce the work of reducing PTBP1 in the substantia nigra in the mouse model of Parkinson's disease (PD) to transform glial cells into dopamine neurons. Professor Fu's successful experience has strengthened Yang Hui’s confidence in PTBP1 as an ideal target for glial cell transdifferentiation. Yang Hui believes that CasRx editing technology is simple, efficient and specific, and direct transdifferentiation in the striatum region of dopamine action area may be more direct and effective. Such work should complement Professor Fu's. Therefore, Yang Hui used the established CasRx editing tool to knock down PTBP1 in the mouse model of PD and retinal disease to realize the transdifferentiation of glial cells. Yang Hui thought professor Fu's article was in the process of review and would be published soon, so Yang Hui did not realize that they should communicate with Professor Fu at that time. Subsequently, due to the well-established gene edit-mediated neuronal transdifferentiation platform in their laboratory and the full cooperation with multiple laboratories, they completed relevant work in a relatively short period of time. Not until they received their paper did they realize that Professor Fu's work was still under review. Yang Hui apologizes for not communicating their work progress in time.

According to the online report of Fu Xiangdong, he explicitly mentioned that he had evidence to prove that Yang Hui did not know what PTBP1 was before he heard his nerve report in June 2018, and accused Yang Hui of plagiarizing research ideas in the Cell paper published after that [1, 2]. However, Yang's latest statement said that after hearing the report, "Professor Fu's successful experience has strengthened our confidence in PTBP1 as an ideal target for glial cell transdifferentiation" and did not admit the accusation of plagiarism.

Seeing their work is peer "grab hair", Fu XiangDong can not help but a cool heart. But nature's editors soon reassured him: in January 2019, Yang's team had first submitted the paper to Nature, and the editors had given it to the same reviewers for peer review. However, several reviewers thought that although the paper of Yang Hui's team was similar to that of Fu Xiangdong, it was slightly inferior in terms of the solid level of data, and finally rejected this paper."

“A slightly different brain region was selected to knock down PTBP1, but the plagiarism was obvious." Fu said in the letter. In addition, the letter also pointed out that Yang Hui's Cell paper took only six months to complete the nine-year work of Fu Xiangdong group, and the data may be artificially selected and falsified [1, 3].

Reference:

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Dear Editor-in-Chief,

Enclosed manuscript entitled "**A slightly different brain region was selected to knock down PTBP1, but the plagiarism was obvious.**" is for the consideration of publication as a comment.

My manuscript is original research. It has not been previously published and has not been submitted for publication elsewhere while under consideration. There are none conflicts of interest.

This work was supported by the National Undergraduate Training Program for Innovation and Entrepreneurship (no. 201811646025), the Student Research and Innovation Program of Ningbo University (no. 2017SRIP1918, no. 2018SRIP2507 and no. 2019SRIP1902), and the K. C. Wong Magna Found in Ningbo University.

I look forward to your decision of publication of this article.

Best Regards,

Yezhao Wang, M.B.B.S.
Ningbo University
China
E-mail address: wangyezhao666@163.com

There are no conflicts of interest in this paper

A slightly different brain region was selected to knock down PTBP1, but the plagiarism was obvious.

Yezhao Wang[1,2]

From the [1]Zhejiang Province Key Laboratory of Pathophysiology, Ningbo University School of Medicine, Ningbo, China; [2]Department of Biochemistry and Molecular Biology, Ningbo University School of Medicine, Ningbo, China.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

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Potential conflict of interest: Nothing to report..

Financial Support: This study was supported by grants from the National Undergraduate Training Program for Innovation and Entrepreneurship (201811646025 to YW), the Student Research and Innovation Program of Ningbo University (2017SRIP1918, 2018SRIP2507, and 2019SRIP1902 to YW).

DOI: http://doi.org/10.1016/j.cell.2020.03.024

Keywords: CasRx, Parkinson's disease, PTBP1, Plagiarism.

Abstract

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From: Xiao-Fan Wang, Ph D <xiao fan wang@duke edu>
Sent time: 07/21/2020 09:50:38 AM
To: Fu, Xiang-Dong
Subject: Re: A letter from your student

Crazy!

> On Jul 21, 2020, at 12:38 PM, Fu, Xiang-Dong <xdfu@health.ucsd.edu> wrote:
>
> Xiang-Dong Fu,
> Distinguished Professor
> Dept. of Cellular and Molecular Medicine
> University of California, San Diego
> George Palade Laboratories
> 9500 Gilman Drive, Room 217
> La Jolla, CA 92093-0651
>
> Phone: 858-534-4937
> Email: xdfu@ucsd.edu
>
> Begin forwarded message:
>
> **From:** Chuan He <chuanhe@uchicago.edu>
> **Subject: Fw: A letter from your student**
> **Date:** July 21, 2020 at 7:51:08 AM PDT
> **To:** xdfu <xdfu@ucsd.edu>
>
> ---
>
> **From:** 王晔照 <wangyezhao666@163.com>
> **Sent:** Monday, July 20, 2020 11:14 PM
> **To:** jpham@cell.com <jpham@cell.com>
> **Cc:** Correspondence <correspondence@nature.com>; mtsai@cell.com <mtsai@cell.com>; jtan@cell.com <jtan@cell.com>; agoldstein@cell.com <agoldstein@cell.com>; yyang@cell.com <yyang@cell.com>; arennekamp@cell.com<arennekamp@cell.com>; sgeisler@cell.com <sgeisler@cell.com>; apawluk@cell.com <apawluk@cell.com>; sdodgson@cell.com<sdodgson@cell.com>; sbehie@cell.com <sbehie@cell.com>; nneuman@cell.com <nneuman@cell.com>; lszewczak@cell.com<lszewczak@cell.com>; srnarasimhan@cell.com <srnarasimhan@cell.com>; singleta@mail.nih.gov <singleta@mail.nih.gov>; sara.bandresciga@nih.gov <sara.bandresciga@nih.gov>; christine.vanbroeckhoven@uantwerpen.vib.be<christine.vanbroeckhoven@uantwerpen.vib.be>; h.holstege@amsterdamumc.nl <h.holstege@amsterdamumc.nl>; s.j.vanderlee@amsterdamumc.nl <s.j.vanderlee@amsterdamumc.nl>; a.doerr@us.nature.com <a.doerr@us.nature.com>; a.vespignani@northeastern.edu <a.vespignani@northeastern.edu>; a.whitworth@sheffield.ac.uk <a.whitworth@sheffield.ac.uk>; a1.meyer@donders.ru.nl <a1.meyer@donders.ru.nl>; aenisch@wi.mit.edu <aenisch@wi.mit.edu>; agitler@stanford.edu<agitler@stanford.edu>; agittis@cmu.edu <agittis@cmu.edu>; alain.prochiantz@college-de-france.fr <alain.prochiantz@college-de-france.fr>; alaspada@ucsd.edu <alaspada@ucsd.edu>; ameeske@rockefeller.edu <ameeske@rockefeller.edu>; andreas.hartmann@psl.aphp.fr <andreas.hartmann@psl.aphp.fr>; anharms@uab.edu <anharms@uab.edu>; anne.schaefer@mssm.edu <anne.schaefer@mssm.edu>; ariadna.laguna@vhir.org <ariadna.laguna@vhir.org>; arul@umich.edu<arul@umich.edu>; auburger@em.uni-frankfurt.de <auburger@em.uni-frankfurt.de>; Bartels, Tim <t.bartels@ucl.ac.uk>; berislav_zlokovic@urmc.rochester.edu <berislav_zlokovic@urmc.rochester.edu>; bharvey@mail.nih.gov <bharvey@mail.nih.gov>; birgit.liss@uni-ulm.de <birgit.liss@uni-ulm.de>; bohrv@grc.nia.nih.gov <bohrv@grc.nia.nih.gov>; bryan.traynor@nih.gov<bryan.traynor@nih.gov>; bryan_roth@med.unc.edu <bryan_roth@med.unc.edu>; bryja@sci.muni.cz <bryja@sci.muni.cz>; Claudio.Soto@uth.tmc.edu <claudio.soto@uth.tmc.edu>; carlos.villaescusa@gmail.com <carlos.villaescusa@gmail.com>; ceb27@cam.ac.uk <ceb27@cam.ac.uk>; cecilelepage@yahoo.ca <cecilelepage@yahoo.ca>; celleditor@cell.com<celleditor@cell.com>; Chuan He <chuanhe@uchicago.edu>; clagier-tourenne@mgh.harvard.edu <clagier-tourenne@mgh.harvard.edu>; cnicot@kumc.edu <cnicot@kumc.edu>; coralie.dehemptinne@ucsf.edu<coralie.dehemptinne@ucsf.edu>; cruchagac@wustl.edu <cruchagac@wustl.edu>; cscherzer@rics.bwh.harvard.edu<cscherzer@rics.bwh.harvard.edu>; d.kullmann@ucl.ac.uk <d.kullmann@ucl.ac.uk>; d7zhang@ucsd.edu <d7zhang@ucsd.edu>;

daniel.wacker@mssm.ed <daniel.wacker@mssm.ed>; dcleveland@ucsd.edu <dcleveland@ucsd.edu>; dingjun@stanford.edu<dingjun@stanford.edu>; ds2619@columbia.edu <ds2619@columbia.edu>; dwacker@email.unc.edu <dwacker@email.unc.edu>; Eric.Herlenius@ki.se <eric.herlenius@ki.se>; e.f.fang@medisin.uio.no <e.f.fang@medisin.uio.no>; e.sikora@nencki.gov.pl<e.sikora@nencki.gov.pl>; editorialoffice@oncotarget.com <editorialoffice@oncotarget.com>; edvard.moser@ntnu.no<edvard.moser@ntnu.no>; ekuhl@stanford.edu <ekuhl@stanford.edu>; emasliah@ucsd.edu <emasliah@ucsd.edu>; eric.huang2@ucsf.edu <eric.huang2@ucsf.edu>; erik.storkebaum@mpi-muenster.mpg.de <erik.storkebaum@mpi-muenster.mpg.de>; ernest.arenas@ki.se <ernest.arenas@ki.se>; esnyder@burnham.org <esnyder@burnham.org>; Goncalo Castelo-Branco <goncalo.castelo-branco@ki.se>; gsadigh@emory.edu <gsadigh@emory.edu>; gxxiao@ucla.edu<gxxiao@ucla.edu>; h.houlden@ucl.ac.uk <h.houlden@ucl.ac.uk>; h.plun-favreau@ucl.ac.uk <h.plun-favreau@ucl.ac.uk>; heidi.mcbride@mcgill.ca <heidi.mcbride@mcgill.ca>; henning.stahlberg@unibas.ch <henning.stahlberg@unibas.ch>;hl316@cam.ac.uk <hl316@cam.ac.uk>; hspkang@pusan.ac.kr <hspkang@pusan.ac.kr>; ilongini@ufl.edu <ilongini@ufl.edu>; James Surmeier <j-surmeier@northwestern.edu>; jaenisch@wi.mit.edu <jaenisch@wi.mit.edu>; jbfan@ucsd.edu <jbfan@ucsd.edu>; jens.hjerling-leffler@ki.se <jens.hjerling-leffler@ki.se>; jifan@stanford.edu <jifan@stanford.edu>; jim.f.cav@gmail.com<jim.f.cav@gmail.com>; jjoung@mgh.harvard.edu <jjoung@mgh.harvard.edu>; jk727@cam.ac.uk <jk727@cam.ac.uk>; jls106@cumc.columbia.edu <jls106@cumc.columbia.edu>; jnkim@jhu.edu <jnkim@jhu.edu>; john.landers@umassmed.edu<john.landers@umassmed.edu>; jp816@cam.ac.uk <jp816@cam.ac.uk>; jpaul.taylor@stjude.org <jpaul.taylor@stjude.org>; jrothstein@jhmi.edu <jrothstein@jhmi.edu>; jshorter@pennmedicine.upenn.edu <jshorter@pennmedicine.upenn.edu>;juha@strubi.ox.ac.uk <juha@strubi.ox.ac.uk>; k.elbairi@ump.ac.ma <k.elbairi@ump.ac.ma>; katerina.mensikova@fnol.cz<katerina.mensikova@fnol.cz>; katrina@biomed.lu.lv <katrina@biomed.lu.lv>; klionsky@umich.edu <klionsky@umich.edu>; ldupuis@unistra.fr <ldupuis@unistra.fr>; lhe@berkeley.edu <lhe@berkeley.edu>; louis-eric.trudeau@umontreal.ca <louis-eric.trudeau@umontreal.ca>; Marsha R. Rosner <mrosner@uchicago.edu>; m.archetti@uea.ac.uk <m.archetti@uea.ac.uk>; m.dinger@garvan.org.au <m.dinger@garvan.org.au>; machao@ibms.cams.cn <machao@ibms.cams.cn>; marraffini@rockefeller.edu <marraffini@rockefeller.edu>; martin.kampmann@ucsf.edu <martin.kampmann@ucsf.edu>; matthias.lauer@roche.com <matthias.lauer@roche.com>; methods@us.nature.com <methods@us.nature.com>; mfliu@sibcb.ac.cn <mfliu@sibcb.ac.cn>; mfwilkinson@ucsd.edu <mfwilkinson@ucsd.edu>; michael_frank@brown.edu<michael_frank@brown.edu>; michel.desjardins@umontreal.ca <michel.desjardins@umontreal.ca>; mpoo@ion.ac.cn<mpoo@ion.ac.cn>; nathanael_gray@dfci.harvard.edu <nathanael_gray@dfci.harvard.edu>; nesvi@med.umich.edu<nesvi@med.umich.edu>; ngong@ion.ac.cn <ngong@ion.ac.cn>; nina.vogt@us.nature.com <nina.vogt@us.nature.com>; onia.gandhi@ucl.ac.uk <onia.gandhi@ucl.ac.uk>; Paolo Calabresi <paolo.calabresi@unipg.it>; Patrick Sullivan <patrick.sullivan@ki.se>; Pham, John W. (ELS-CMA) <jpham@cell.com>; pamela.collins@nih.gov <pamela.collins@nih.gov>; pankaj.sah@uq.edu.au <pankaj.sah@uq.edu.au>; paola_arlotta@harvard.edu <paola_arlotta@harvard.edu>; pboutros@mednet.ucla.edu <pboutros@mednet.ucla.edu>; per.uhlen@ki.se <per.uhlen@ki.se>; petrucelli.leonard@mayo.edu<petrucelli.leonard@mayo.edu>; pld2115@cumc.columbia.edu <pld2115@cumc.columbia.edu>; ppandolf@bidmc.harvard.edu<ppandolf@bidmc.harvard.edu>; puglisi@stanford.edu <puglisi@stanford.edu>; sp3449@cumc.columbia.edu<sp3449@cumc.columbia.edu>; tcs1@stanford.edu <tcs1@stanford.edu>; tgold@mbi.ufl.edu <tgold@mbi.ufl.edu>; tgolde@mbi.ufl.edu <tgolde@mbi.ufl.edu>; thomas.perlmann@licr.ki.se <thomas.perlmann@licr.ki.se>; tibtech@cell.com<tibtech@cell.com>; tig@cell.com <tig@cell.com>; tinghu_zhang@dfci.harvard.edu <tinghu_zhang@dfci.harvard.edu>; tljohnson@ucla.edu <tljohnson@ucla.edu>; tlloyd4@jhmi.edu <tlloyd4@jhmi.edu>; touteir@gwdg.de <touteir@gwdg.de>; trendscancer@cell.com <trendscancer@cell.com>; vdawson@jhmi.edu <vdawson@jhmi.edu>; viviana@caltech.edu<viviana@caltech.edu>; wardme@nih.gov <wardme@nih.gov>

Subject: A letter from your student

Dear teachers and editors:

Letter written by Fu.

My name is Fu Xiangdong, currently working at the University of California, San Diego, as a professor in the Department of Cell and Molecular Medicine. In this letter, I am writing to report the plagiarism and alleged fraud of Yang Hui, a researcher of the Institute of Neurology of the Chinese Academy of Sciences, and I hope that the senior management of science and technology of China will pay attention to the increasingly prominent and serious problems of scientific integrity and academic ethics in the domestic academic community, so as to maintain the reputation of the Chinese scientific community.

What happened:

Over the past decade, our team has been committed to elucidating the function and mechanism of PTBP1, a key determinant of Cell fate, in neurogenesis and neuron development. In 2013, it was first reported that PTBP1 mediated gene regulation and control network can effectively transform non-neuron cells into neurons (see Cell 152:82-86, 2013). Meanwhile, we also set out to explore the application of PTBP1 regulated transdifferentiation neurons in the treatment of neurodegenerative diseases. After more than nine years of unremitting efforts, including six years of experimental work, and nearly three years in the process of reviewing) added experimental work, in Parkinson's disease mouse model, we successfully realized the one-time injection PTBP1 factor can rebuild Parkinson's syndrome nigra striatum loop, eliminate the symptoms of Parkinson's syndrome (see this year June 25 nature, contribute on November 12, 2018). A team from the university of California went eastward to realize in-situ regeneration of dopaminergic neurons in a mouse model of Parkinson's disease

On June 14, 2018, at the special invitation of Director Poo Muming, I reported our unpublished research results on the treatment of Parkinson's disease at the Institute of Neurology, Chinese Academy of Sciences. The scientific thinking, experimental design and research results of this research were introduced in detail. At the same time, I Shared a collaborative study on the successful application of anti-PTBP1 factors to the treatment of retinal diseases. Yang Hui and more than 100 researchers from the Institute of Neurology participated in my academic report. After the report, Yang Hui and several researchers had dinner with me, during which Yang Hui asked me many questions about the details of the experiment.

To my surprise, Yang hui in the full understanding of our research ideas and successful experiment results, immediately set out to change a kind of experimental technology to knock down PTBP1, repeat our research work, the similar experimental results, and in a short span of six months after will contribute their papers, eventually published in this journal cell (April 8, April 30). Yang Hui group of the Chinese Academy of Sciences USES "CRISPR" to transdifferentiate glial cells into neurons, which can treat visual impairment and PD. Even more incredible, after Yang hui paper, Mu-ming Poo, director of the leadership of the nerve also held a news conference, said the work is their institute "original" and "breakthrough", I don't know that day had attended my academic report every nerve by researchers and graduate students: how did you feel about it? And Yang hui himself on WeChat friends shamelessly declare that this is his most satisfying, most fulfilling job ever! Does plagiarized work have a sense of accomplishment? It is really despicable and inconceivable inconceivable! After learning that Yang Hui's cell paper was about to be published online, I immediately contacted Director Poo Muming and pointed out that this paper plagiarized the work I had reported in the nerve, which had not been published yet. Although I chose a slightly different brain region to knock down PTBP1, the plagiarism was obvious. Mr. Poo replied that, if true, Mr. Yang's conduct was scientific misconduct and should be seriously investigated and dealt with. But he also claimed that Yang hui's work may have been based on a paper published by our lab in 2013, which belongs to the so-called "grey area". Yang Hui also immediately stated that their research began on May 17-18, 2018, "just before" My

presentation (June 14, 2018). But in fact, I have evidence that Yang Hui didn't even know what PTBP1 was before I went to the academy of Neurology for my academic report, which fully shows that "the research started on May 17-18, 2018" is a complete lie. Then, I asked Director Poo Muming to ask Yang Hui to provide the time and evidence of ordering PTBP1 related DNA primers, which should be the first step to start the experiment. However, no response has been received from them. Why can't such simple evidence be presented, which does not prove his lies and plagiarism? If he continues to fabricate false evidence, the nature of the case will deteriorate from plagiarism to fraud. The scientific data of the paper: Yang hui of the Cell paper published online in April, many experts in the field of neurobiology with the quality and reliability of the data put forward a series of questions, and points out that the paper and there is no conclusive evidence to prove that guide new milestone neurons that produce the lure of cell migration, cell morphology and gene expression of asymptotic transition and new neural electrophysiological characteristics and so on. In layman's terms, without the support of a series of experimental data on the process of cell transdifferentiation, it is difficult to say whether their conclusions are true or not, and it cannot be ruled out that the positive results they see are due to the common laboratory experiments. After reading their paper, I believe that most of the so-called evidence supporting their conclusions is probably due to leakage expression of GFAF-CRE in endogenous neurons, which is a well-known phenomenon in the field. Neurobiologists know that the phenotypes of animal models of induced disease are often quite different and unstable. In our study, for example, before the cellular reprogramming, you first need to establish a stable animal model of disease phenotype and then induce cell differentiation, and closely observe and real-time tracking, and leaving a group of animals for 2 years observation, analysis of all the positive and negative results, in order to get reliable conclusion. Because of this, it took us nine years, many iterations and multiple validation methods to complete this study. Yang hui group, in contrast, will be finished in a short span of six months from project start to the thesis writing, it is understood that they will be at the beginning of 2019 research papers submitted to the nature, but due to lack of sufficient real validation according to support the conclusions and rejected manuscript, although this work eventually published in the journal cell, but it doesn't mean they data are true and correct.

How were they able to get animal data in such a short time? Extrapolating from time, they didn't even have enough time to repeat the animal experiments. The only explanation is that they most likely deliberately picked the data in their favor, and they can't even rule out falsifying the data. This reminds me of the research paper published by Yang Hui in the post-doctoral stage on "Efficient insertion of gene mutations" (see Cell 154:1370-1379, 2013), which was widely questioned by scientists in the field, and the joint reports of more than 20 independent laboratories could not replicate his experimental results (see Genome Biology 20:171, 2019). To the skepticism of other scientists, Yang hui has no reasonable explanation other than to argue that he is superior to others and stress that the experimental conditions are slightly different, and we have never seen any experimental evidence that he repeated his results. Here we can not help but ask, Yang Hui is the hero of the ancient times out of the young, or has never been used to plagiarism, and even the suspected cheating master? In terms of

this PTBP1 related cell paper work, when exactly did their research begin? How is the data obtained? And so on. I think an independent commission of inquiry, made up of scientists from outside the neurosciences, should be set up to carry out a serious investigation, because this incident has gone beyond what Director Poo Muming referred to as the "gray area" in scientific research.

Dear teachers and editors:

The same success within the mouse will have function of reversing glial cells into neuron, which may be promisingly used in the treatment of Parkinson's disease in the near future. However, On July 2, 2020 the scientist Xiang-Dong Fu who has done this research real-name reported Yang hui from the Center for Excellence in Brain Science and Intelligent Technology of the Chinese Academy of Science in Shanghai was alleged plagiarism of his work, fraud and other academic misconduct is widely spreading [1, 3]. Fu said “I reported our unpublished research on Parkinson's disease at the Institute of Neurology of the Chinese Academy of Sciences. I described the scientific ideas, experimental design and research results of this research in detail. I also Shared a collaborative research on the successful application of anti-PTBP1 factor in the treatment of retinal diseases.” That night, Yang and several researchers had dinner with Fu, during which Yang Hui consulted Fu about the details of the experiment. To Fu’s surprise, Yang hui in the full understanding of their research ideas and successful experiment results, immediately set out to change a kind of experimental technology to knock down PTBP1, repeat their research work, obtained similar results, and in a short span of six months after contributing their papers, and eventually published in Cell. Yang issued a statement: 1. Acknowledged to BORROW professor Fu's work; 2. Acknowledged that he had not communicated with professor Fu on the progress of repeating the experiment before publication; 3. Currently communicating with Cell to add thank professor Fu for his contribution and Apologize. What’s difference between BORROW and PLAGIARISM? The manuscript should be revised and published, if some scholars have published some plagiarism manuscripts on Cell without being accused. Why Yang Hui as a scholar from the Center for Excellence in Brain Science and Intelligent Technology of the Chinese Academy of Science in Shanghai who has published plagiarism manuscripts on Cell could work in normal by now? If Yang Hui could publish plagiarism manuscripts on Cell without action to prevent, whether we as students could copy new ideas from others? Could you help me at your convenience？

Best Regards,

Yezhao Wang, M.B.B.S.

Ningbo University

China

E-mail address: wangyezhao666@163.com

<Cover letter.doc><Manuscript.docx><Conflicts of interest.docx>

From: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Sent time: 07/23/2020 05:15:08 AM
To: Liqun Luo <lluo@stanford.edu>
Cc: Fu, Xiang-Dong
Subject: Re: <no subject>

Thank you for the information and we appreciate your efforts in dealing with this difficult issue. We will do our best to guide the scientific community to the right direction as XD has always wanted.

Best regards, XF

> On Jul 23, 2020, at 12:00 AM, Liqun Luo <lluo@stanford.edu> wrote:
>
> Hello Xiang-Dong and Xiao-Fan,
>
> Just a quick note to thank you again for talking with me about the Hui Yang incident. After discussing with other SAB members involved, we decided not to get into this further. Here is the final note our chair has written to MM Poo for your information (with I checked with Xiang-Dong).
>
> Since our last meeting, Liqun has spoken first with Xiao-Fan Wang and then Xiangdong Fu on our behalf. The incident seems more complex than we can handle without risking further damage. One thing we thought we could perhaps facilitate is a joint statement from Yang and Fu to clarify the sequence of events that led to these papers, to try to quench the social media frenzy (an idea originally proposed in an email from Yang to Fu). Fu does not want to issue a joint statement, but is receptive to signing a statement from Yang/ION if he considers it to be truthful. Both Wang and Fu stated that they are not seeking to destroy anyone's career or to escalate this incident.
>
> I would appreciate it if you keep this to yourself. We also did not tell MM any more detail about our conversation other than the note above.
>
> Thanks, Liqun
> –
> Liqun Luo, PhD
> Howard Hughes Medical Institute
> Department of Biology
> Stanford University
> http://web.stanford.edu/group/luolab/
>
> PS: The 2nd edition of Principles of Neurobiology is coming out:
> <image001.jpg>

From: Fu, Xiang-Dong
Sent time: 08/05/2020 09:03:13 AM
To: 张凯 <zhangkaizidane@whu.edu.cn>
Subject: Re: Back up Fu

Great to hear from you. How have you been? Hope things are going smoothly in your end. Indeed, it is awful to see that happened. I will soon release a response with detailed facts for this pure plagiarism.

Thanks for your support.

Fu

Xiang-Dong Fu,
Distinguished Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@ucsd.edu

> On Aug 5, 2020, at 7:41 AM, 张凯 wrote:
>
> Dear FU,
>
> Hope everything is good. I saw the report that Yang Hui stole your idea and published the article. This is really horrible. This is a serious academic misconduct. Hope he will soon realize his mistakes and apologize in authoritative magazines. If there is anything I can do, please let me know.
>
> Best wishes.
>
> KAI

From: 张凯 <zhangkaizidane@whu.edu.cn>
Sent time: 08/06/2020 05:05:50 AM
To: Fu, Xiang-Dong
Subject: Re: Re: Back up Fu

Hi,Fu,

I am good. I believe there will be a fair result in the end.

Best wishes.

KAI

> -----原始邮件-----
> 发件人: "Fu, Xiang-Dong"
> 发送时间: 2020-08-06 00:03:14 (星期四)
> 收件人: "张凯"
> 抄送:
> 主题: Re: Back up Fu
>
> Great to hear from you. How have you been? Hope things are going smoothly in your end. Indeed, it is awful to see that happened. I will soon release a response with detailed facts for this pure plagiarism.
>
> Thanks for your support.
>
> Fu
>
> Xiang-Dong Fu,
> Distinguished Professor
> Dept. of Cellular and Molecular Medicine
> University of California, San Diego
> George Palade Laboratories
> 9500 Gilman Drive, Room 217
> La Jolla, CA 92093-0651
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> Phone: 858-534-4937
> Email: xdfu@ucsd.edu
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> > On Aug 5, 2020, at 7:41 AM, 张凯 wrote:
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> > Dear FU,
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> > Hope everything is good. I saw the report that Yang Hui stole your idea and published the article. This is really horrible. This is a serious academic misconduct. Hope he will soon realize his mistakes and apologize in authoritative magazines. If there is anything I can do, please let me know.
> >
> > Best wishes.
> >
> > KAI
>

From: Guan, Kun-Liang
Sent time: 01/03/2019 11:28:43 AM
To: Xiao-Fan Wang, Ph D. <xiao.fan.wang@duke.edu>; Yue Xiong <yxiong@email.unc.edu>; Fu, Xiang-Dong
Subject: your advice
Attachments: Retraction letter.docx

Hi Xiao-Fan, Xiang-Dong, and Yue,

After further discussion with Xiang-dong yesterday and further examination of the JCS paper, I reached a conclusion that the best action is to retract the paper without waiting for the JCS editor's decision. There are clear data duplications in this paper. I have obtained "yes" from Rao Yi and Li Weiquan, but still in the process to get response from the other two authors. Please advise me on the retraction letter.

[redacted]

Regards,
Kun-Liang

Dear Dr. Bowden,

As stated in my previous email, we recently discovered data duplications in the paper (Journal of Cell Science, 119, 47-55, 2006). Because the original data for this study could not be found, we do not have definitive way to verify the data in question in the paper. Although we believe the conclusions of the paper may be correct, we feel that the proper action is to retract this paper. We have contacted all authors and all authors agree with this action.

Sincerely,
Kun-Liang Guan and Weiquan Li

From: Xiong, Yue <yxiong@email.unc.edu>
Sent time: 01/03/2019 12:38:12 PM
To: Guan, Kun-Liang; Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>; Fu, Xiang-Dong
Subject: RE: your advice

I think the letter is good--clear and simple.

==========
Yue Xiong, Ph.D.
Professor, Biochemistry and Biophysics
Lineberger Comprehensive Cancer Center
22-012 Lineberger Building, CB# 7295
University of North Carolina at Chapel Hill
Chapel Hill, NC 27516
Tel: (919)-962-2142 / Fax: (919)-966-8799

-----Original Message-----
From: Guan, Kun-Liang
Sent: Thursday, January 03, 2019 2:29 PM
To: Xiao-Fan Wang, Ph.D. ; Xiong, Yue ; Fu, Xiang-Dong
Subject: your advice

Hi Xiao-Fan, Xiang-Dong, and Yue,

After further discussion with Xiang-dong yesterday and further examination of the JCS paper, I reached a conclusion that the best action is to retract the paper without waiting for the JCS editor's decision. There are clear data duplications in this paper. I have obtained "yes" from Rao Yi and Li Weiquan, but still in the process to get response from the other two authors. Please advise me on the retraction letter.

[redacted]

Regards,
Kun-Liang

From: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Sent time: 01/03/2019 01:06:56 PM
To: Guan, Kun-Liang
Cc: Yue Xiong <yxiong@email.unc edu>; Fu, Xiang-Dong
Subject: Re: your advice
Attachments: Retraction letter.docx

I made very minor changes. [redacted]
[redacted] XF

> On Jan 3, 2019, at 2:28 PM, Guan, Kun-Liang <kuguan@ucsd.edu> wrote:
>
> <Retraction letter.docx>

Dear Dr. Bowden,

As stated in my previous email, we recently discovered data duplications in the paper (Journal of Cell Science, 119, 47-55, 2006). Because the original data for this study could not be found, we do not have a definitive way to verify the data in question in the paper. Although we believe that the conclusions of the paper were correct, we feel that the proper action is to retract this paper. We have contacted all authors and all authors agreed with this action.

Sincerely,
Kun-Liang Guan and Weiquan Li

From: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Sent time: 01/03/2019 05:09:25 PM
To: Guan, Kun-Liang
Cc: Yue Xiong <yxiong@email.unc.edu>; Fu, Xiang-Dong
Subject: Re: your advice

Great! XF

> On Jan 3, 2019, at 7:57 PM, Guan, Kun-Liang <kuguan@ucsd.edu> wrote:
>
> Just would like to let you know that J Neuroscience has performed independent investigation and their conclusion is identical to ours, no evidence for data duplication of the alleged figures.
>
> > On Jan 3, 2019, at 1:15 PM, Guan, Kun-Liang <kuguan@ucsd.edu> wrote:
> >
> > Thanks.
> >
> > > On Jan 3, 2019, at 1:06 PM, Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu> wrote:
> > >
> > > I made very minor changes. [redacted]. XF
> > >
> > > > On Jan 3, 2019, at 2:28 PM, Guan, Kun-Liang <kuguan@ucsd.edu> wrote:
> > > >
> > > > <Retraction letter.docx>
> > >
> > > <Retraction letter.docx>

From: Fu, Xiang-Dong
Sent time: 01/07/2019 12:28:32 PM
To: Zhang Xiaorong <zhangxiaorong52@163.com>; Zhou Yu <yu.zhou@whu.edu.cn>
Subject: potential china trip

Dear Xiaorong and Zhou Yu,

[redacted]

The question is when it is the best timing for me to make this trip, and how I might couple the trip with some more productive things to do. For example, we need to work together to get the mitochondrial paper submitted. Zou Xinxin has been sending me updates periodically, and I can thus talk to her in Wuhan while working on her manuscript in my spare time.

I learnt from Guo Lin that most students will be gone by Jan. 18 until after Feb. 20. What are your rough schedules in this holiday season? I will be heading to a local coffee shop to work on Hu Jing's manuscript. When you see this message, you may give me a WeChat call to discuss various issues, including your latest experiments.

Best,

Fu

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

From: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Sent time: 01/21/2019 06:47:27 AM
To: dingsw@ucr.edu; haobo.jiang@okstate.edu; sluan@berkeley.edu; maj@rib.okayama-u.ac.jp; SongQ@missouri.edu; dbsyuhao@nus.edu.sg; zhao5@illinois.edu; Xinnian Dong, Ph.D. <xdong@duke.edu>; Fu, Xiang-Dong; Guan, Kun-Liang; Zhao, Yunde
Subject: Fwd: Han Bin 转发: Your PAG plenary lecture

Please see the feedback from Dr. Bin Han on our report.

Best regards and Happy Chinese New Year! XF

Begin forwarded message:

From: Bin Han <bhan@ncgr.ac.cn>
Subject: Han Bin 转发: Your PAG plenary lecture
Date: January 21, 2019 at 12:10:21 AM EST
To: "'Xiao-Fan Wang, Ph.D.'" <xiao.fan.wang@duke.edu>

Dear Xiao-Fan,

I am pleased to let you know that I had sent the evaluation reports together with my letter to every PIs individually 10 days ago. I received positive responses from all of PIs. We will have further meetings to discuss what discussions (closing some groups) we should make according to the results of the evaluations very soon. I will report to you the regarding progress.

I just came back from San Diego after attending the 27th International Plant and Animal Genomics conference, which is the biggest plant genomics conference with about 3,000 attendees in the world. I am the first person to be invited from China or Asian countries to give a plenary talk at this conference, and just received an email for nice comments from the Chairman of the PAG. I do agree with you that Chinese scientists should go to attend international meetings regularly for sharing research experiences with the community. We will encourage the PIs to attend the international meetings.

Best wishes,

Bin

发件人: Steve Heller [mailto:steve@hellers.com]
发送时间: 2019年1月19日 0:58
收件人: bhan@ncgr.ac.cn
抄送: Steve Heller; Darrin Scherago - Scherago International Inc. (darrins@scherago.com)
主题: Your PAG plenary lecture

Dear Bin,

Thank you for coming to PAG and giving a fascinating, unique, and excellent first rate plenary lecture at PAG XXVII.
A number of attendees and colleagues came to me after your talk and said it was really good.

Regards,

Steve

Steve Heller
Chairman, PAG XXVII

From: Fu, Xiang-Dong
Sent time: 03/12/2019 06:15:25 PM
To: Yu Zhou <yu.zhou@whu.edu.cn>
Subject: Re: China trip

Thanks a lot. If [redacted] can make it, that will be great.

Sent from my iPhone

On Mar 12, 2019, at 5:31 PM, Yu Zhou <yu.zhou@whu.edu.cn> wrote:

> Dear Fu,
>
> Sure, I have already booked the two flights for you.
>
> Thanks for the message on the ms. We will finish it up quickly.
>
> For [redacted] defense, we make it happen on 4/15, OK? [redacted]
>
> ---
>
> Best regards,
> Yu
>
> -----Original Messages-----
> **From:**"Fu, Xiang-Dong" <xdfu@ucsd.edu>
> **Sent Time:**2019-03-13 05:19:15 (Wednesday)
> **To:** "Zhou Yu" <yu.zhou@whu.edu.cn>
> **Cc:**
> **Subject:** China trip
>
> Hi Yu,
>
> I am asked to review a paper submitted to Mol Cell from the Kristen Lynne lab, showing APA regulation through binding CELF2 at 3'UTRs to compete with U2AF during T cell activation. I just heard the story at the Keystone meeting I organized. The story is related to Tang Peng's story. We thus need to hurry a bit. I will send you the ms after I click into the website.
>
> I have scheduled a trip back in April. I will land in Beijing in 4/5 and plan to immediately connect to Wuhan, as I need to attend a summit on global health organized by the mayer of Wuhan and the president of Taikang Insurance in 4/8. Afterward, I need to fly to Shengzhen, Beijing, and then Hefei for a series of meetings. I will return to Wuhan in 4/14 and stay until 4/16. My international flights will be covered by my hosts in Shengzhen and Hefei.
>
> According to this schedule, I will be in Wuhan between 4/6-4/9 and then 4/14-4/16. In these windows, I will have only two days (likely 4/7 and 4/15) to spend with your guys.
>
> I have checked for potential domestic flights for a round trip from Beijing to Wuhan in 4/5 and 4/16. The convenient flights appear to be CZ3140 (19:15-21:35) for 4/5 and CA8203 (12:40-14:40) for 4/16. If possible,

can you book these flights for me?

Thanks,

Fu

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
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George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

From: 陈亮 <liang_chen@whu.edu.cn>
Sent time: 03/30/2019 04:01:06 PM
To: Fu, Xiang-Dong
Subject: Re: Re: meeting in Wuhan

I was half done yesterday and will continue today. I will be finished before Jerry get up. So yes. Liang

----- 原始邮件 -----
发件人: xdfu@ucsd.edu
收件人: liang_chen@whu.edu.cn
发送时间: 2019-03-31 06:15:50
主 题: Re: meeting in Wuhan

Great! I will see you then.

By the way, do you think you and Jiayu can get the proof done today?

Fu

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
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Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

On Mar 30, 2019, at 3:02 PM, 陈亮 <liang_chen@whu.edu.cn> wrote:

Dear Fu, I will be glad to serve as a committee member for [redacted] defense. Maybe we can have a causal chat before and after her defense. You are always very busy. Please take care and keep in touch. Best, Liang

----- 原始邮件 -----
发件人: xdfu@ucsd.edu
收件人: 00031945@whu.edu.cn,liang_chen@whu.edu
发送时间: 2019-03-30 23:57:37
主 题: Re: meeting in Wuhan

Dear Liang,

Great to hear from you. April 8 is an option to meet, as I will be attend a health summit organized by the Mayer of Wuhan and the President of Taikang. At this point, however, I am not clear where the meeting is and when we may have to meet. Another option is April 15. Zhou Yu proposed to let [redacted] to defend her thesis that day. You can serve as a committee member for her and we can talk before and after her defense. Either way, let's figure out the timing.

Fu

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
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9500 Gilman Drive, Room 217
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Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

On Mar 29, 2019, at 6:47 PM, 00031945 <00031945@whu.edu.cn> wrote:

Hi Fu,

I heard you will be in Wuhan from April 6th to 9th. Sorry that I will in Shenzhen during that weekend and be back to Wuhan in the early morning on April 8th. [redacted]

Maybe I will have the chance to talk to you on April 8th and glad to know that our Nature protocol paper is close to the publishing stage.

Best wishes,

Liang

From: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Sent time: 04/16/2019 03:10:41 AM
To: Fu, Xiang-Dong
Subject: Re: CAS

Had meeting until lunch time and then took a flight to Xi'an, just arrived hotel. I will return home on Sunday. XF

> On Apr 15, 2019, at 11:47 PM, Fu, Xiang-Dong <xdfu@ucsd.edu> wrote:
>
> Hi Xiaofan,
>
> I am in Wuhan airport on my way back to the US today. You still have a few days in China, right?
>
> Greatly appreciate your efforts in pushing CAS-related issues.
>
> Fu
>
> Xiang-Dong Fu, Professor
> Dept. of Cellular and Molecular Medicine
> University of California, San Diego
> George Palade Laboratories
> 9500 Gilman Drive, Room 217
> La Jolla, CA 92093-0651
>
> Phone: 858-534-4937
> Fax: 858-822-6692
> Email: xdfu@ucsd.edu
>
> > On Apr 15, 2019, at 11:09 PM, Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu> wrote:
> >
> > Hi XD:
> >
> > I just talked to Dr. Zhongli Ding again to push for increase in the slots for foreign members of CAS in this year's election as he is now in charge of the CAS elections, and he agreed with me and will raise this matter at the meeting of Presidential Committee of CAS. Before this conversation with Ding, I mentioned this matter to Chunli Bai, as well as Yiyu Chen, Zihe Rao and Gang Pei who are all members of the Presidential Committee. Hope the increase would make easier for more candidates who are Chinese descents to be elected as CAS always wanted to have a wide representation of newly elected foreign members in terms of countries from different continents.
> >
> > Best regards, XF

From: Fu, Xiang-Dong

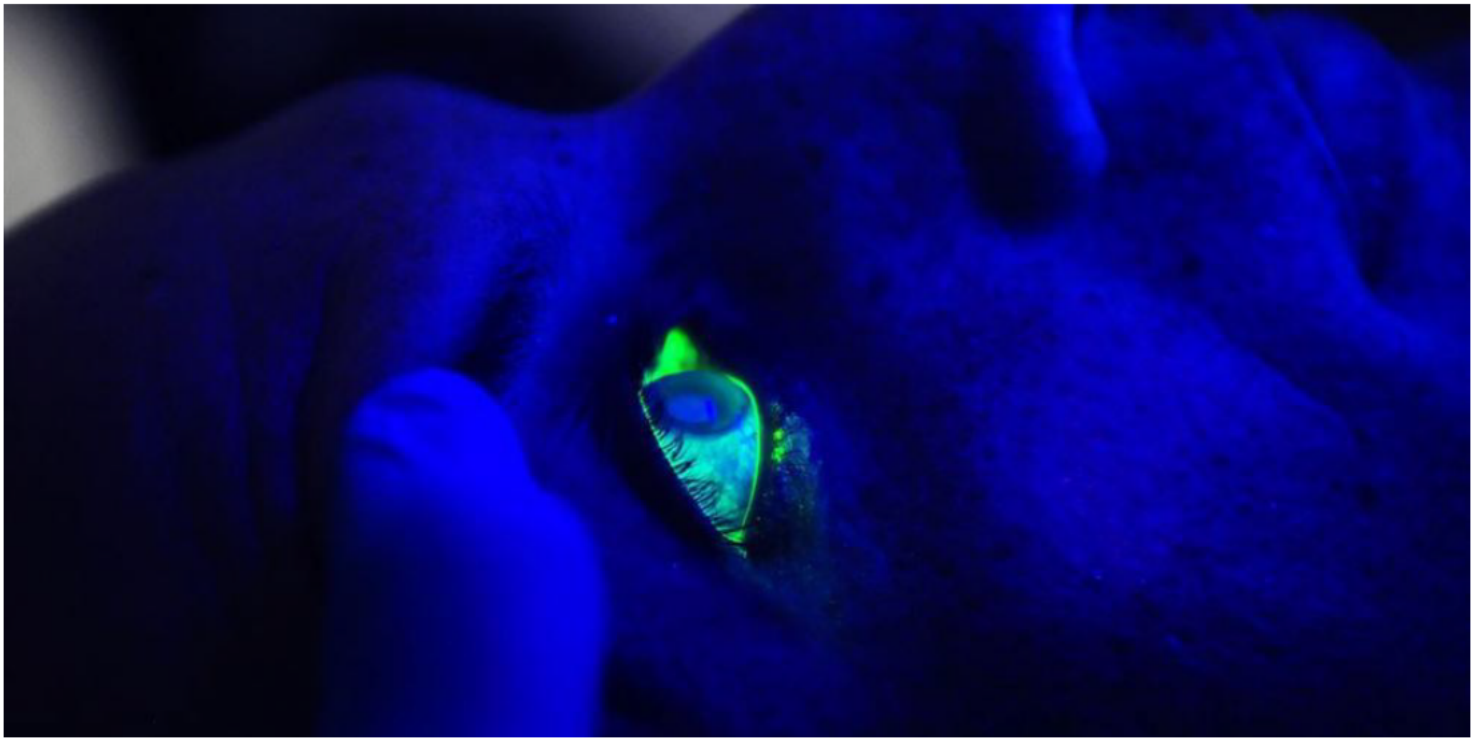
Sent time: 04/18/2019 10:50:46 AM

To: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>

Subject: Our fiend Zhang Kang seems to get into some trouble

Attachments: UCSD Dr. Kang Zhang's human research violations showcase national issue.pdf ATT00001.htm

inewsource INVESTIGATIVE, DATA-DRIVEN REPORTING



A black light illuminates a man's eye after he received fluorescein drops during an exam. *(U.S. Department of Defense)*

UCSD eye doctor broke human research rules, putting patients at risk

by **Brad Racino** & **Jill Castellano** | *April 18, 2019*

Tens of millions of people have volunteered their time and bodies to help create breakthroughs in medicine. You see the results with the pain relievers in your medicine cabinet, the vaccines that protect you from disease, the pacemakers that keep your heart beating and the innovations happening now with stem cells.

Yet the systems meant to protect those volunteers from harm are far from perfect, and research violations by Dr. Kang Zhang, an eye doctor at the University of California San Diego, show just how easily that well-intentioned framework can collapse.

Read this story completely backed up by primary documents

Click Here

Zhang is the chief of eye genetics at UCSD and has a lab named after him at the university. He receives millions of dollars in federal grants and presents at symposiums around the world.

A few years ago, he helped develop a way to remove cataracts from infants and regenerate their lenses using their own stem cells. He also built a tool that scanned over a million patient records and diagnosed illnesses with more than 90% accuracy.

But several of Zhang's studies were riddled with violations of basic human research standards. A U.S. Food and Drug Administration warning in 2017 and a UCSD audit that followed reveal a pattern that put patients in harm's way for years.

Why This Matters

When people volunteer to be human research subjects, they accept potential health risks in order to contribute to a growing bank of scientific and medical knowledge.

Their medical history, blood, organs or DNA are mined to improve the diagnosis and treatment of diseases, or to develop new technologies to help people live longer, healthier lives.

The researchers are expected to follow ethical guidelines meant to protect their patients.

The 56-year-old doctor enrolled people he shouldn't have for his medical trials, failed to document what happened to 25 units of a study drug, performed HIV tests on participants without their permission, kept poor records on his patients and didn't complete necessary ethics training for a stem cell study.

When asked by the FDA to create a plan to prevent more violations from happening in the future, Zhang didn't provide one.

"There ought to be some serious penalties for this sort of thing," said Spencer Hey, a Harvard Medical School expert in biomedical research ethics.

inewsource reached out to Zhang, the director of the eye institute where he works and the director of UCSD's human research protection program for interviews. In response, UCSD sent a statement that said the university had "implemented a comprehensive management plan to address these issues" and suspended Zhang indefinitely from serving as a primary researcher overseeing human research studies at UCSD. He may continue to apply for federal grants, publish in medical journals and train the next generation of scientists.

Dr. Kang Zhang is the chief of eye genetics at the University of California San Diego. *(UCSD)*

UCSD later told *inewsource,* "Zhang's research had undergone multiple audits since 2012," which prompted his suspension. When asked if that meant the university had known about Zhang's violations for five years before taking action, a UCSD spokeswoman would not comment further.

After speaking with five ethics experts for this story, it appears Zhang's violations — and what happened after they were discovered — are symptomatic of larger problems impacting the field of human subject research in the U.S. Those include patchwork oversight and poor communication between watchdog agencies, a lack of transparency and dialogue with the public, and a combination of money and prestige that sometimes safeguard an institution's reputation more than patient welfare.

"Science is accelerating always," said Stacey Springs, Harvard University's research integrity officer. "But it feels that it's accelerating in ways that are

pushing on regulatory compliance like never before. So we really need to focus now, and learn from each other, and apply these best practices – because it's coming fast."

An early warning

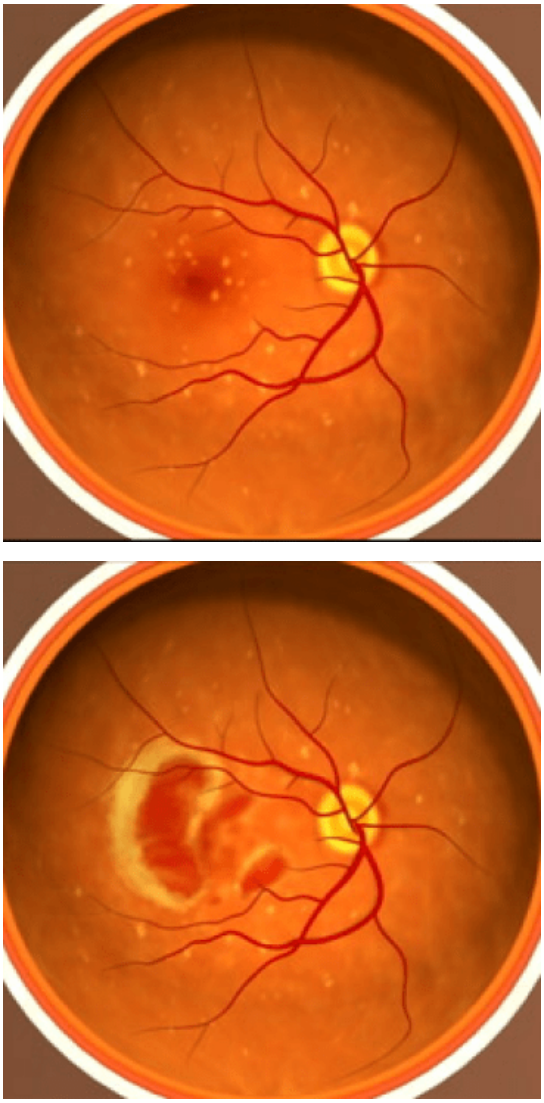
Zhang received his medical degree and doctorate in genetics from Harvard, then taught at Johns Hopkins University and the University of Utah before founding UCSD's Institute for Genomic Medicine in 2009.

His accomplishments have landed him on CBS' "60 Minutes" and in The New York Times, The Wall Street Journal and the Los Angeles Times. He's received dozens of honors from national and international associations and universities, published or co-authored more than 100 peer-reviewed manuscripts in top journals and recruited human research subjects from around the world – including from the San Diego VA and UCSD's Shiley Eye Institute on the La Jolla campus.

It was during Zhang's time at the institute, in the summer of 2016, when the FDA inspected one of his ongoing human trials to ensure the "rights, safety, and welfare" of his patients were protected.

For five years, Zhang had been testing a drug to reverse the effects of a common age-related eye disease. He received approval to enroll patients whose vision had already started to decline – to see if the drug could restore their sight.

Zhang's research team injected ranibizumab once a month into each test subject's eyes, 12 times total for each patient. The drug can produce side effects that include eye haemorrhages, pain, inflammation and spots in a field of vision. In rare cases, it can prompt serious cataracts or blindness.



Photos of the back of the eye showing early (left) and advanced age related macular degeneration. *(National Eye Institute, National Institutes of Health)*

Twelve people had participated in the study by the time the FDA stepped in and found five of them were ineligible because they didn't have the vision problems Zhang outlined for participants. Another patient's eyesight wasn't correctly evaluated before the person was injected with the drug.

"If it had been one out of a hundred, we could probably chalk that up to an error that doesn't reflect a pattern of misconduct," said Michael Carome, a former associate director at the U.S. Office for Human Research Protections, one of many federal agencies that protects human research subjects.

"But to enroll half the subjects not meeting enrollment criteria – that is more than just an occasional error. That suggests something systematically wrong with how they're doing the research," said Carome, who spent years investigating these kind of violations while at the agency.

He left the Office for Human Research Protections in 2010 during a decade of decline, when the office all but stopped using its enforcement tools in favor of "a more friendly approach toward institutions," he said.

Carome is now a director of the health research group at Public Citizen, a consumer advocacy nonprofit based in Washington, D.C.

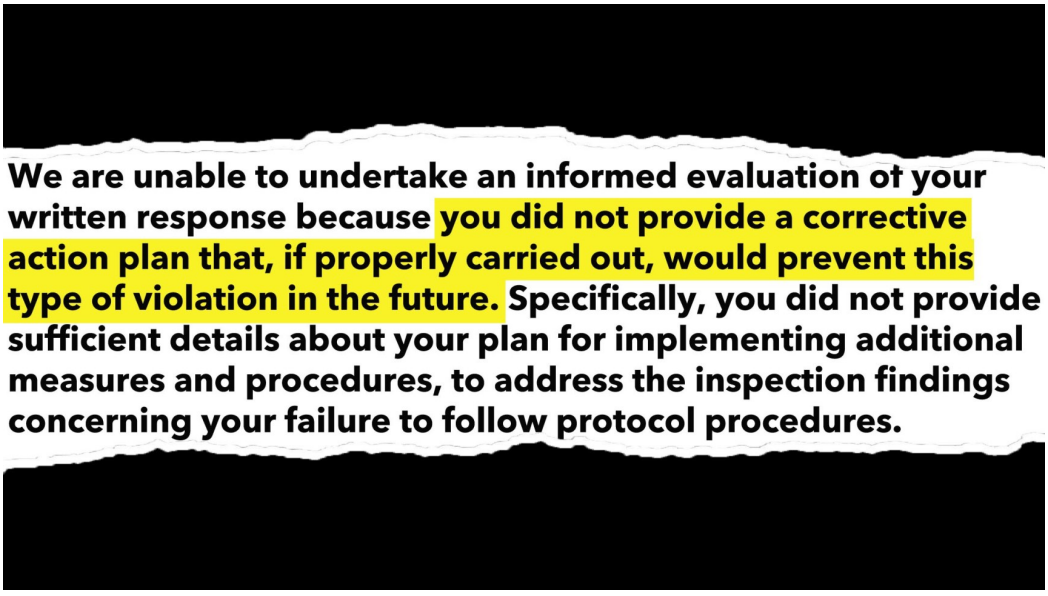
He told *inewsource* that research on otherwise healthy patients needs to be performed carefully, because they aren't sick enough to justify taking chances.

"Both from a scientific standpoint and ethical human subjects standpoint, not complying with the enrollment criteria is a big deal," Carome said, calling the guidelines "crucial in terms of ensuring that human subjects are protected."

The FDA agreed. It issued Zhang a warning letter in January 2017 that called out his use of ineligible patients and his failure to perform required screenings and procedures, poor recordkeeping and lack of documentation about what happened to 25 units of the unused study drug (which Zhang said were destroyed).

Though not mentioned in the letter, the UCSD audit that followed said Zhang also enrolled patients while the study was suspended.

The FDA uses warning letters to document serious research problems and mandate corrective actions. Three times in the letter, it told Zhang his actions raised "concerns about the validity and integrity of the data collected," and three times it told Zhang he didn't have an adequate plan to keep his patients safe moving forward.



The U.S. Food and Drug Administration issued Dr. Kang Zhang a warning letter in January 20 7. Read the

full FDA report.

The study was eventually shut down, and *inewsource* could find no articles published based on the research.

The FDA letter prompted UCSD to suspend enrollment in all of Zhang's active research projects at the time, pending the results of an internal audit.

Amy Caruso Brown is an assistant professor of bioethics, humanities and pediatrics at New York's Upstate Medical University. She also is a member of an institutional review board – a safety committee that approves and oversees projects like Zhang's.

Brown spoke to *inewsource* after reading the UCSD audit and said, "I have not seen this number of issues in the five years that I've been on an IRB."

'Major league science'

Zhang's work at UCSD should be viewed in context.

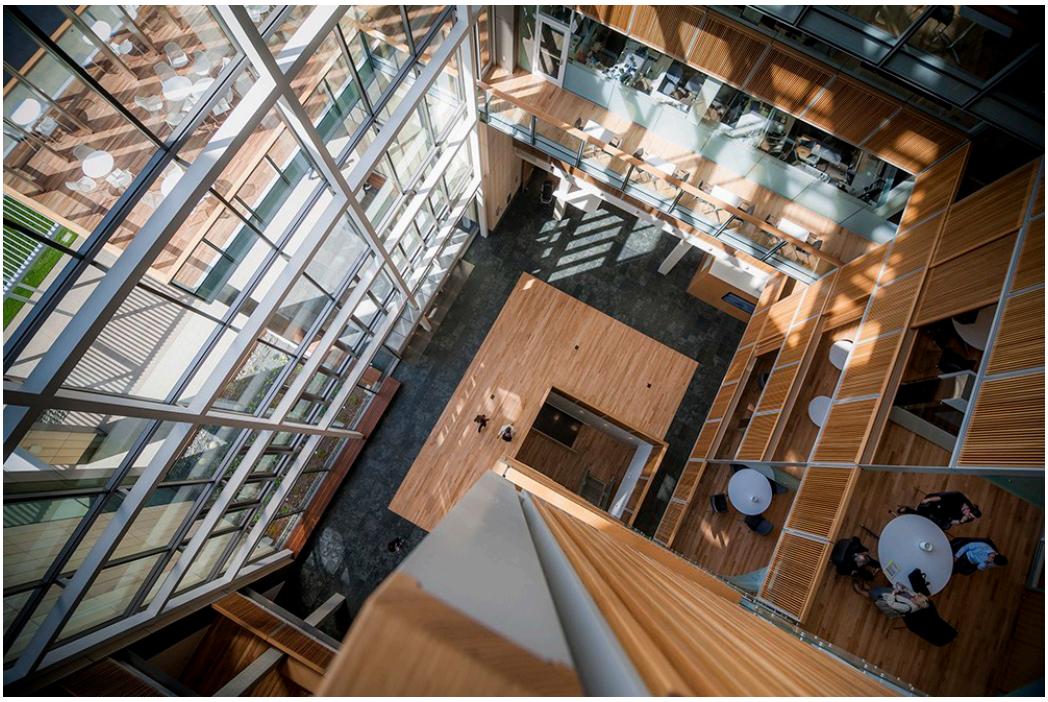
He is one of more than 1,600 faculty members in the schools of medicine and pharmacy, one part of a healthcare system at a university ranked among the top research institutions in the country.

UCSD secured $1.2 billion in sponsored research support in 2018 – with $686 million going toward UC Health Sciences – and had more than 7,000 patients participating in clinical trials. Its scientists have made breakthroughs in diabetes research, understanding cancer genes, identifying early signs of autism and treating Alzheimer's disease. It counts 16 Nobel laureates among current and former faculty.

All of that makes UCSD's investigation of Zhang unique. The university has published 249 internal audits since July 2010, and the Zhang report is the only one *inewsource* could find specific to an individual researcher.

Auditors reviewed Zhang's training records, enrollment logs, regulatory binders and files for ongoing projects that had enrolled human research patients. They found problems everywhere they looked: Zhang failed to get the proper consent from all patients; didn't report problems to UCSD's institutional review board; lost documents; kept inaccurate records; wrongly billed patients; and didn't complete the training required to work with human embryonic stem cells.

In one study, Zhang's staff tested patients' blood for HIV and AIDS without



The UCSD Biomedical Research Facility. *(Regents of the University of California)*

telling them, against federal policy.

"He's lucky there weren't any major patient harms," Brown said. "But if you act like this all the time, eventually you will hurt someone."

The auditors found Zhang's actions may have "negatively impacted the rights, welfare, and safety of human subjects in clinical research." One of his studies, sponsored by the California Institute for Regenerative Medicine, collected tissue from donors with blinding eye disease for a stem cell bank. California voters created the institute in 2004 to fund this type of research.

The study's rules stated no one under 50 years old was allowed to enroll. UCSD audited files for 50 of the more than 400 patients and found seven were too young, including a minor.

Carome, the former federal director, laughed when he read that section.

"That's not a subtle mistake," he said.

Another finding noted the importance of "credible and valid data" when describing a study that was missing 25 of 50 patient progress reports.

"This isn't minor league stuff. This is major league science," said Hey, the Harvard bioethicist, who added "this sort of pattern should raise questions about the validity of (Zhang's) published work."

Zhang did publish a correction in January, but not for a study included in the audit. It involved gene editing in animals, and Zhang's paper said UCSD supervised and approved the research. That wasn't true – it was overseen by a university and medical center in China.

inewsource couldn't find any published articles based on the six studies reviewed by the FDA and UCSD. Yet during the audits and study suspensions, Zhang is listed as having continued a genetics research project at the San Diego VA, which did result in 10 published articles.

UCSD doctors often work as attending physicians at the San Diego VA and share funding, research samples, data and lab space. The VA Hospital is less than a mile from the Shiley Eye Institute and on the same campus. Yet the VA said it was never notified of the UCSD or FDA reports until *inewsource* asked about them in March.

The San Diego VA, shown on Nov. 5, 20 8, provides services to the nearly quarter million veterans in San Diego and Imperial counties, and has one of the largest research programs in the national VA network. *(Megan Wood)*

A VA spokeswoman would not answer questions about whether Zhang was still practicing at the VA, enrolling patients in trials or proposing new research at the institution. The San Diego VA has one of the largest research programs in the national VA network.

Nor were other related federal or state regulators notified. That includes the federal Office for Human Research Protections, which protects research subjects from harm; the National Institutes of Health, which funds many of Zhang's studies; the Office of Research Integrity, which oversees research misconduct cases; or the California State Medical Board, which gave Zhang a license to practice medicine.

"Communication is fraught with complexity in compliance matters," said Springs, Harvard's research integrity officer. Things sometimes happen on a need-to-know basis, she said, and confidentiality plays a big part.

But, she said, "If there are active studies and participants are in danger, the confidentiality is out the window."

Symptoms of a larger problem

Picture the framework for protecting research subjects as a house.

The foundation consists of a study, planned with sound scientific and ethical principles, and a responsible, ethical researcher. If and when things go wrong or change, they are communicated and addressed immediately. That didn't happen in this case.

Institutional review boards, the next floor up, are often composed of expert volunteers who spend countless hours poring over hundreds of pages of research protocols, guidelines and regulations while also working their regular jobs. They rely on researchers to keep them updated, alert them to problems and speak the truth, but they may also have the power and responsibility to audit ongoing studies. It's often a proactive system, but it wasn't in Zhang's case.

And the institutional review board system is "vulnerable to unethical manipulation, particularly by companies or individuals who intend to abuse the system or to commit fraud," according to an undercover federal investigation from 2009.

An undated photo of the Shiley Eye Institute at the University of California San Diego campus in La Jolla. *(UCSD)*

Higher-ups at an institution – the upper floor – may have reasons and methods to keep violations quiet and away from public scrutiny. The Zhang audit is a perfect example: It was published more than two years ago but didn't reach the VA across campus, never made the news, and likely wouldn't have shocked anyone who stumbled upon it because it never named Zhang as the researcher under scrutiny. The only place his name appears is on the report's cover page – as one of 16 people copied on its transmittal within the UC system, including UCSD's chief ethics and compliance officer, vice chancellors, various directors and others.

"It doesn't look good for the university to be calling out these high-profile faculty for these kinds of violations and making a big deal out of it and applying sanctions, because that's not the kind of attention you want to draw to your researchers," Harvard's Hey said.

Problems with internal probes

An opinion article published by three ethics experts last year in The Journal of the American Medical Association said when internal investigations are completed, the reports are often not standardized, not peer reviewed, have limited oversight and contain conflicts of interest. "Even when institutions act, the information they release to the public is often limited and unhelpful," they wrote.

Calling out lucrative researchers can result in lost funding. Last fiscal year, federal agencies including the National Institutes of Health, National Science Foundation and U.S. Department of Defense supplied UCSD with $681 million in research funding. UCSD prides itself on how much grant money flows its

way each year and has defended that stream aggressively: It sued the University of Southern California in 2015 for poaching one of its most lucrative researchers.

And as quickly as those funding agencies give, they can take away – or even require repayment if serious violations happened using taxpayer dollars.

At the very top of the house, the roof is made up of agencies that regulate human subject protection across the country. The big one – the Office for Human Research Protections – protects those involved in research funded or conducted by the U.S. Health and Human Services Department. It can investigate allegations of wrongdoing but often does not, choosing instead to refer investigations back to the institutions themselves. It can also revoke an entire institution's ability to perform human research, though that hasn't happened since 2007.

At Harvard, Springs said she often uses these agencies as a lever in talks with researchers to get them to understand and follow rules. She said the patchwork of institutional, academic and statewide regulations can be messy, so there's a hope that the feds will act consistently, "because they really are the heavy in these conversations."

But, she added, "Then they aren't predictable, and you're like, 'Wow, OK. So they have these enforcement mechanisms and they're not using them. Or they're using them selectively.'"

The Office for Human Research Protections never took action in the Zhang case, which isn't surprising for two reasons. One, they weren't informed by the FDA or UCSD of his violations. Two, the agency has drastically cut down on enforcement over the past decade.

For example, it charged institutions with investigating misconduct allegations 94 times in 2002. In 2015, it did that three times. For the same period, the agency went from issuing 146 "determination letters" – an important tool for communicating findings of misconduct – to issuing five.

It's not due to a lack of funding or a drop in complaints. In fact, institutional misconduct reports sent to the office jumped 400 percent from 2002 to 2014.

Carome said his former agency's current leadership is "less interested in issuing harsh findings and embarrassing institutions."

The problem with that, he said, is enforcement actions are "one of the more important tools the office has to change behavior."

The Office of Research Integrity, another federal agency that oversees research misconduct investigations, has also been criticized for slowing its enforcement. It recently went an entire year without issuing a single finding of research misconduct – "nothing short of appalling," according to one medical ethicist quoted in an industry publication in 2017 – though the agency has since stepped up its actions.

Even if oversight agencies were operating at full speed, a lack of transparency and data sharing would still be major flaws in safeguarding patients that could rip the roof apart.

Compliance data at the Office for Human Research Protections is kept in-house and offline, and getting at it requires a public records request, weeks to months of wait time and then skilled data analysis. The California Medical Board publishes doctor information online, but it's more concerned with things like medical malpractice judgments, physician substance abuse and negligence in the course of routine health care than monitoring human research and clinical trials. Its database isn't designed to incorporate audit findings, FDA warning letters or federal databases.

Academic investigations – at least in California – are kept far from Google's reach, and typically require a public records request and the knowledge they exist. The same goes for institutional review board investigations, reviews and audits.

And none of these systems communicate with each other in any meaningful way.

Carome added one more problem plaguing the field: "Much noncompliance goes undetected or unnoticed."

Zhang's audit likely would have gone unnoticed if *inewsource* weren't digging into the risks associated with human research, yet Springs said this may prove an opportunity for UCSD.

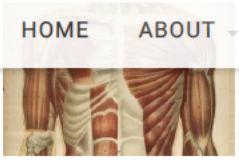
"When these cases emerge in the press, or people come to hear about them in some way, it highlights our failures – and that should happen," she said.

But even then, Springs said, it doesn't always "turn into constructive discussion and dialogue around how we can fix it."

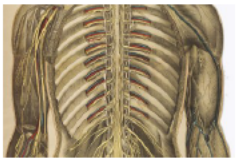
Audits like Zhang's are often unintelligible to the community, to patients enrolled and even to academics, even though they are the people who should be providing feedback and criticism, she said.

"These are opportunities where we can actually promote transparency," she said, "and say, 'Hey, this is what happened. This is how we approached it,' and model effective dialogue with communities on how we can work better on this.

More on the Risky Research project...



Dangerous human research alleged at San Diego VA
Two whistleblowers say dangerous medical research was performed on veterans suffering from alcoholism and liver disease at the San Diego VA.



San Diego VA confirms liver samples taken from sick veterans without their consent
The October 2018 report found "serious noncompliance occurred" when extra pieces of liver were removed from at least nine veterans.

About Brad Racino:

Brad Racino is a senior investigative reporter and assistant director at *inewsource*. To contact him with tips, suggestions or corrections, please email bradracino [at] inewsource [dot] org. You can contact him securely on Signal (845-553-4170).

About Jill Castellano:

Jill Castellano is an investigative data reporter for inewsource. To contact her with tips, suggestions or corrections, please email jillcastellano [at] inewsource [dot] org.

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Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

From: Fu, Xiang-Dong
Sent time: 04/18/2019 05:09:06 PM
To: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Subject: Re: Our fiend Zhang Kang seems to get into some trouble

Not clear. It seems that the problem has been around for some time, only surfaced to the public more recently. I forgot to carry phone with me today, and have not yet got a chance to talk to him. He never mentioned any of these problems to me before.

Fu

Xiang-Dong Fu, Professor
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Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

> On Apr 18, 2019, at 5:04 PM, Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu> wrote:
>
> Will he get punishment from UCSD in addition to the ban on human research? This will hurt the chance of his collaborator Liu Yizhi to get elected to CAS. XF
>
> > On Apr 18, 2019, at 1:49 PM, Fu, Xiang-Dong <xdfu@ucsd.edu> wrote:
> >
> > Xiang-Dong Fu, Professor
> > Dept. of Cellular and Molecular Medicine
> > University of California, San Diego
> > George Palade Laboratories
> > 9500 Gilman Drive, Room 217
> > La Jolla, CA 92093-0651
> >
> > Phone: 858-534-4937
> > Fax: 858-822-6692
> > Email: xdfu@ucsd.edu
> >
> > <UCSD Dr. Kang Zhang's human research violations showcase national issue.pdf>

From: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Sent time: 04/24/2019 01:59:01 PM
To: Fu, Xiang-Dong
Subject: Re: UCSD eye doctor Kang Zhang 'on leave' following investigation into human research violations

Thanks. XF

On Apr 24, 2019, at 4:53 PM, Fu, Xiang-Dong <xdfu@ucsd.edu> wrote:

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

Begin forwarded message:

From: "Mobley, William" <wmobley@ucsd.edu>
Subject: UCSD eye doctor Kang Zhang 'on leave' following investigation into human research violations
Date: April 24, 2019 at 1:12:09 PM PDT
To: "Fu, Xiang-Dong" <xdfu@ucsd.edu>, Don Cleveland <dcleveland@ucsd.edu>

This is more than concerning. It is an indictment of his methods.

We should eliminate any role for Zhang.

Bill

https://inewsource.org/2019/04/23/ucsd-eye-doctor-kang-zhang-investigation/

Please forgive the brevity of messages sent from my iPhone.

From: 肖锐 <00031889@whu.edu.cn>
Sent time: 06/25/2019 06:54:12 PM
To: Fu, Xiang-Dong
Subject: Re: Re: A news release to report our paper on Whu website

---

Dear Prof. Fu,

Yes, I fully agree and I didn't write this sentence in the original version. And I already send the corrected version to **武大新**闻办.

I am writing a news release for BioArt as well, and I will use more precise words. And will let you take a look first.

Thanks,

Rui

> -----**原始**邮**件**-----
> **发件人:**"Fu, Xiang-Dong" <xdfu@ucsd.edu>
> **发送时间:**2019-06-26 09:31:43 (**星期三**)
> **收件人:**"**肖**锐" <xiaorui9@whu.edu.cn>
> **抄送:**
> **主题:** Re: A news release to report our paper on Whu website
>
> I worry that any obvious overstatement will be picked by a lot of watch dogs in China, including **方舟子**。If the work was "mainly" carried out at Wuhan University, people will question why Wuda was not listed as the first author unit. They will then check when you returned to China. Given such a large amount of work involved and it is part of ENCODE, people will accuse you, which will cause a lot of damage to your career. Believe me, I just want to avoid you from getting into trouble.
>
> Xiang-Dong Fu, Professor
> Dept. of Cellular and Molecular Medicine
> University of California, San Diego
> George Palade Laboratories
> 9500 Gilman Drive, Room 217
> La Jolla, CA 92093-0651
>
> Phone: 858-534-4937
> Fax: 858-822-6692
> Email: xdfu@ucsd.edu
>
> > On Jun 25, 2019, at 6:23 PM, **肖**锐 <xiaorui9@whu.edu.cn> wrote:
> >
> > Dear Prof. Fu,
> >
> > I will use the version corrected by you which are more concise. By the way, Dr. Ye Wen in our institute add the

sentence about "mainly", and her idea is to emphasize my contribution to the work at Medical Research Institute to better support me to apply "青年拔尖"人才 which more values the work in China. That's not my words and it's OK to remove.

Thanks,

Rui

-----原始邮件-----
发件人:"Fu, Xiang-Dong" <xdfu@ucsd.edu>
发送时间:2019-06-26 02:57:20 (星期三)
收件人:"肖锐" <xiaorui9@whu.edu.cn>
抄送:
主题: Re: A news release to report our paper on Whu website

Here is the revised news release. You will get into trouble if you claim the work was mainly carried out in China. Thus, it is better to keep it short and simple.
Fu

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
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9500 Gilman Drive, Room 217
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Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

On Jun 25, 2019, at 6:24 AM, 肖锐 <xiaorui9@whu.edu.cn> wrote:

Dear Prof. Fu,

I worte a news release attached to report our paper on Whu website, and it will be highlighted as headline news. Could you please take a look at it? Any points I need to highlight or correct?

Thanks,
Rui<Cell文章宣传稿-肖锐-2019625.docx>

From: 肖锐 <xiaorui9@whu.edu.cn>
Sent time: 08/07/2019 04:51:06 PM
To: Fu, Xiang-Dong
Subject: Re:Re: Several things to discuss with you

---

ear Prof. Fu,

Got it.
1. Let me submit our abstract this week and try my best to get a chance to present our work on the conference.
2. The time for the lecture is up to you since we are flexible. You decide.
3. [redacted]
4. Thank you for your help :)

Best,
Rui

在 2019-08-07 23:13:36,"Fu, Xiang-Dong" 写道:

>Hi Rui,
>
>I address your questions below:
>
>> On Aug 7, 2019, at 2:13 AM, 肖锐 wrote:
>>
>> Dear Prof. Fu,
>>
>> Several things to discuss with you:
>>
>> 1. The 6th International Symposium on 3D Genomics will be held at Tsinghua University from October 10th -12th, 2019. And you are one of the invited speakers. Are you going to present our work on RBP ChIP-seq that we just published? I am going to submit an abstract and/or a poster request to the conference committee to advertise our work. So I want to discuss this with you about it.
>
>I do not plan to talk about your work, and thus, please feel free to submit your abstract.
>>
>> 2. I want to invite you to give a talk for 东湖名师讲坛 at Medical Research Institute, Wuhan University on your next trip to China in October.
>
>When is the lecture and in what format? If time permits, I can do it.
>>
>> 3. [redacted]
>>
>> [redacted]
>>
>> Thank you and have a great day!
>> Rui
>

From: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Sent time: 09/04/2019 06:31:22 PM
To: Fu, Xiang-Dong
Subject: PKU candidate

Please complete the evaluation of the candidate soon. Thanks! XF

From: Fu, Xiang-Dong
Sent time: 11/20/2019 09:06:26 AM
To: Zhou Yu <yu.zhou@whu.edu.cn>; xinxinzuo2012 <xinxinzuo2012@aliyun.com>
Subject: NSMB account

Hi Yu and Xinxin,

My account at NSMB is:

[redacted]

Fu
Xiang-Dong Fu,
Distinguished Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

From: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>

Sent time: 11/22/2019 06:46:47 AM

To: Chen, Eugene <echenum@med.umich.edu>

Cc: lim@mskcc.org; dianqing.wu@yale.edu; xdfu@ucsd.edu; kuguan@ucsd.edu; Guo-Min.Li@UTSouthwestern.edu; wshou@iu.edu; mhan@colorado.edu; xhfeng@zju.edu.cn; liux@sibs.ac.cn

Subject: Re: RE: SINH-SAB meeting (November 13, 2019)

Thank you both for the great job! XF

> On Nov 22, 2019, at 9:39 AM, Chen, Eugene wrote:
>
>

From: liangyi@whu.edu.cn
Sent time: 12/23/2019 07:59:03 PM
To: xdfu <xdfu@ucsd.edu>
Subject: Merry Christmas and Happy New Year

Dear Xiangdong Fu,

Thank you very much for your continuous encouragement to my work during the past so many years. Welcome you visiting Wuhan University again in 2020!

I currently focus on the structures and functions of prion protein, Tau protein, TDP-43, and SOD1 causing neurodegenerative diseases.

Merry Christmas and Happy New Year! Have a good harvest in 2020!

With my best regards to you and your family,
Looking forward to hearing from you soon.

Sincerely Yours
Yi Liang

Dr. Yi Liang, Professor of Biochemistry
College of Life Sciences, Wuhan University
Wuhan 430072, China
+86-13871018180

liangyi@whu.edu.cn

From: Hongtao Yu <Hongtao.Yu@UTSouthwestern.edu>
Sent time: 02/18/2020 07:57:06 PM
To: Fu, Xiang-Dong
Cc: Guan Kunliang <kuguan@ucsd.edu>; Xiao-Fan Wang, Ph.D. <xiao fan.wang@duke.edu>
Subject: Re: Are you in the US or China

I have forwarded your message to Kaina. She will book the flights for you all.

Hongtao

> On Feb 18, 2020, at 9:09 PM, Fu, Xiang-Dong <xdfu@health.ucsd.edu> wrote:
>
> Hi Hongtao,
>
> [redacted]
>
> I have checked the flight information. There is only one airline (AA) that has direct flights. The most convenient ones for me and Kunliang are:
>
> March 6: AA1611, 8:54am - 1:50pm
> March 7: AA1624, 4:00pm - 5:07pm
>
> There is no need to book first class tickets for such short trip.
>
> My date of birth: [redacted]
> Passport number: [redacted]
>
> Kunliang will send you those information separately.
>
> Fu
>
> Xiang-Dong Fu,
> Distinguished Professor
> Dept. of Cellular and Molecular Medicine
> University of California, San Diego
> George Palade Laboratories
> 9500 Gilman Drive, Room 217
> La Jolla, CA 92093-0651
>
> Phone: 858-534-4937
> Email: xdfu@health.ucsd.edu
>
> > On Feb 18, 2020, at 6:59 PM, Hongtao Yu <Hongtao.Yu@UTSouthwestern.edu> wrote:
> >
> > [redacted]
> >
> > Yes, Kunliang has agreed to come. Xiao-fan is also coming. It should be fun.
> >
> > Hongtao

On Feb 18, 2020, at 8:52 PM, Fu, Xiang-Dong <xdfu@health.ucsd.edu> wrote:

Hi Hongtao,

[redacted]

For the interview session in March 7, are you going to invite Kunliang? If so, I can coordinate with him. It is quite short to arrange the trip.

Fu

Xiang-Dong Fu,
Distinguished Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

> On Feb 18, 2020, at 3:06 PM, Hongtao Yu <Hongtao.Yu@UTSouthwestern.edu> wrote:
>
> Hi Xiang-Dong,
>
> [redacted]
>
> In addition, it will be great if you can come to Dallas on March 7 to serve as a panel member for the interview of other candidates. If so, I can send you the application materials of the candidates we plan to interview.
>
> Hongtao
>
>> On Feb 18, 2020, at 3:24 PM, Fu, Xiang-Dong <xdfu@health.ucsd.edu> wrote:
>>
>> EXTERNAL MAIL
>>
>> Hi Hongtao,
>>
>> I wonder whether you are in the US or China. It is a bad timing if you are trapped in China. Hope you are ok. At certain point, we may chat a bit. I do not have your phone or WeChat. My cell phone is [redacted] If you happen to be in the US, give me a call.
>>
>> Fu
>>
>>
>>
>> Xiang-Dong Fu,
>> Distinguished Professor
>> Dept. of Cellular and Molecular Medicine
>> University of California, San Diego
>> George Palade Laboratories
>> 9500 Gilman Drive, Room 217

>> La Jolla, CA 92093-0651
>>
>> Phone: 858-534-4937
>> Email: xdfu@health.ucsd.edu
>>
>>
>>
>>
>> CAUTION: This email originated from outside UTSW. Please be cautious of links or attachments, and validate the sender's email address before replying.
>
>
> _____
>
> UT Southwestern
>
>
> Medical Center
>
>
>
> The future of medicine, today.
>
>

From: Guan, Kun-Liang <kuguan@health.ucsd.edu>
Sent time: 02/18/2020 08:08:01 PM
To: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Cc: xdfu@ucsd.edu
Subject: Re: Dallas

Yes, we will.

On 2/18/20, 6:23 PM, "Xiao-Fan Wang, Ph.D." wrote:

Great! Hongtao wanted to have dinner with us without candidates, so it would be nice if you two can arrive early (I purposely chose an earlier flight, otherwise the next one will get there just before 6 pm, too tight for a normal dinner from the airport). XF

> On Feb 18, 2020, at 9:18 PM, Guan, Kun-Liang wrote:
>
> I have not booked the ticket, but will try to catch your schedule, arrive early enough for a dinner on 03/06.
>
>
> On 2/18/20, 6:05 PM, "Xiao-Fan Wang, Ph.D." wrote:
>
> XD and KL:
>
> I will go to Dallas on March 6 arriving there at 1:44 pm. If you two get there before dinner, we can have a chance to chat. I will depart for home the next day with a 2:37 pm flight. XF
>

From: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Sent time: 02/27/2020 02:06:23 PM
To: Fu, Xiang-Dong
Subject: Re:

Yes, it was a very comprehensive article on this topic. XF

> On Feb 27, 2020, at 4:57 PM, Fu, Xiang-Dong wrote:
>
> The article is worth reading from the protective of globule competition and how China can adapt, which is also related to the current problem of SCI paper-based valuation of scientists and physicians.
>
> I will go over [redacted] in the weekend.
>
> Fu
>
> Sent from my iPhone
>
>> On Feb 27, 2020, at 12:01 PM, Xiao-Fan Wang, Ph.D. wrote:
>>
>> Thanks! Also, when you finish the evaluation [redacted] please send to me. XF
>>
>>> On Feb 27, 2020, at 1:25 PM, Fu, Xiang-Dong wrote:
>>>
>>> 【中美"科技脱钩"对中国全球价值链体系造成重构性冲击】
https://urldefense.com/v3/__https://nd.mbd.baidu.com/xjjpgtj?f=cp&u=64cb54a33566f13c__;!!OToaGQ!7Q_oFyI_3SxlB9KPmoqDZz079XqMMKvn0OCK_zwCYXRUSt1LwkCPBAx6WTdmy9RQR2z9$
>>>
>>> Sent from my iPhone
>>

From: Guan, Kun-Liang <kuguan@health.ucsd.edu>
Sent time: 03/06/2020 08:30:29 AM
To: Hongtao Yu <Hongtao.Yu@UTSouthwestern.edu>
Cc: xdfu@ucsd.edu; Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Subject: Re: trip

Hi Hongtao,

Can you send us the web link to join tomorrow's interview?

Regards,
Kun-Liang

On 3/5/20, 5:58 PM, "Guan, Kun-Liang" wrote:

Hi Hongtao,

Xiang-dong and I would like to ask your advice whether we should cancel our travel and participate in the interview view the Web. The state of California has declared public emergency and actually, there are confirmed CORVID 19 in San Diego, including AT-T store staff.

Regards,
Kun-Liang

On 3/5/20, 5:25 PM, "Xiao-Fan Wang, Ph.D." wrote:

XD and KL:

Considering the possibility that I may unknowingly bring the coronavirus back home from the trip that could endanger [redacted], I have decided to cancel my trip, and instead participating in the interview via the web, just like those at WLU. I called Hongtao and he fulling understood the situation and will send me the link for the web. Duke this afternoon sent all employees and students advising us to reconsider any unnecessary trips, including domestic ones, after a person from Seattle brought the disease to our area about ten days ago, but just identified two days ago with his illness, and now many people need to be tested.

It is a pity that we will miss this opportunity to meet, but can chat via the phone when we have an opportunity.

Best regards, XF

From: Hongtao Yu <Hongtao.Yu@UTSouthwestern.edu>
Sent time: 03/06/2020 11:02:10 AM
To: Guan, Kun-Liang
Cc: xdfu@ucsd.edu; Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Subject: Re: Prof. Xiao-Fan Wang's Schedule and Faculty Candidate Interview Agenda (Westlake University, March 6-7)

Many thanks to Xiao-Fan for sharing the info. It will be a good idea for you to test the connections tonight with Kaina.

Hongtao

> On Mar 6, 2020, at 11:43 AM, Guan, Kun-Liang <kuguan@health.ucsd.edu> wrote:
>
> Thanks.
>
> ---
>
> **From:** "Xiao-Fan Wang, Ph.D." <xiao.fan.wang@duke.edu>
> **Date:** Friday, March 6, 2020 at 9:10 AM
> **To:** "Guan, Kun-Liang" <kuguan@ucsd.edu>, "xdfu@ucsd.edu" <xdfu@ucsd.edu>
> **Cc:** "Hongtao.Yu@UTSouthwestern.edu" <Hongtao.Yu@UTSouthwestern.edu>
> **Subject:** Fwd: Prof. Xiao-Fan Wang's Schedule and Faculty Candidate Interview Agenda (Westlake University, March 6-7)
>
> Please follow Kaina's instructions. XF
>
> > Begin forwarded message:
> >
> > **From:** Kaina LI 李凯娜 <likaina@westlake.edu.cn>
> > **Subject: RE: Prof. Xiao-Fan Wang's Schedule and Faculty Candidate Interview Agenda (Westlake University, March 6-7)**
> > **Date:** March 6, 2020 at 8:25:00 AM EST
> > **To:** "Xiao-Fan Wang, Ph.D." <xiao.fan.wang@duke.edu>
> >
> > Dear Xiao-Fan,
> >
> > Hongtao told me that you will participate in the interview via internet. Thanks for your support!
> >
> > Our interview will be conducted via WeChat Work. A laptop with microphone and camera is recommended. Pls add me as your WeChat friend and my ID is [redacted]". Then you may download "WeChat Work" from App Store or by link https://work.weixin.qq.com/ - indexDownload to install app. An invitation message will be sent from me. Please click the invitation message to enter. If it's convenient for you, we can also test it in advance.
> >
> > In addition, please find attached Candidate Evaluation Form, and send the signed form to my email after the interview.
> >
> > Thanks so much and look forward to your reply.
> >
> > Best,
> >
> > Kaina
> >
> > ---
> >
> > **From:** Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
> > **Sent:** Thursday, March 5, 2020 12:58 PM
> > **To:** Kaina LI 李凯娜 <likaina@westlake.edu.cn>
> > **Subject:** Re: Prof. Xiao-Fan Wang's Schedule and Faculty Candidate Interview Agenda (Westlake University, March 6-7)

Thanks!

Sent from my iPhone

> On Mar 4, 2020, at 11:54 PM, Kaina LI 李凯娜 <likaina@westlake.edu.cn> wrote:
>
> Dear Xiao-Fan,
>
> Well received and thanks so much! That is no problem.
> Due to the coronavirus outbreak, Please take care.
>
> Look forward to seeing you in Hangzhou. Thanks!
>
> Best,
>
> Kaina

发件人: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
发送时间: Thursday, March 5, 2020 12:23:28 PM
收件人: Kaina LI 李凯娜 <likaina@westlake.edu.cn>
主题: Re: Prof. Xiao-Fan Wang's Schedule and Faculty Candidate Interview Agenda (Westlake University, March 6-7)

This form contains the information for the bank. Thanks and best regards, XF

> On Mar 3, 2020, at 4:32 AM, Kaina LI 李凯娜 <likaina@westlake.edu.cn> wrote:
>
> Dear Prof. Xiao-Fan,
> It's our great honor to invite you to attend the Faculty Candidate Interview of Westlake University on March 7 in US. The interview will be held in Hilton Anatole, 2201 North Stemmons Freeway, Dallas. Please find Annex 1 for your schedule and Faculty Candidate Interview Agenda.
>
> We will provide consulting fees and travel subsidies for you. Please fill in the form for TT Overseas (Annex 2) and send it to me at your convenience.
> In addition, the applicant materials will be sent by March 4. Many thanks for your support! Please feel free to contact me if you have any questions.
> Best,
> Kaina
> ---

> 李凯娜
> 生命科学学院
> **Kaina LI**
> **School of Life Sciences**
>
> T +86 571 8796 3632
> M +86 18506816876
> E likaina@westlake.edu.cn
> A 中国浙江省杭州市西湖区云栖小镇石龙山街18号
> Shilongshan Road No.18, Cloud Town, Xihu District, Hangzhou, Zhejiang, China.

From: Kaina LI 李凯娜 <likaina@westlake.edu.cn>
Sent: Wednesday, February 19, 2020 8:35 PM
To: xiao.fan.wang@duke.edu
Cc: Hongtao Yu <Hongtao.Yu@UTSouthwestern.edu>
Subject: 回复: trip

Dear Prof. Xiao-Fan,
I am Kaina, the staff member of the office of the School of Life Sciences. Many thanks for your support. The ticket has been reserved for you. Please kindly refer to the attached itinerary for details.
The information of the hotel reservation will be provided later.
Please let me know if there's anything I can do to help.
Thanks!
Best wishes,
Kaina

李凯娜
生命科学学院
Kaina Li
School of Life Sciences
T +86 571 8796 3632
M +86 185 0681 6876
E likaina@westlake.edu.cn

发件人: Hongtao Yu <Hongtao.Yu@UTSouthwestern.edu>
发送时间: 2020年2月19日 10:00
收件人: Kaina LI 李凯娜 <likaina@westlake.edu.cn>
主题: Fwd: trip

FYI

> Begin forwarded message:
>
> **From:** "Xiao-Fan Wang, Ph.D."
> <xiao.fan.wang@duke.edu>
> **Subject: trip**
> **Date:** February 18, 2020 at 7:58:51 PM CST
> **To:** "Hongtao.Yu@UTSouthwestern.edu"
> <Hongtao.Yu@UTSouthwestern.edu>
>
> EXTERNAL MAIL
>
> Hi Hongtao:
>
> Thanks for the invitation. I checked flight information and would like them to book the following flights from AA (direct flights):
>
> My DOB is [redacted], and AA number is [redacted].
> Xiao-Fan Wang
>
> Thanks, XF

Your trip summary

Main Cabin

Round trip (Non-refundable)

$ 595 per person

Total $594.81 (all passengers)
Price and tax information , Opens in a new window.

Good value with benefits

- Choose your seat (fee may apply)
- Eligible for upgrades on American flights
- Flight changes allowed (fee applies)
- General boarding

Includes taxes and carrier imposed fees.
Bag and optional fees , Opens in a new window.

Depart

Raleigh/ Durham, NC to Dallas/ Fort Worth, TX

Friday, March 6, 2020

11:31 AM 1:44 PM 3h 13m Nonstop Main Cabin

AA 1478 738-Boeing 737

Wi-Fi on-board

Power on-boardSeatbackApple music

- Details, for RDU to DFW, departing at 11:31 AM Nonstop
- Changefor RDU to DFW, departing at 11:31 AM Nonstop

Return

Dallas/ Fort Worth, TX to Raleigh/ Durham, NC

Saturday, March 7, 2020

2:54 PM 6:37 PM 2h 43m Nonstop Main Cabin

AA 2356 738-Boeing 737

Wi-Fi on-board

Power on-boardApple music

- Details, for DFW to RDU, departing at 2:54 PM Nonstop
-

address before replying.

UT Southwestern

Medical Center

The future of medicine, today.

<Annex 1 Prof. Xiao-Fan Wang ‘s Schedule and Faculty Candidate Interview Agenda (March 6-7).pdf><Annex 2 Information for TT Overseas.docx>

From: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Sent time: 03/07/2020 05:12:54 AM
To: Kaina LI 李凯娜 <likaina@westlake.edu.cn>
Cc: kunliang guan <guankunliang@yahoo.com>; Fu, Xiang-Dong
Subject: Re: Zoom: Meeting ID and Password

Thanks! Are you going to send another message that I can link to the meeting as last night? XF

> On Mar 7, 2020, at 4:49 AM, Kaina LI 李凯娜 <likaina@westlake.edu.cn> wrote:
>
> Dear all,
>
> Our interview will be conducted via Zoom. The information is as follows:
>
> **Meeting ID:** [redacted]
> **Password:** [redacted]
> **Time:**
> Beijing Time: 21:50-1:00
> Durham Time: 8:50- 12:00
> San Diego Time: 5:50- 9:00
>
> We'd really appreciate it if you could enter the meeting 5 minutes in advance. Thanks a lot and Hope it doesn't inconvenience you too much.
> Please feel free to contact me if you have any questions.
>
> Best,
>
> Kaina

From: Xiao-Fan Wang, Ph D. <xiao.fan.wang@duke.edu>
Sent time: 04/13/2020 05:59:42 PM
To: Fu, Xiang-Dong
Subject: Re: Filled forms
Attachments: Fu Passport Front page.JPG

Thanks!

Sent from my iPhone

> On Apr 13, 2020, at 8:48 PM, Fu, Xiang-Dong <xdfu@health.ucsd.edu> wrote:
>
> I attached the two review forms with my evaluations and the two reimbursement forms. I also attach the front page of my passport.
> <Fu Passport Front page.JPG>
>
> Fu
>
> Xiang-Dong Fu,
> Distinguished Professor
> Dept. of Cellular and Molecular Medicine
> University of California, San Diego
> George Palade Laboratories
> 9500 Gilman Drive, Room 217
> La Jolla, CA 92093-0651
>
> Phone: 858-534-4937
> Email: xdfu@health.ucsd.edu
>
> > On Apr 13, 2020, at 5:27 PM, Xiao-Fan Wang, Ph.D. <xiao fan.wang@duke.edu> wrote:
> >
> > Thanks!
> >
> > Sent from my iPhone
> >
> [redacted] Candidate evaluation form.doc>
> [redacted] Candidate evaluation form.doc>
> [redacted] reimbursment form-[redacted]
> [redacted]
> [redacted] -reimbursment form-[redacted]

From: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Sent time: 04/30/2020 05:06:17 PM
To: xdfu@ucsd.edu
Subject: Fwd:

He will write to KL. XF

Begin forwarded message:

From: Hongtao Yu <Hongtao.Yu@UTSouthwestern.edu>
Subject: Re:
Date: April 30, 2020 at 7:42:40 PM EDT
To: "Xiao-Fan Wang, Ph.D." <xiao.fan.wang@duke.edu>

We will have another interview session in a couple of weeks. I am thinking of inviting different people for each panel. Otherwise it will be too much work for you guys. I am going to invite him and others for the next panel. Purely logistical. I will send an email to him to explain.

Hongtao

On May 1, 2020, at 2:55 AM, Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu> wrote:

I received the documents related to the interview of candidates next Thursday evening our time. However, I noticed that Kun-Liang was not invited this time, was there a reason? He has been seriously considering to go to WLU because of all the problems here, and I do not want to hurt his feelings if he finds out about this event [redacted]). One more person on the panel does not make a difference, in my opinion, but you do not want to create a problem.

Just want to make sure that this was not an issue for the future. XF

From: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Sent time: 05/05/2020 05:53:15 PM
To: Fu, Xiang-Dong
Subject: Re: comments

Thanks! XF
> On May 5, 2020, at 8:45 PM, Fu, Xiang-Dong wrote:
>
>

From: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
Sent time: 06/21/2020 09:02:02 AM
To: Fu, Xiang-Dong
Subject: Re: another one

Thank you very much! XF

> On Jun 21, 2020, at 11:55 AM, Fu, Xiang-Dong wrote:
>
>

From: xinxinzuo2012
To: Fu, Xiang-Dong; Yu Zhou
Subject: The work progress of TDP43 revision
Date: Sunday, August 2, 2020 11:15:17 PM
Attachments: 2020-07 TDP work progress.pptx

Dear all,

Two months have passed since I went back to the lab. I would like to share the summary of recent work progress. Most of the questions have been answered and all the experiments were carried out more than three times to make the conclusion.

Besides, we got the latest RNA-seq data (siNC/mock cells) last Friday. Zhoujie has downloaded for analysis. Meanwhile, I will continue to improve the data related to Fig3, [redacted]. If all goes well, we may finish all the work by the end of August.

Wish all you safe and sound.

Xinxin

From: 陈亮
To: Fu, Xiang-Dong
Cc: Chen, Jiayu; Dohwan; Liang Chen; Xuan Zhang
Subject: Re: [SPAM] Editor"s Decision MOLECULAR-CELL-D-20-00717
Date: Wednesday, June 3, 2020 7:33:20 AM

Sure, I prefer R-ChIP in different cell cycle stages. We will next discuss and come up with a more detailed plan.

Liang

> On Jun 3, 2020, at 9:05 AM, Fu, Xiang-Dong <xdfu@health.ucsd.edu> wrote:
>
> We need to divide up who should do what among the 3 experiments. Which one you feel most comfortable to do?
>
> Fu
>
> Xiang-Dong Fu,
> Distinguished Professor
> Dept. of Cellular and Molecular Medicine
> University of California, San Diego
> George Palade Laboratories
> 9500 Gilman Drive, Room 217
> La Jolla, CA 92093-0651
>
> Phone: 858-534-4937
> Email: xdfu@health.ucsd.edu
>
> > On Jun 2, 2020, at 6:00 PM, 陈亮 <00031945@whu.edu.cn> wrote:
> >
> > Dear Fu,
> >
> > Great! Thank you for forwarding us the response from the editor. I have learned a lot from this submission and communication process just like before.
> >
> > Please let me know if there is anything I can do to improve the ms during revision.
> >
> > Thank you again and good luck to all of us.
> >
> > Cheers,

Liang

On Jun 3, 2020, at 7:19 AM, Fu, Xiang-Dong <xdfu@health.ucsd.edu> wrote:

We got encouraging response from the editor.

Fu

Begin forwarded message:

From: "Navarro, Caryn (ELS-CMA)" <cnavarro@cell.com>
Subject: Re: Editor's Decision MOLECULAR-CELL-D-20-00717
Date: June 2, 2020 at 4:13:14 PM PDT
To: "Fu, Xiang-Dong" <xdfu@health.ucsd.edu>, CELL PRESS Molecular Cell Online Manuscripts <molecule@cell.com>
Cc: "Sollier, Julie (ELS-CMA)" <jsollier@cell.com>

Dear Fu,

Thank you for your message. I appreciate that you would like to put in the extra effort to improve the results for your manuscript and would be willing to take a look at your revised version when you are ready. As you know there is no guarantee but I am open to reading your revised submission and proceeding from there. Please let me know if you have additional questions.

Best wishes,
Caryn

Caryn Navarro, PhD
Scientific Editor, *Molecular Cell*
50 Hampshire Street, 5th floor
Cambridge, MA 02139

From: "Fu, Xiang-Dong" <xdfu@health.ucsd.edu>
Date: Tuesday, June 2, 2020 at 6:37 PM
To: CELL PRESS Molecular Cell Online Manuscripts <molecule@cell.com>, "Navarro, Caryn (ELS-CMA)" <cnavarro@cell.com>
Cc: "Sollier, Julie (ELS-CMA)" <jsollier@cell.com>
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[redacted]

[redacted]

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A simple email from you would be highly appreciated.

Best regards,

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Email: xdfu@health.ucsd.edu

> On May 29, 2020, at 4:22 AM, Molecular Cell Editorial Office <em@editorialmanager.com> wrote:
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> Dr. Xiang-Dong Fu
> Div Of Cellular And

Molecular Medicine Ucsd
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UNITED STATES

Two Distinct Types of RNA:DNA Hybrids Revealed by Evaluating Divergent “R-loop” Profiles Detected with Different Mapping Strategies
MOLECULAR-CELL-D-20-00717

May 29, 2020

Dear Dr. Fu,

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[redacted] I am sorry that the

outcome for this manuscript could not have been more positive and I hope the comments of the reviewers will prove constructive as you prepare the manuscript for submission to another journal. I do want to emphasize, however, that this is not intended to imply a lack of interest on our part in either your work in particular or this field in general, and we hope that you will continue to consider Molecular Cell for other submissions in the future when it seems appropriate.

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Decline to Transfer

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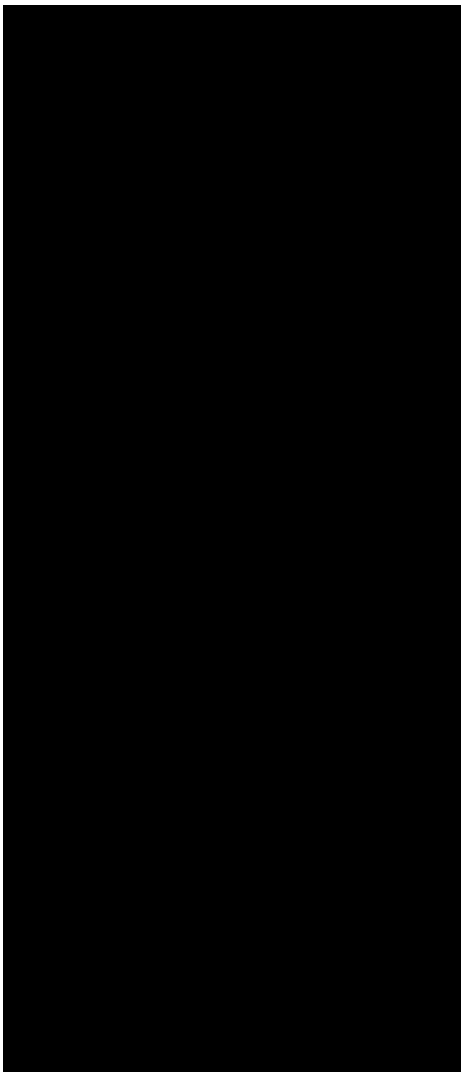
Best wishes,

Caryn

Caryn Navarro, Ph.D.
Scientific Editor, Molecular Cell

Reviewer Comments:



From: 陈亮
To: Fu, Xiang-Dong
Cc: Chen, Jiayu; Dohwan; Liang Chen; Xuan Zhang
Subject: Re: [SPAM] Fwd: Editor"s Decision MOLECULAR-CELL-D-20-00717
Date: Tuesday, June 2, 2020 6:00:26 PM

Dear Fu,

Great! Thank you for forwarding us the response from the editor. I have learned a lot from this submission and communication process just like before.

Please let me know if there is anything I can do to improve the ms during revision.

Thank you again and good luck to all of us.

Cheers,

Liang

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A simple email from you would be highly appreciated.

Best regards,

Fu

Xiang-Dong Fu,
Distinguished Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

> On May 29, 2020, at 4:22 AM, Molecular Cell Editorial Office <em@editorialmanager.com> wrote:
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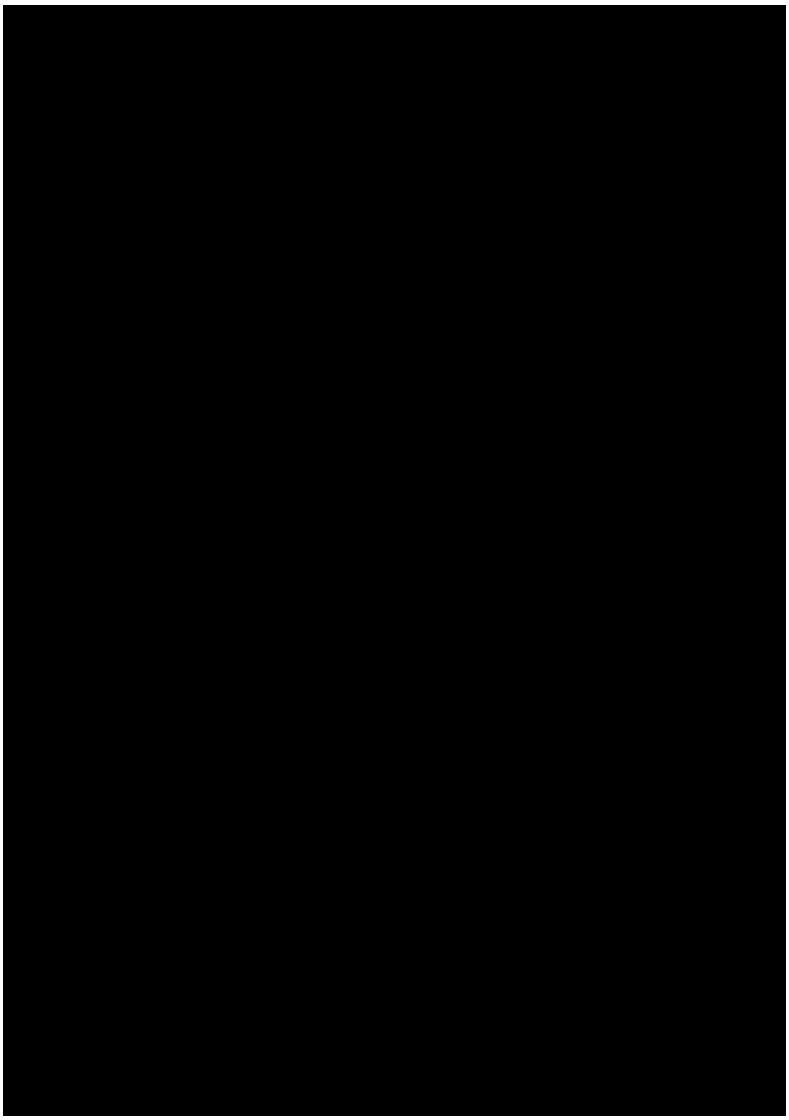
Reviewer Comments:



From: Fu, Xiang-Dong
To: Chen, Jiayu; Dohwan; Liang Chen; Xuan Zhang
Subject: Fwd: Editor"s Decision MOLECULAR-CELL-D-20-00717
Date: Tuesday, June 2, 2020 4:19:55 PM

We got encouraging response from the editor.

Fu

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Caryn

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Scientific Editor, Molecular Cell

Reviewer Comments:

From: Fu, Xiang-Dong
To: Chen, Jiayu; Dohwan; Liang Chen
Subject: Fwd: Editor"s Decision MOLECULAR-CELL-D-20-00717
Date: Tuesday, June 2, 2020 3:38:47 PM

This is the email I just sent to the Mol Cell editor.

Fu

Begin forwarded message:

From: "Fu, Xiang-Dong" <xdfu@health.ucsd.edu>
Subject: Re: Editor's Decision MOLECULAR-CELL-D-20-00717
Date: June 2, 2020 at 3:37:31 PM PDT
To: Molecular Cell Editorial Office <molecule@cell.com>, cnavarro@cell.com
Cc: "Sollier, Julie (ELS-CMA)" <jsollier@cell.com>

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Scientific Editor, Molecular Cell

Reviewer Comments:

[redacted]

From:	Chen, Jiayu
To:	Fu, Xiang-Dong
Cc:	Lim, Do-Hwan; Liang CHEN
Subject:	draft of rebuttal letter
Date:	Sunday, May 31, 2020 11:07:07 PM
Attachments:	Rebuttal.docx

Dear Fu,

Please find the attached for a draft of rebuttal letter. I have incorporated both Liang's and Dohwan's comments. Highlighted in yellow are what we need to discuss. You mentioned that you will be present in the lab tomorrow. I will too. We'd like to hear your advices how to proceed then.

Best,

Jiayu (Jerry) Chen, Ph.D.
Postdoc, Xiang-Dong Fu's lab
Department of Cellular and Molecular Medicine,
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 219
La Jolla, CA 92093-0651

From: Chen, Jiayu
To: Fu, Xiang-Dong
Cc: Lim, Do-Hwan; Liang CHEN
Subject: Re: Editor"s Decision MOLECULAR-CELL-D-20-00717
Date: Friday, May 29, 2020 9:00:05 AM

Dear Fu,

Those comments related to data analysis are quite easy to address [redacted]

How we are gonna proceed? I think three options are available. (1) design and perform a few new set of experiments and argue back. My concern is that it will take extra time and the output is unpredictable. And the editor seems not so optimistic to publication even with revision. (2) transfer to other Cell Press journal after a quick revision. But it seems that there is no specialized bioinformatics journal. (3) try Genome Biology / PNAS / NAR, or Genome Research, although its reviewing process is so slow.

In the meanwhile we can perform a few key experiments, intended to improve our manuscript and address potential comments from new reviewers.

What do you think?

Jiayu (Jerry) Chen, Ph.D.
Postdoc, Xiang-Dong Fu's lab
Department of Cellular and Molecular Medicine,
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 219
La Jolla, CA 92093-0651

From: Fu, Xiang-Dong <xdfu@health.ucsd.edu>
Sent: Friday, May 29, 2020 7:51 AM
To: Chen, Jiayu <jic386@health.ucsd.edu>
Subject: Fwd: Editor's Decision MOLECULAR-CELL-D-20-00717

As we predicted, the reviewers hammered on us with a lot of questions.

Xiang-Dong Fu,
Distinguished Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

Begin forwarded message:

From: "Molecular Cell Editorial Office" <em@editorialmanager.com>
Subject: Editor's Decision MOLECULAR-CELL-D-20-00717
Date: May 29, 2020 at 4:22:41 AM PDT
To: "Xiang-Dong Fu" <xdfu@ucsd.edu>
Reply-To: "Molecular Cell Editorial Office" <molecule@cell.com>

Dr. Xiang-Dong Fu
Div Of Cellular And
Molecular Medicine Ucsd
9500 Gilman Dr.
La Jolla, CA 92093 0651
UNITED STATES

Two Distinct Types of RNA:DNA Hybrids Revealed by Evaluating Divergent "R-loop" Profiles Detected with Different Mapping Strategies
MOLECULAR-CELL-D-20-00717

May 29, 2020

Dear Dr. Fu,

I'd like to apologize for the delay in getting back to you, the review process took longer than I anticipated. I am now enclosing the comments that the reviewers have made on your paper, and unfortunately, the overall recommendation is against publication in Molecular Cell. [redacted] I am sorry that the outcome for this manuscript could not have been more positive and I hope the comments of the reviewers will prove constructive as you prepare the manuscript for submission to another journal. I do want to emphasize, however, that this is not intended to imply a lack of interest on our part in either your work in particular or this field in general, and we hope that you will continue to consider Molecular Cell for other submissions in the future when it seems appropriate.

At this stage, you have the option of transferring your paper to another Cell Press journal. If you would like to pursue this option, please click on the link below.

Agree to Transfer

This link will bring you to a page where you can select the journal, and your files will be transferred. You will then have an opportunity to update and approve your

materials before they are ultimately delivered to the editor. For more information on the transfer process, please read here.

If you decide not to transfer this manuscript, please click here to decline:

Decline to Transfer

Declining to transfer will officially close out the manuscript in our system. If you do not accept or decline by Jun 28, 2020, the system will automatically decline on your behalf. If you prefer, you do have the choice of submitting this manuscript or a revised version of it to another Cell Press journal as a regular new submission, in which case you can decline the transfer.

Best wishes,

Caryn

Caryn Navarro, Ph.D.
Scientific Editor, Molecular Cell

Reviewer Comments:

From: Fu, Xiang-Dong
To: Yi Rao; Shi, Yigong; Xiao-Fan Wang, Ph.D.
Subject: Submitted ms yesterday
Date: Tuesday, April 7, 2020 9:39:10 AM
Attachments: Submitted PTB PD ms 472020.pdf

Hi Yi, Yigong and Xiaofan,

Here is our manuscript we uploaded to the Nature website yesterday. Because of the large size for 20 supplementary figures, I only send you the main text with 7 main figures.

Fu

Xiang-Dong Fu,
Distinguished Professor
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9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

From:	Fu, Xiang-Dong
To:	Yi Rao; Shi, Yigong; Xiao-Fan Wang, Ph.D.
Subject:	Submitted ms yesterday
Date:	Tuesday, April 7, 2020 9:30:58 AM
Attachments:	Submitted PTB PD ms 472020.pdf Extended Data Figures and Legends.pdf

---

Hi Yi, Yigong and Xiaofan,

Here is our manuscript we uploaded to the Nature website yesterday.

Fu

Xiang-Dong Fu,
Distinguished Professor
Dept. of Cellular and Molecular Medicine
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George Palade Laboratories
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La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

From:	陈亮
To:	Fu, Xiang-Dong
Cc:	Jerry Chen; Lim, Do-Hwan; Zhang, Dong-Er; dongwang@ucsd.edu; Liang Chen; Changwei Shao; Xuan Zhang; Hai-Ri Li
Subject:	Re: R-loop ms for your proofreading
Date:	Wednesday, April 1, 2020 6:42:23 AM
Attachments:	R loop ms 20200330-CL.docx

Dear Fu,

Great work! It is a very thorough and deep comparison among various R-loop mapping technologies to date and glad to see R-ChIP stands out as a superior method in most of these comparisons. Well done, Jerry. I added my comments in the attached draft.

Cheers,

Liang

> On Apr 1, 2020, at 12:54 PM, Lim, Do-Hwan <dol112@health.ucsd.edu> wrote:
>
> <R loop ms 20200330_edit.docx>

From:	Wang, Dong
To:	Fu, Xiang-Dong
Cc:	Zhang, Dong-Er; dongwang@ucsd.edu; Liang Chen; Dohwan; Shao, Changwei; Xuan Zhang; Li, Hai; Chen, Jiayu
Subject:	Re: R-loop ms for your proofreading
Date:	Tuesday, March 31, 2020 10:29:11 PM
Attachments:	R loop ms 20200330_DW.docx R loop ms 20200330.docx

---

Hi Fu
It reads great, I really enjoyed reading the manuscript and I believe it is an important work that systematically investigate discrepancy among different R-loop methods and help clarify some confusions. Importantly, also identify two types of RNA:DNA hybrid profiles. I added my comments in attachment.
best
Dong

Dong Wang
Professor
Division of Pharmaceutical Sciences,
Skaggs School of Pharmacy & Pharmaceutical Sciences;
Department of Cellular and Molecular Medicine,
School of Medicine;
Department of Chemistry and Biochemistry,
University of California San Diego
PSB 2266, MC 0751
9500 Gilman Drive,
La Jolla, CA 92093-0751
Phone: 858 822 5561
Email: dongwang@ucsd.edu
Lab Website: https://dongwang.ucsd.edu

> On Mar 31, 2020, at 1:42 PM, Fu, Xiang-Dong <xdfu@health.ucsd.edu> wrote:
>
> Dear all,
>
> Jiayu and I have been working intensively on a new R-loop manuscript, as attached. Initially, we intended to address various technical issues associated with individual R-loop mapping technologies. When the story is developed along the way, we ended up learning a lot of new information, which will be instrumental to the field. It has taken a lot of efforts in describing the results and findings in a logical fashion, as such we may be blinded for various points we are making that may not be apparent to you.
>
> Therefore, each of you please read it carefully to identify potential holes. You may simply add your comments to indicate which points are confusing and thus in need of further elaboration/clarification.
>
> We may first give it try at Mol Cell. Please help judge if we are aiming too high, and if so, please let us which journal you would suggest.

Best,

Fu

Xiang-Dong Fu,
Distinguished Professor
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9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

From: Lim, Do-Hwan
To: Fu, Xiang-Dong; Jerry Chen
Cc: Zhang, Dong-Er; dongwang@ucsd.edu; Liang Chen; Changwei_UCSD; Xuan Zhang; Hai-Ri Li
Subject: Re: R-loop ms for your proofreading
Date: Tuesday, March 31, 2020 9:54:52 PM
Attachments: R loop ms 20200330_edit.docx

Dear all,

Great job !! This version is much better!!

I found some typos in the manuscript and I have some questions and comments.

Best,

Dohwan

Dohwan Lim, Ph.D.
University of California, San Diego
Department of Cellular and Molecular Medicine
Email: dol112@ucsd.edu / wjdohwan1002@gmail.com

> On Mar 31, 2020, at 1:42 PM, Fu, Xiang-Dong <xdfu@health.ucsd.edu> wrote:
>
> Dear all,
>
> Jiayu and I have been working intensively on a new R-loop manuscript, as attached. Initially, we intended to address various technical issues associated with individual R-loop mapping technologies. When the story is developed along the way, we ended up learning a lot of new information, which will be instrumental to the field. It has taken a lot of efforts in describing the results and findings in a logical fashion, as such we may be blinded for various points we are making that may not be apparent to you.
>
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>
> We may first give it try at Mol Cell. Please help judge if we are aiming too high, and if so, please let us which journal you would suggest.
>
> Best,
>
> Fu
>
> Xiang-Dong Fu,
> Distinguished Professor
> Dept. of Cellular and Molecular Medicine
> University of California, San Diego

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9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

<R loop ms 20200330.docx>

From:	Shao, Changwei
To:	Fu, Xiang-Dong
Cc:	Zhang, Dong-Er; dongwang@ucsd.edu; Liang Chen; Dohwan Lim; Shao, Changwei; Xuan Zhang; Li, Hai; Chen, Jiayu
Subject:	Re: R-loop ms for your proofreading
Date:	Tuesday, March 31, 2020 6:58:11 PM
Attachments:	R loop ms 20200330_Changwei.docx

Dear all,

Good job, great improvement comparison with last version.

I made some comments to confusing points, and raised some questions for clarification, and also gave some suggestions from the perspective of reviewer.

Hope to be helpful.

Best,
Changwei

> On Mar 31, 2020, at 13:42, Fu, Xiang-Dong <xdfu@health.ucsd.edu> wrote:
>
> Dear all,
>
> Jiayu and I have been working intensively on a new R-loop manuscript, as attached. Initially, we intended to address various technical issues associated with individual R-loop mapping technologies. When the story is developed along the way, we ended up learning a lot of new information, which will be instrumental to the field. It has taken a lot of efforts in describing the results and findings in a logical fashion, as such we may be blinded for various points we are making that may not be apparent to you.
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>
> We may first give it try at Mol Cell. Please help judge if we are aiming too high, and if so, please let us which journal you would suggest.
>
> Best,
>
> Fu
>
> Xiang-Dong Fu,
> Distinguished Professor
> Dept. of Cellular and Molecular Medicine
> University of California, San Diego
> George Palade Laboratories
> 9500 Gilman Drive, Room 217
> La Jolla, CA 92093-0651
>
> Phone: 858-534-4937
> Email: xdfu@health.ucsd.edu

<R loop ms 20200330.docx>

From: Fu, Xiang-Dong
To: Zhang, Dong-Er; dongwang@ucsd.edu; Liang Chen; Dohwan; Shao, Changwei; Xuan Zhang; Li, Hai
Cc: Chen, Jiayu
Subject: R-loop ms for your proofreading
Date: Tuesday, March 31, 2020 1:42:19 PM
Attachments: R loop ms 20200330.docx

Dear all,

Jiayu and I have been working intensively on a new R-loop manuscript, as attached. Initially, we intended to address various technical issues associated with individual R-loop mapping technologies. When the story is developed along the way, we ended up learning a lot of new information, which will be instrumental to the field. It has taken a lot of efforts in describing the results and findings in a logical fashion, as such we may be blinded for various points we are making that may not be apparent to you.

Therefore, each of you please read it carefully to identify potential holes. You may simply add your comments to indicate which points are confusing and thus in need of further elaboration/clarification.

We may first give it try at Mol Cell. Please help judge if we are aiming too high, and if so, please let us which journal you would suggest.

Best,

Fu

Xiang-Dong Fu,
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Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

From: 陈亮
To: Fu, Xiang-Dong
Subject: Re: Greetings
Date: Friday, March 27, 2020 6:00:53 PM

Hi Fu,

Thank you for your reply and very glad to know you are working at home now, since it is the most effective way to stay away from COVID-19. Please try to be safe and keep social distancing.

Jerry contacted me yesterday and it is my great pleasure to be of help on the manuscript.

Best wishes and hopefully see you soon after the pandemic is over.

Liang

> On Mar 28, 2020, at 2:10 AM, Fu, Xiang-Dong <xdfu@health.ucsd.edu> wrote:
>
> Dear Liang,
>
> Thanks for your warm message. So far, I have been working at home. The campus is pretty much shut down for now and it is unclear when it will be re-open. However, people can still go to the lab to take care of some key, minimal essential experiments.
>
> Also thanks for offering masks. Liu Mofang has sent me a package. As we do not go out often except shopping for foods once a month, I think we have enough. If needed, I will let you know.
>
> Hopefully, the pandemic will be over by the summer and I will be able to travel in the second half of the year. I am close to be done in working with Jiayu on a new R-loop manuscript. We hope to send a reasonable draft for your comments soon.
>
> Stay in touch,
>
> Fu
>
> Xiang-Dong Fu,
> Distinguished Professor
> Dept. of Cellular and Molecular Medicine
> University of California, San Diego
> George Palade Laboratories
> 9500 Gilman Drive, Room 217
> La Jolla, CA 92093-0651
>
> Phone: 858-534-4937
> Email: xdfu@health.ucsd.edu
>
>
>
>> On Mar 25, 2020, at 6:09 PM, 陈亮 <00031945@whu.edu.cn> wrote:
>>
>> Dear Fu,
>>
>> It is has been a few months since our last email. Hope things goes well with you and your family under such a difficult time.

>>
>> After a long time of fighting against COVID-19, most part of China is gradually getting back to normal now and Wuhan is going to catch up soon. However, the global spreading of COVID-19 pandemic seems to be accelerating and inevitable. Under such an unexpected situation, I sincerely wish you and your family all the best. Please be sure to take care of yourself and protect well. Also please let me know if you need masks for protection. It might be easy to buy some from China and I may help.
>>
>> Best wishes and wish to see you soon in Wuhan.
>>
>> Liang
>>
>>
>

From: Fu, Xiang-Dong
To: xinxinzuo2012
Cc: Yu Zhou
Subject: Re: quick comments on the reviews of your ms
Date: Tuesday, January 14, 2020 6:00:36 PM

Sound great! I know you are working hard to get the experiments done in a timely manner. In this round of review, I think the reviewers are reasonable and the editor is clearly on our side.

Cheers and see you soon.

Fu

Xiang-Dong Fu,
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9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

> On Jan 14, 2020, at 5:34 PM, xinxinzuo2012 <xinxinzuo2012@aliyun.com> wrote:
>
> Dear Fu,
>
> Thank you for your letter. I have quickly go through your modified response, and I'd like to share the recent progress.
>
> Briefly, several experiments have done or ongoing: 1) sodium arsenite induces TDP-43 aggregation with N2a cells. 2) Validation of additional miRNAs sequestered by TDP-43 such as miR-669c. 3) KD or OE of specific mitochondrial proteins.
>
> Besides, we still need a set of RNA-seq data of non-treated cells (which used as control to siNC). RNA samples could be soon prepared but it could not be sent out until the Spring Festival holiday is over. Meanwhile, ZhouJie could analyze with our existing data.
>
> Happy coming Spring Festival and looking forward to the thorough discussion with you in Wuhan!

Xinxin

发件人:Fu, Xiang-Dong <xdfu@health.ucsd.edu>
发送时间:2020年1月15日(星期三) 04:46
收件人:Yu Zhou <yu.zhou@whu.edu.cn>
抄 送:xinxinzuo2012 <xinxinzuo2012@aliyun.com>
主 题:Re: quick comments on the reviews of your ms

Sorry for the delay. I have gone through your proposed response. In most parts, you did a great job. I have made some initial modification and added a few comments in the attached file. From my judgement, we just need to do 3 additional sets of experiments, 2 addressing the points raised by reviewer 1 and 1 to the remaining point by reviewer 3. As the editor is in our side, we can largely ignore reviewer 2.

We will discuss various details during the lunar new year when we meet. As Xinxin is very efficient, some of those experiments may have been already done or in progress.

I have great confidence that this paper will sail at NSMB.

Fu

Xiang-Dong Fu,
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Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

> On Jan 6, 2020, at 3:18 AM, Yu Zhou <yu.zhou@whu.edu.cn> wrote:
>
> Dear Fu,
>
> We have drafted an initial point-to-point response letter, in which RED points are what we plan to do. Please review it and let us know your suggestions. Thanks a lot!
>
>
> Best,
> Yu
>

From: xinxinzuo2012
To: F...X ang-Dong; ...hou...Y...
Subject: 回复:quick comments on the ...eviews of your ms
Date: Friday ,January 3 2020 5:29:35 PM

Dear Fu,

It's a pleasure to receive this news!

I have talked with Zhouyu and decide to answer these questions point to point. Later after we package all the answers and the experiments, we w ll sent to you for your perusal.

Best wishes!

Xinxin

发件人:Fu, Xiang-Dong <xdfu@health.ucsd.edu>
发送时间:2020年1月4日(星期六) 06:31
收件人:x nxinzuo2012 <xinxinzuo2012@aliyun.com>; Zhou Yu <yu.zhou@whu.edu.cn>
主 题:quick comments on the rev ews of your ms

Hi Xinxin and Zhou Yu,

I just glanced the reviews. Most are easy to address, even the nasty comments from reviewer #2. Reviewer 1 and 3 suggested a few simple experiments, some of which you have already done, but not included in the manuscr pt. Other than that, most questions just need some clarif cation.

In any case, please go through the reviews and develop a revision plan. You may indicate how you will address each specific question, either exper mentally or through clarif cation. Once you have the plan, send it to me for suggestions. We should be able to get through with easy revis on.

Fu

Xiang-Dong Fu,
Distingu shed Professor
Dept. of Ce lular and Molecular Medicine
Univers ty of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

From: Yu Zhou
To: Fu, Xiang-Dong
Cc: xinxinzuo2012
Subject: Re: quick comments on the reviews of your ms
Date: Friday, January 3, 2020 4:08:42 PM

I just find the email with comments in the SPAM box, probably due to your new email address.

Thanks!

Yu
> 在 2020年1月4日,上午8:04,Yu Zhou <yu.zhou@whu.edu.cn> 写道:
>
> Dear Fu,
>
> OK! Could you please forward us the reviewer comments? Thanks a lot!
>
> Best,
> Yu
>
>> 在 2020年1月4日,上午6:31,Fu, Xiang-Dong <xdfu@health.ucsd.edu> 写道:
>>
>> Hi Xinxin and Zhou Yu,
>>
>> I just glanced the reviews. Most are easy to address, even the nasty comments from reviewer #2. Reviewer 1 and 3 suggested a few simple experiments, some of which you have already done, but not included in the manuscript. Other than that, most questions just need some clarification.
>>
>> In any case, please go through the reviews and develop a revision plan. You may indicate how you will address each specific question, either experimentally or through clarification. Once you have the plan, send it to me for suggestions. We should be able to get through with easy revision.
>>
>> Fu
>>
>> Xiang-Dong Fu,
>> Distinguished Professor
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>>
>> Phone: 858-534-4937
>> Email: xdfu@health.ucsd.edu
>>
>>
>>
>

From: Fu, Xiang-Dong
To: xinxinzuo2012; Zhou Yu
Subject: Fwd: Decision on Nature Structural & Molecular Biology submission NSMB-A42584
Date: Friday, January 3, 2020 12:16:30 PM

The reviews are back. In general, the criticisms are addressable. Reviewer 2 was nasty, but the editor clearly indicated that she will ignore him/her, and in fact, the lack of details in his/her criticisms makes it easier to respond.

Please digest the reviews and develop a plan for revision.

Fu

Xiang-Dong Fu,
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La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

Begin forwarded message:

From: Anke.Sparmann@nature.com
Subject: Decision on Nature Structural & Molecular Biology submission NSMB-A42584
Date: January 4, 2020 at 12:00:57 AM GMT+10
To: xdfu@ucsd.edu
Reply-To: Anke.Sparmann@nature.com

3rd Jan 2020

Dear Fu,

Happy New Year! I hope you had a good start into 2020. Thank you again for submitting your manuscript "Oxidative Stress Induces TDP-43 Aggregation to Cause Global Mitochondrial Imbalance in ALS". My apologies for the delay in reaching a decision due to the intervening winter holidays and the associated difficulties in obtaining timely referee reports. Nevertheless, we now have comments from the three reviewers who evaluated your paper (appended below). In light of those reports, we remain interested in your study and would like to invite you to respond to the comments of the referees, in the form of a revised manuscript.

[redacted] Please also be sure to address/respond to all other concerns of the
reviewers in full in a point-by-point response and highlight all changes in the revised manuscript text file.

We appreciate that the requested revisions are extensive. Given the time and effort such a revision would entail and the competitive situation, we would of course understand if you prefer to seek publication elsewhere. However, if you wish to resubmit a suitably revised manuscript we would expect to see it within 6 months. If you cannot send it within this time, please let us know. We will be happy to consider your revision so long as nothing similar has been accepted for publication at Nature Structural & Molecular Biology or published elsewhere. Should your manuscript be delayed and your article is eventually published, the received date would be that of the revised, not the original, version. If you decide to submit the work as is elsewhere, please let us know, so that our process can be closed (otherwise, it would be considered dual submission).

We are committed to providing a fair and constructive peer-review process. Do not hesitate to contact us if there are specific requests from the reviewers that you believe are technically impossible or unlikely to yield a meaningful outcome.

As you already know, we put great emphasis on ensuring that the methods and statistics reported in our papers are correct and accurate. As such, if there are any changes that should be reported, please submit an updated version of the Reporting Summary along with your revision.

Reporting Summary:
https://www.nature.com/documents/nr-reporting-summary.pdf

Please note that the form is a dynamic 'smart pdf' and must therefore be downloaded and completed in Adobe Reader.

Please note that all key data shown in the main figures as cropped gels or blots should be presented in uncropped form, with molecular weight markers. These data can be aggregated into a single supplementary figure. While these data can be displayed in a relatively informal style, they must refer back to the relevant figures. These data should be submitted with the last revision, prior to acceptance, but you may want to start putting it together at this point.

SOURCE DATA: We urge authors to provide, in tabular form, the data underlying the graphical representations used in figures. This is to further increase transparency in data reporting, as detailed in this editorial (http://www.nature.com/nsmb/journal/v22/n10/full/nsmb.3110.html). Spreadsheets can be submitted in excel format. Only one (1) file per figure is permitted; thus, for multi-paneled figures, the source data for each panel should be clearly labeled in the Excel file; alternately the data can be provided as multiple, clearly labeled sheets in an Excel file. When submitting files, the title field should indicate which figure the source data pertains to. We encourage our authors to provide source data at the revision stage, so that they are part of the peer-review process.

While we encourage the use of color in preparing figures, please note that this will incur a charge to partially defray the cost of printing. Information about color charges can be found at http://www.nature.com/nsmb/authors/submit/index.html#costs

We require deposition of coordinates (and, in the case of crystal structures, structure factors) into the Protein Data Bank with the designation of immediate release upon publication (HPUB). Electron microscopy-derived density maps and coordinate data must be deposited in EMDB and released upon publication. Deposition and immediate release of NMR chemical shift assignments are highly encouraged. Deposition of deep sequencing and microarray data is mandatory, and the datasets must be released prior to or upon publication. To avoid delays in publication, dataset accession numbers must be supplied with the final accepted manuscript and appropriate release dates must be indicated at the galley proof stage. Please find the complete NRG policies on data availability at http://www.nature.com/authors/policies/availability.html.

Nature Structural & Molecular Biology is committed to improving transparency in authorship. As part of our efforts in this direction, we are now requesting that all authors identified as ‘corresponding author’ on published papers create and link their Open Researcher and Contributor Identifier (ORCID) with their account on the Manuscript Tracking System (MTS), prior to acceptance. This applies to primary research papers only. ORCID helps the scientific community achieve unambiguous attribution of all scholarly contributions. You can create and link your ORCID from the home page of the MTS by clicking on ‘Modify my Springer Nature account’. For more information please visit please visit www.springernature.com/orcid.

Please use the link below to submit your revised manuscript and related files:

https://mts-nsmb.nature.com/cgi-bin/main.plex?el=A7J3ByV1A4DuK7J4A9ftdCfoNx4mf5ctsCP6Phfv5GAZ

Note: This URL links to your confidential home page and associated information about manuscripts you may have submitted, or that you are reviewing for us. If you wish to forward this email to co-authors, please delete the link to your

homepage.

We look forward to seeing the revised manuscript and thank you for the opportunity to review your work.

With kind regards,
Anke

Anke Sparmann, PhD
Senior Editor
Nature Structural and Molecular Biology
ORCID 0000-0001-7695-2049

Referee expertise:

Reviewers' Comments:

From: Yu Zhou
To: Fu, Xiang-Dong
Cc: xinxinzuo2012
Subject: Re: NSMB: NSMB-A42584 - Checklist request
Date: Tuesday, November 26, 2019 2:48:55 PM

Dear Fu,

Great news. You can use the completed forms sent you previously (You may update the dates in the two forms).

Thanks a lot!
Best,
Yu

> 在 2019年11月27日,上午2:32,Fu, Xiang-Dong <xdfu@health.ucsd.edu> 写道:
>
> Encouraging news.
>
> Xiang-Dong Fu,
> Distinguished Professor
> Dept. of Cellular and Molecular Medicine
> University of California, San Diego
> George Palade Laboratories
> 9500 Gilman Drive, Room 217
> La Jolla, CA 92093-0651
>
> Phone: 858-534-4937
> Email: xdfu@health.ucsd.edu
>
> Begin forwarded message:
>
> **From:** Anke.Sparmann@nature.com
> **Subject: NSMB: NSMB-A42584 - Checklist request**
> **Date:** November 26, 2019 at 9:52:23 AM PST
> **To:** xdfu@ucsd.edu
> **Reply-To:** Anke.Sparmann@nature.com
>
> Our ref: NSMB-A42584
>
> 26th Nov 2019
>
> Dear Fu,
>
> Thanks for submitting your paper, "Oxidative Stress Induces TDP-43 Aggregation to Cause Global Mitochondrial Imbalance in ALS", to Nature Structural & Molecular Biology. I'm writing to let you know

that we have decided to send your manuscript for peer review.

We want to ensure that the methods and statistics reporting in our papers are of the highest quality. To that end, we ask authors to fill out a Reporting Summary that collects information on experimental design and reagents, as well as an editorial Policy Checklist, which confirms compliance with our editorial policies, including the declaration of Competing Interests. If your paper includes ChIP-seq, flow cytometry or MRI data, we ask you take special care to complete those sections of the Reporting Summary as this data will aid greatly in the review of your manuscript.

These documents can be found by following the links below:

Reporting Summary:
https://www.nature.com/documents/nr-reporting-summary.pdf

Editorial Policy Checklist: https://www.nature.com/documents/nr-editorial-policy-checklist.pdf

Please complete the relevant forms and return them within 48 hours. Please note that these forms are dynamic 'smart pdfs' and must, therefore, be downloaded and completed in Adobe Reader. We will then flatten them for ease of use by the reviewers. If you would like to reference the guidance text as you complete the template, please access these flattened versions at
http://www.nature.com/authors/policies/availability.html.

Note that you are not required to revise your paper to include the information provided in the reporting summary. However, all points on the policy checklist must be addressed; please send me a new version of the manuscript with your completed checklist if needed.

Once we receive these documents and review them to ensure that all requested information is provided, we will proceed to send your paper for review. If you have questions or anticipate delays, please let me know as soon as possible.

With kind regards,
Anke

Anke Sparmann, PhD
Senior Editor
Nature Structural and Molecular Biology
ORCID 0000-0001-7695-2049

System NY-610A-NPG&MTS

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From:	Yeo, Eugene
To:	Yu Zhou
Cc:	Fu, Xiang-Dong; xinxinzuo2012; Jiang, Li
Subject:	Re: Request for TDP-43 mutant ES cells
Date:	Thursday, November 21, 2019 9:37:00 AM

We have these mutations N352S and G298S but not the ones you want here.

You have to get the MTA for the G298S line from Kevin Eggan - since we don't own that line.

We don't have the M337V line but it's likely a Harvard (George Daley) IPSC line.
You can see Table S2
https://www.cell.com/cell-reports/pdfExtended/S2211-1247(17)30072-4
You can email George Daley for it.

gene

Gene Yeo, PhD, MBA
Professor
Dept of Cellular and Molecular Medicine, UCSD
Co-Director, UCSD Bioinformatics and Systems Biology Graduate Program
University of California, San Diego
Institute for Genomic Medicine
UCSD Stem Cell Program
http://yeolab.github.io

geneyeo@ucsd.edu
ewyeo@health.ucsd.edu

> On Nov 20, 2019, at 6:11 AM, Yu Zhou <yu.zhou@whu.edu.cn> wrote:
>
> Dear Gene,
>
> We want the iPS lines with TDP-43 mutations M337V, A315T, Q331K, or G335D. M337V is the one we want most.
>
> We would like to differentiate the iPS lines into neurons, and then compare the mutants with wt-human iPSCs-induced neurons in the following three aspects.
> 1) The sensitivity to oxidative stress
> 2) The ability of TDP-43 mutant on trapping miRNAs
> 3) Mitochondria-related assays (ROS production, mitochondrial morphology, expression level of specific mitochondrial proteins).
>
> Look forward to your suggestions. Thanks a lot!
>
> Best,
> Yu

在 2019年11月20日,下午12:04,Yeo, Eugene <ewyeo@health.ucsd.edu> 写道:

HI Yu,

Thanks for the invite!

I'm not sure we have ES lines anymore. But I will check. I believe if it's ES lines they must have come from WiCell or Harvard (G198S most likely).

We have IPS lines that we have reprogrammed from fibroblasts from John Ravits, let me check with my students which mutations we have - do you know which ones you want?

The MTA request from Wuhan should indicate the specific use that the lines will be constrained to, as we are legally required to fill in before exporting lines. Also, if it's a collaboration, it'll be necessary for my lab to know what they will be used for since it sounds like there's some overlap with our existing work (not a bad thing, but just checking).

gene

Gene Yeo, PhD, MBA
Professor
Dept of Cellular and Molecular Medicine, UCSD
Co-Director, UCSD Bioinformatics and Systems Biology Graduate Program
University of California, San Diego
Institute for Genomic Medicine
UCSD Stem Cell Program
http://yeolab.github.io

geneyeo@ucsd.edu
ewyeo@health.ucsd.edu

> On Nov 19, 2019, at 5:44 PM, Yu Zhou <yu.zhou@whu.edu.cn> wrote:
>
> Dear Gene,
>
> Could you please provide us the ES cells containing specific ALS-linked mutations? Please let me know any

paper work I need to complete. This will count as our collaborations.

P.S.: If you have time, I would like to invite you to visit our college and lab at Wuhan University. I think our PIs and students will enjoy your research and your visit will give us a lot of help. Wuhan is one of the top 5 biggest cities in China. :)

Best regards,
Yu

Yu Zhou, Ph.D.
Principal Investigator
College of Life Sciences, Room 6109
Wuhan University, China

From: Yu Zhou
To: Yeo, Eugene
Cc: Fu, Xiang-Dong; xinxinzuo2012; Jiang, Li
Subject: Re: Request for TDP-43 mutant ES cells
Date: Wednesday, November 20, 2019 6:11:55 AM

Dear Gene,

We want the iPS lines with TDP-43 mutations M337V, A315T, Q331K, or G335D. M337V is the one we want most.

We would like to differentiate the iPS lines into neurons, and then compare the mutants with wt-human iPSCs-induced neurons in the following three aspects.
1) The sensitivity to oxidative stress
2) The ability of TDP-43 mutant on trapping miRNAs
3) Mitochondria-related assays (ROS production, mitochondrial morphology, expression level of specific mitochondrial proteins).

Look forward to your suggestions. Thanks a lot!

Best,
Yu

> 在 2019年11月20日,下午12:04,Yeo, Eugene <ewyeo@health.ucsd.edu> 写道:
>
> HI Yu,
>
> Thanks for the invite!
>
> I'm not sure we have ES lines anymore. But I will check. I believe if it's ES lines they must have come from WiCell or Harvard (G198S most likely).
>
> We have IPS lines that we have reprogrammed from fibroblasts from John Ravits, let me check with my students which mutations we have - do you know which ones you want?
>
> The MTA request from Wuhan should indicate the specific use that the lines will be constrained to, as we are legally required to fill in before exporting lines. Also, if it's a collaboration, it'll be necessary for my lab to know what they will be used for since it sounds like there's some overlap with our existing work (not a bad thing, but just checking).
>
> gene
>
>
> Gene Yeo, PhD, MBA
> Professor
> Dept of Cellular and Molecular Medicine, UCSD
> Co-Director, UCSD Bioinformatics and Systems Biology Graduate Program
> University of California, San Diego
> Institute for Genomic Medicine
> UCSD Stem Cell Program
> http://yeolab.github.io
>
> geneyeo@ucsd.edu
> ewyeo@health.ucsd.edu

>
>
>
>> On Nov 19, 2019, at 5:44 PM, Yu Zhou <yu.zhou@whu.edu.cn> wrote:
>>
>> Dear Gene,
>>
>> Could you please provide us the ES cells containing specific ALS-linked mutations? Please let me know any paper work I need to complete. This will count as our collaborations.
>>
>> P.S.: If you have time, I would like to invite you to visit our college and lab at Wuhan University. I think our PIs and students will enjoy your research and your visit will give us a lot of help. Wuhan is one of the top 5 biggest cities in China. :)
>>
>> ----------
>> Best regards,
>> Yu
>>
>> Yu Zhou, Ph.D.
>> Principal Investigator
>> College of Life Sciences, Room 6109
>> Wuhan University, China
>

From: Fu, Xiang-Dong
To: Yu Zhou
Subject: Re: Decision on Nature Neuroscience submission NN-A69947
Date: Tuesday, November 19, 2019 4:23:13 PM

I just sent you an email for you to request ES cells from Gene Yeo. You can pursue various options in parallel.

Fu

Xiang-Dong Fu,
Distinguished Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

> On Nov 19, 2019, at 4:14 PM, Yu Zhou <yu.zhou@whu.edu.cn> wrote:
>
> Dear Fu,
>
> Zuo Xinxin and I agree with sending it to NSMB.
>
> Best,
> Yu
>
> > 在 2019年11月20日,上午6:43,Fu, Xiang-Dong <xdfu@health.ucsd.edu> 写道:
> >
> > Just saw this bad news. Should we send it to NSMB? You just need to change the editor number to Anke Sparmann.
> >
> > Fu
> >
> > Xiang-Dong Fu,
> > Distinguished Professor
> > Dept. of Cellular and Molecular Medicine
> > University of California, San Diego
> > George Palade Laboratories
> > 9500 Gilman Drive, Room 217
> > La Jolla, CA 92093-0651
> >
> > Phone: 858-534-4937

Email: xdfu@health.ucsd.edu

Begin forwarded message:

From: rebecca.wright@nature.com
Subject: Decision on Nature Neuroscience submission NN-A69947
Date: November 19, 2019 at 9:58:42 AM PST
To: xdfu@ucsd.edu
Reply-To: rebecca.wright@nature.com

Our ref: NN-A69947

19th Nov 2019

Dear Dr. Fu,

Thank you for submitting your manuscript "Oxidative Stress Induces TDP-43 Aggregation to Cause Global Mitochondrial Imbalance in ALS" to Nature Neuroscience. We have now had the opportunity to carefully consider your paper, and I'm afraid we have decided not to send this out for peer review. While we are sure the findings will be of interest to those working directly in this area, we unfortunately do not feel they represent a sufficient level of conceptual advance over prior literature for our journal.

Although we cannot offer to publish your manuscript, I suggest that you consider transferring your manuscript to our sister journal, Communications Biology, a selective open-access Nature Research title led by an in-house editorial team that publishes research bringing new insight into a focused area of biology (www.nature.com/commsbio). I have provided a link to automatically transfer your files in the footnote below, and no reformatting is required.

Please note that Communications Biology is a fully open-access journal and an article processing charge will apply to any papers accepted for publication.

We are sorry to have to send disappointing news, but we receive many more manuscripts than we can publish each month and are therefore forced to make difficult decisions about which ones are most likely to be of

greatest interest to our broad multidisciplinary readership. Thank you again for allowing us to consider the manuscript and we hope that you will soon find another suitable venue in which to publish your work.

Yours sincerely,

Rebecca Wright, PhD
Senior Editor
Nature Neuroscience

http://orcid.org/0000-0002-9144-7996

** Your manuscript has been recommended for Communications Biology based on our familiarity with the journal's criteria. While our editorial teams are independent and the editors there will make their own decision, recommended manuscripts have a higher probability of success. Chief Editor Dr Brooke LaFlamme leads the editorial team and would be happy to answer any questions you have about the journal (brooke.laflamme@us.nature.com). Providing good service to authors is a journal priority, and the team will make a rapid editorial decision on your manuscript (mean time to editorial decision in 2018: 10 days). Our open access pages contain information about article processing charges, open access funding, and advice and support from Springer Nature.

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From: Fu, Xiang-Dong
To: Gene Yeo
Cc: xinxinzuo2012; Zhou Yu; Jiang, Li
Subject: request for TDP-43 mutant ES cells
Date: Tuesday, November 19, 2019 4:22:21 PM

Hi Gene,

As we discussed over the phone, we would like to have a few ES cells containing specific ALS-linked mutations in order to finish up a manuscript.

Gene: Please let me know which mutant cells you have in your freezer. I will ask a former student of mine, now a postdoc in Jeremy lab, Lili Jiang to come to get those cells from your lab, culture them up for putting into vital for someone to take them back next Monday.

Zhou Yu: Could you write to Gene to make a request for these reagents so that he can send you a MTF to complete. This is required for material transfer. As I indicated to Gene, this will be part of collaboration.

Thanks to all of you.

Fu

Xiang-Dong Fu,
Distinguished Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

From:	mfliu
To:	戴鹏; 王鑫; Gou, Lantao; 李智彤; 温泽; 华敏敏; 汪凌波; zhongai2017; 施惠娟; 李劲松; Tian, Bin; 李 党生; xdfu; Yu Zhou; chenzonggui; Seasunshine; 782899103; k.qian; ljliao
Subject:	Fw: Cell Editorial Decision CELL-D-18-02653R3
Date:	Thursday, November 14, 2019 4:27:17 PM

Dear All,

Below I forwarded you the exciting news of the acceptance of our paper at Cell. I truly appreciate your great efforts that you have made on the beautiful work. I am looking forward to further collaboration with you on new projects. Many thanks again!

Best wishes
Mofang

2019-11-15

Mofang Liu, Ph.D.
Principle Investigator
Institute of Biochemistry and Cell Biology
Shanghai Institutes of Biological Sciences
Chinese Academy of Sciences
320 Yue Yang Road
Shanghai 200031 China
Tel: +86-21-54921146
Email: mfliu@sibs.ac.cn

发**件人:** Cell Editorial Office
发**送**时间**:** 2019-11-15 00:09:43
收件人: Mofang Liu
抄**送:**
主题**:** Cell Editorial Decision CELL-D-18-02653R3

CC: cellms@cell.com

Dr. Mofang Liu
Institute of Biochemistry and Cell Biology Shanghai Institutes of Biological Sciences Chinese Academy of Sciences
320 Yue-Yang Rd
Shanghai 200031
CHINA

A Translation-Activating Function of MIWI/piRNA during Mouse Spermiogenesis
CELL-D-18-02653R3

Nov 14, 2019

Dear Mofang,

It is a pleasure to let you know that we will be publishing your paper and that it is being tentatively scheduled for the December 12th issue of Cell. Congratulations on a very

interesting story; we are pleased to be bringing it to the attention of our readers.

At this time, I also wanted to introduce our Senior Production Editor, tarpin@cell.com, who heads up the production team that will guide your paper through copyediting, proofing, and publication. They will be contacting you shortly with some initial information on the production process. If you anticipate being unreachable by email at any time between now and the publication date, please send them (tarpin@cell.com) the email address of an alternate author who can rapidly respond to queries from our production department.

In the coming weeks, your assigned copyeditor will be in contact with you concerning queries on the manuscript and PDF proofs. We would greatly appreciate it if you can keep an eye out for emails concerning these finishing steps so that we can move your paper efficiently through to publication. Please note that at this stage we can only allow minor corrective changes to the manuscript, and none that will add or change results or significantly alter the length/style of the title, abstract or manuscript text. If any concerns about this arise, please contact me directly. Please see below for further details about proofs.

At this point, I would like to outline our policy with regard to press coverage. Our general policy is that authors are free to talk with the popular press (starting one week before publication) and to release information provided that its use is embargoed. Information about embargo time will be provided from our press office shortly.We also allow authors to discuss their work in press with other scientific journals. Because journals could in principle use that information to speed publication of their own competitive manuscripts, it is best if you refer any inquiries to us. Once the requesting journal has confirmed that they do not have any related work under consideration or in press, we'll be glad to send page proofs with a note of the embargo date.

If your press office wishes to issue a press release, they should contact us in advance for final embargo information. **Please contact our press office at press@cell.com.** Prior to publication, please discuss any possibility of the paper being referenced elsewhere in the literature with the handling editor.

Again, congratulations on a very nice paper! I hope you found the review process to be constructive and are pleased with how the manuscript was handled editorially. We look forward to future exciting submissions from your lab.

Best wishes,
April

April Pawluk, Ph.D.
Scientific Editor, Cell

Proofs

- You should receive PDF proofs 2-3 weeks prior to your publication date. Only printer's errors should be corrected on the page proofs.
- You can expect to receive a link to an online copyright assignment form from our Production Department to authorize publication of your paper.
- **For further clarifications regarding the production process, please contact Trina Arpin (tarpin@cell.com)**.

Databases

- Authors are encouraged to deposit materials used in their studies to the appropriate repositories for distribution to researchers.

In addition to the information that is required to be deposited in public databases (as stated in our Instructions to Authors), we also encourage our authors to contribute additional information to the appropriate databases. For example, papers that include data on biomolecular interactions (e.g., protein-protein, protein-RNA) can be submitted to the Biomolecular Interaction Network Database. For a link to additional databases and repositories, please see the Distribution of Materials and Data section of our Instructions for Authors.

Cover Submissions

- Please keep in mind that although the submission may be based on or resemble the figures in the article, it should be both artistic and informative. Feel free to submit several different images for consideration, as we like to have as many images as possible to choose from. The editors make the cover selection based on (1) the aesthetic quality of the image and (2) the scientific scope of the study. Please try to make any submissions interesting and creative.
- For all guidelines, please see our webpage. Here you will also find a cover template that contains the Cell logo and crop lines. You do not have to use the template but are welcome to.
- Please note the deadlines for cover submission on our webpage. Typically, we can accept cover submissions up to one month before the print issue date, but this may vary by issue.

From: Yu Zhou
To: Fu, Xiang-Dong
Subject: Re: Receipt of NN-A69947
Date: Thursday, November 14, 2019 2:46:16 PM
Attachments: nr-editorial-policy-checklist.pdf
nr-reporting-summary.pdf

Dear Fu,

Here are the two completed PDF files. Please email them to the editors at neurosci@us.nature.com

Yesterday during submission, we do not have the options to upload them.

Best,
Yu

在 2019**年**11**月**15**日**,**上午**6:32,Fu, Xiang-Dong <xdfu@health.ucsd.edu> **写道**:

Fu

-------- 原**始**邮**件** --------
发**件人**: neurosci@us.nature.com
日期: 2019**年**11**月**14**日周四 半夜**11:15
收件人: xdfu@ucsd.edu
主 题: Receipt of NN-A69947
Our ref: NN-A69947

14th Nov 2019

Dear Dr. Fu,

Thank you for the manuscript you have submitted to Nature Neuroscience entitled "Oxidative Stress Induces TDP-43 Aggregation to Cause Global Mitochondrial Imbalance in ALS". We will be in touch with you as soon as we are able to reach a decision. In the event of any query, please quote the reference number NN-A69947.

We are trying to improve the quality of methods and statistics reporting in our papers. To that end, we have recently revised the reporting checklist we introduced in 2014. We are now asking all life sciences authors to complete two items: an editorial policy checklist that verifies compliance with all required editorial policies and a reporting summary that collects information on experimental design and reagents.

Reporting summary: https://www.nature.com/documents/nr-reporting-summary.pdf
Editorial policy checklist: https://www.nature.com/documents/nr-editorial-policy-checklist.pdf

We will only need these items if your article is sent for external review. However, we encourage you to fill these out now during the journal's internal review to avoid any unnecessary delays if the manuscript is externally reviewed. Please note that these forms are dynamic 'smart pdfs' and must therefore be downloaded and opened directly in Adobe Reader (they are unopenable within a browser due to the form fields). Please email them to us at neurosci@us.nature.com. We will then flatten them for ease of use by the reviewers. If you would like to reference the guidance text as you complete the template, please access these flattened versions at http://www.nature.com/authors/policies/availability.html.

You may check the status of your manuscript by selecting the "Check manuscript status" link under the following URL:

https://mts-nn.nature.com/cgi-bin/main.plex?el=A5F6fAP1A7BKsr2F1A9ftdVVI1KfF3hhpB8yJmzy9pPAZ

You can use a single sign-on for all your accounts, view the status of all your manuscript submissions and reviews, access usage statistics for your published articles and download a record of your refereeing activity for the Nature journals. Please check your account regularly to ensure that we have your current contact information.

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For your reference, please note that all published original research manuscripts, Reviews and Perspectives must contain a declaration of any Financial and non-financial competing interests.

Full details of the policy can be found at
"https://www.nature.com/licenceforms/nrg/competing-interests.pdf"

Yours sincerely,
Adam Lipkin
Senior Editorial Assistant
Nature Neuroscience
212.726.9319

From:	xinxinzuo2012
To:	Fu Xiang-Dong
Cc:	Zhou Yu
Subject:	The latest version of TDP manuscript and figures
Date:	Sunday, November 10, 2019 7:14:11 PM
Attachments:	Figures_11_11.rar TDP43ms Nat Neurosci 11_11.docx

---

Dear Fu,

Here are the latest version of TDP manuscript and figures. The figures were updated according to your arrangement with minor modifications. Several spelling mistakes in the text were corrected and I also supplemented the methods. Looking forward to your comments.

On Wednesday, Zhouyu will return from the meeting, and we will submit together then.

Hope everything goes on well!

Xinxin

From: xinxinzuo2012
To: Fu, Xiang-Dong; Zhou Yu
Subject: 回复:revised TDP-43 ms
Date: Wednesday, November 6, 2019 1:51:54 AM

Dear Fu,

I just finished packaging all the figures in illustrator according to your suggested arrangement. Tomorrow Zhouyu and I will go through the figures together and maybe we will make further modifications, especially the model in Fig.7. The proofreading of the text is undergoing as well as the updating of new material & method. After finish all these, I think it is better to send to you for a final check.

Best wishes!

Xinxin

发**件人**:Fu Xiang-Dong <xdfu@ucsd.edu>
发**送**时间:2019**年**11**月**6**日**(**星期三**) 05:38
收件人:Zhou Yu <yu.zhou@whu.edu.cn>
抄 **送**:xinxinzuo2012 <xinxinzuo2012@aliyun.com>
主 题:Re: revised TDP-43 ms

Dear Yu and Xinxin,

Your model is fine. However, if both of you feel that we should proceed with the submission of the current version, I also agree. Here is the cover letter I have drafted and my account at Nature Neuroscience.
Username: [redacted]
Password: [redacted]

If you need to make some changes in the manuscript and wish me to take a final look, please send me the revised figures and manuscript for proofreading. Otherwise, if you feel that it is sufficiently well crafted and you have only corrected some minor mistakes, please go ahead submitting it.

I will be flying to China the day after tomorrow. I will not come to Wuhan in this trip, but please feel free to contact me if you have questions.

Cheers,

Fu

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

On Nov 4, 2019, at 6:32 PM, Yu Zhou <yu.zhou@whu.edu.cn> wrote:

Dear Fu,

Xinxin and I have discussed the arrangement of splitting into two papers. In that way, we feel that manuscript 1 to Nat Neurosci would be weakened in both concept and mechanism, as shown in the enclosed model figure, which may not satisfy Nat Neurosci. In consideration of her time, Xinxin prefers to proceed as original idea to submit whole manuscript to Nat Neurosci. We look forward to your comments, and now we are working to generating high-quality figures according to your previous arrangement. Thanks a lot!

Best,
Yu

在 2019年11月4日,上午10:27,xinxinzuo2012 <xinxinzuo2012@aliyun.com> 写道:

Dear Fu,

Thank you so much for your efforts in polishing the manuscript and rearranging figures. I agree with your idea that we can separate the manuscript into two part which will be easier to digest.

As you suggested we can take the data related to mitochondrial imbalance (Fig. 6, Fig. S6, and part of Fig. 7 and S7) to make another story fit for PNAS. But I still have some questions, one is that the current data may not enough to make a complete story, what specific experiments we need to do to fulfil it? Another is the rewrite and the rearrangement of two paper, which will be quite challenging.

I am looking forward to your reply to these concerns. And thank you again for your understanding of my current situation.

Best wishes!

Xinxin

发**件人**:Fu Xiang-Dong <xdfu@ucsd.edu>
发**送**时间:2019**年**11**月**4**日**(**星期一**) 05:29
收件人:xinxinzuo2012 <xinxinzuo2012@aliyun.com>; Zhou Yu <yu.zhou@whu.edu.cn>
主 题:Re: revised TDP-43 ms

Hi Xinxin and Zhou Yu,

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TDP-43. Please let me know if you like the idea. This strategy would be good for Xinxin's career, as now days, both quality and quantity of papers count.

Fu

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

On Nov 3, 2019, at 12:29 PM, Fu Xiang-Dong <xdfu@ucsd.edu> wrote:

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Once you have done these, I will prepare a cover letter and provide my account for you to submit from your computer. I must say that Xinxin has done a lot! Hope we have better luck at Nature Neuroscience.

Cheers,
<TDP43ms Nat Neurosci.docx>
<New TDP43 figures.pptx>
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Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

<Model1.pdf>

From:	Fu, Xiang-Dong
To:	Zhou Yu
Cc:	xinxinzuo2012
Subject:	Re: revised TDP-43 ms
Date:	Tuesday, November 5, 2019 1:36:34 PM
Attachments:	Cover letter for TDP43 ms.doc ATT00001.htm

Dear Yu and Xinxin,

Your model is fine. However, if both of you feel that we should proceed with the submission of the current version, I also agree. Here is the cover letter I have drafted and my account at Nature Neuroscience.

From: Yu Zhou
To: Fu, Xiang-Dong
Cc: xinxinzuo2012
Subject: Re: revised TDP-43 ms
Date: Monday, November 4, 2019 6:32:53 PM
Attachments: Model1.pdf

Dear Fu,

Xinxin and I have discussed the arrangement of splitting into two papers. In that way, we feel that manuscript 1 to Nat Neurosci would be weakened in both concept and mechanism, as shown in the enclosed model figure, which may not satisfy Nat Neurosci. In consideration of her time, Xinxin prefers to proceed as original idea to submit whole manuscript to Nat Neurosci. We look forward to your comments, and now we are working to generating high-quality figures according to your previous arrangement. Thanks a lot!

Best,
Yu

在 2019年11月4日,上午10:27,xinxinzuo2012 <xinxinzuo2012@aliyun.com> 写道:

Dear Fu,

Thank you so much for your efforts in polishing the manuscript and rearranging figures. I agree with your idea that we can separate the manuscript into two part which will be easier to digest.

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Phone: 858-534-4937
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Email: xdfu@ucsd.edu

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<TDP43ms Nat Neurosci.docx>
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From: xinxinzuo2012
To: yu.zhou@whu.edu.cn
Cc: Fu, Xiang-Dong
Subject: Re: revised TDP-43 ms
Date: Monday, November 4, 2019 3:26:44 PM

---

ok!

发自我的小米手机
在 Yu Zhou <yu.zhou@whu.edu.cn>,2019年11月4日 下午11:16写道:

> Dear Xinxin,
>
> We will discuss the rearrangement of figures and additional writings for the 2nd manuscript tomorrow morning in my office.
>
> Best,
> Yu
>
> > 在 2019年11月4日,上午10:27,xinxinzuo2012 <xinxinzuo2012@aliyun.com> 写道:
> >
> > Dear Fu,
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From: Yu Zhou
To: Fu, Xiang-Dong
Cc: xinxinzuo2012
Subject: Re: revised TDP-43 ms
Date: Monday, November 4, 2019 6:34:17 AM

Dear Fu,

Thanks a lot for these efforts! I will work with Xinxin to generate publishable figures, edit the text, and prepare other necessary files.

Best,
Yu

> 在 2019年11月4日,上午4:56,Fu, Xiang-Dong <xdfu@ucsd.edu> 写道:
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<TDP43ms Nat Neurosci.docx><New TDP43 figures.pptx>

From: xinxinzuo2012
To: Fu, Xiang-Dong; Zhou Yu
Subject: 回复:revised TDP-43 ms
Date: Sunday, November 3, 2019 6:27:33 PM

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From:	xinxinzuo2012
To:	Fu, Xiang-Dong
Cc:	Zhou Yu
Subject:	TDP43 paper related material
Date:	Sunday, October 20, 2019 9:00:02 PM
Attachments:	2019_10 TDP43ms.docx Figures.rar All updated data.pptx 2019_05 Response to MC review on TDP43.docx

---

Dear Fu,

Here are the material related to TDP43 project. I have changed the present manuscript and figures to the Nature format. And the newly obtained data are arranged into PPT.

Besides, the materials and methods part are under improving. Once you send us the updated manuscript, I will get right to package figures.

Hope everything goes on well!

Xinxin

From:	xinxinzuo2012
To:	Fu, Xiang-Dong
Cc:	Zhou Yu
Subject:	2019-08 work progress of TDP43
Date:	Sunday, August 11, 2019 3:33:30 AM
Attachments:	TDP43 05-08 work progress.pptx

Dear Fu,

Here is the summary of work progress of last three month. I have arranged the data into PPT for your better understanding. The new work progress of this month have also been integrated, mainly about the immunofluorescence assays in primary neurons, such as the co-localization of TDP-43 with RBPs and mito-proteins within granules under oxidative stress and so on.

Besides, ZhouYu and I went through all the data together this afternoon, and he shows great support of me and the work I am doing. I will keep updating and try my best to push this paper forward quickly.

Hope everything goes on well!

Xinxin

From:	Chen, Jiayu
To:	Fu, Xiang-Dong
Cc:	Lim, Do-Hwan; Liang CHEN
Subject:	out manuscript for comparison between DRIP(c)-seq and R-ChIP
Date:	Friday, July 12, 2019 4:59:18 PM
Attachments:	20190709_GB_ms.docx

Hi Fu,

Here is the progress of the DRIP-seq project with Dohwan. Dohwan put a lot of efforts and tried several times the original DRIPc-seq method with or without RNase H treatment after IP and new S9.6-based methods, but the results are not good enough. Only the DRIP-seq with or without RNase H treatment works well in Dohwan's hand. We think that more efforts on repeating and improving DRIPc-seq doesn't mean too much, and instead we may need to focus on some biology.

Anyway, because I want to finish this project as soon as possible and then move on to others, e.g., E2 project with Dohwan, and R-loop and replication project, I prepared a manuscript in Genome Biology format based on the data we have got. I know that you are quite busy these days. When you have time, could you please give it a read? I'd like to know specifically,

1) whether you think it is sufficient to try Genome Biology. If it is ok, we want to have a try.

2) whether we should target some important biological questions and and aim a more higher profile journal. I have discussed with Liang and Dohwan a lot, and both of them have given a lot of thoughts. One candidate is to understand how R-loop in gene body forms? Our previous investigation suggests that the lack of TOP1 activity may underlie the R-loop formation in gene body. We may simply perform RChIP, Pol II and/or GRO-seq before and after TOP1 activity is blocked to gain more insights into this. We can discuss about this in more details, and more other options next week if you are available.

Many thanks.

Jiayu (Jerry) Chen, Ph.D.
Postdoc, Xiang-Dong Fu's lab
Department of Cellular and Molecular Medicine,
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 219
La Jolla, CA 92093-0651

From: Fu, Xiang-Dong
To: 肖锐
Cc: Chen, Jiayu; 肖锐
Subject: Re: I didn"t receive any information about proofread of the paper
Date: Thursday, June 13, 2019 4:40:25 PM

Thanks. I trust you to do it right, which is a good experience to gain.

Fu

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Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

On Jun 13, 2019, at 4:38 PM, 肖锐 <xiaorui5757@163.com> wrote:

Thank you, Jerry! Let me finish it this morning.

Rui

At 2019-06-14 03:47:32, "Chen, Jiayu" <jic386@ucsd.edu> wrote:

> I have already quickly checked the method and supplementary materials after proofreading the main text. All key messages are correct, including the supplementary Figures and Tables, and links to Mendeley data. I didn’t spot any mistakes.
>
> Rui, please make sure the GEO accession numbers are correct. If ok, please also double check the methods and supplementary information.
>
> Jiayu (Jerry) Chen, Ph.D.
> Postdoc, Xiang-Dong Fu’s lab
> Department of Cellular and Molecular Medicine,

University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 219
La Jolla, CA 92093-0651

From: Fu, Xiang-Dong
Sent: Thursday, June 13, 2019 12:28 PM
To: Chen, Jiayu
Cc: 肖锐; 肖锐
Subject: Re: I didn't receive any information about proofread of the paper

Thanks. Between 3 of us, I think we have spotted most errors.

Jiayu: Can you take a quick look at the Methods and supplementary information to see if there are serious mistakes. We can be relaxed a bit, as long as our meaning is not altered.

Rui: If you are able to incorporate all of these changes, you can directly click it off from your computer. There is no need for me to go through the whole thing again.

Congratulations! Please send the proof to Zhou Yu and Daji, as they may need it for their defenses next week.

Fu

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Fax: 858-822-6692
Email: xdfu@ucsd.edu

On Jun 13, 2019, at 12:16 PM, Chen, Jiayu <jic386@ucsd.edu> wrote:

I think Rui is proofreading the manuscript now, and I can not make edits online. Besides Fu's edits, here are some additional ones for Rui to incorporate,

1) legend for Figure 4B. change "Coverage of total..." to "Coverage and annotation of total..."
2) Figure 6C, we'd better change "Bl-HiC" to "BL-Hi-C", because in our main text, we always use BL-Hi-C
3) There are more missing hyphens ("-") except for what Fu pointed out. For example, in the legend of Figure 6C, we should change 'down (upper)' to 'down (upper)-'. Rui, please use Ctr + F to find all others.
4) Page 11, first paragraph, "the vast majority of upregulated genes" should be "the vast majority of up- and down-regulated genes".
5) for Fu's first comment, be sure to also change 'PCC' to 'SCC' in the legend
6) Page 12, the last second paragraph. "... as with other RBPs, its RNA-binding profile does not correlate well to its occupancy on DNA...". Here, we'd better cite Eric's Nature paper (now in BioRxiv), which is already listed in the Reference.

Jiayu (Jerry) Chen, Ph.D.
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From: Fu, Xiang-Dong
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To: 肖锐; Chen, Jiayu
Subject: Re: I didn't receive any information about proofread of the paper

While you are doing the proofing, I have also read through the main text and legends to spot potential mistakes:

1. Legend for Fig. 5F: Should be Spearman's, not Pearson's

2. Page 11, first paragraph on the left, line 1 and 9: Do we need a hyphen "-" between downregulated?

3. Key Resource Table: Should change all "" to ";" before RRID

(note that in line 6, even “,” is missing).

4. If possible, we should include a key missing reference in Page 1, right column, line 11 from the bottom, before Moldon et al., 2008): Cramer, P., Pesce, G.G. Barrage, F.E., and Kornblihtt, A.R. (1997). Functional association between promoter structure and transcript alternative splicing. Proc. Natl Acad Sci94, 11456-11460.

Rui: If possible, can you include these information in the eProof? Once you and Jiayu are done, I can take a final look and click to submit.

Fu

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

> On Jun 13, 2019, at 7:11 AM, 肖锐 <00031889@whu.edu.cn> wrote:
>
> Yes, I just received. Thanks!
>
> Rui
>
> > -----原始邮件-----
> > 发件人: "Fu, Xiang-Dong" <xdfu@ucsd.edu>
> > 发送时间: 2019-06-13 22:04:53 (星期四)
> > 收件人: "肖锐" <xiaorui9@whu.edu.cn>
> > 抄送:
> > 主题: Re: I didn't receive any information about proofread of the paper

Just forward it to you. Please confirm.

Sent from my iPhone

> On Jun 13, 2019, at 6:57 AM, 肖锐 <xiaorui9@whu.edu.cn> wrote:
>
> Dear Prof. Fu,
>
> I didn't receive any information about proofread of the paper, even in junk mail. Could you forward the email to me? Thank you!
>
> Best,
> Rui

From: Fu, Xiang-Dong
To: 肖锐
Subject: Re: I didn"t receive any information about proofread of the paper
Date: Thursday, June 13, 2019 12:05:24 PM

Below are my response:

> On Jun 13, 2019, at 11:41 AM, 肖锐 <00031889@whu.edu.cn> wrote:
>
> **Dear Prof. Fu,**
>
> **Here is my correction:**
>
> **1. Figure 1** General Features of Chromatin-Associated RBPs(A) Summary of RBPs surveyed by ChIP-seq in HepG2 and K562 cells. The 25 RBPs that produced high-quality ChIP-seq data are grouped into five classes: (1) hnRNP proteins, (2) SR proteins, (3) TFs that bind RNA, (4) proteins containing RBM motif, and (5) others. Dark blue, high-quality data that met the
>
> We'd better use "RNA-binding Motif (RBM)" instead of "RBM motif".

Agree.

> Importantly, individual RBPs appear to have distinct preferences for different promoters rather than binding indiscriminately to open chromatins (see Figure 1B). We illustrate this by randomly distributing the RBP-binding sites to open chromatin regions based on mapped DNase I hypersensitive sites and then counting co-localized RBP-binding sites, assuming that all RBP chromatin association would be mediated by their general affinity for open chromatin. The distribution of real data is clearly distinct with the simulated one, with the former showing a trend toward decreased co-binding observed in both cell types (Figure S1F).
>
> "open chromatins" should be "open chromatin".
>
> "Illustrate" should be "illustrated"

Agree.

> Interestingly, the three RBPs XRCC5, HNRNPL, and RBM25 appear to be more generally linked to promoters and enhancers than other RBPs (see below).
>
> Comma here needs to be removed.

It is ok. No need to remove the comma.

The fact that promoters are the primary interface for RBP-chromatin interactions prompted us to look further into the promoter-binding profiles of individual RBPs. By classifying promoters into subgroups based on either epigenetic marks or specific sequence features (see Method Details), we found that RBPs collectively showed a general preference for bivalent promoters marked with both H3K4me3 and H3K27me3, for active promoters modified by H3K4me3 alone, and for CpG island promoters in both cell lines (Figures 2A and S2A).

We'd better use "shows" instead of "showed".

Agree.

Although all RBPs showed binding events on both sides of TSSs, we noted three apparent classes of RBP-chromatin interaction profiles based on their binding profiles around TSS: (1) upstream TSS (i.e., RBM25), (2) centered on TSS (i.e., GTF2F1), and (3) downstream TSS (i.e., RBFOX2), the third class being representative of the majority of RBPs in both cell types (Figure 2D).

Do we need to use "show" here?

No need to change.

(D) The distribution of RNA nuclear retention index (nuclear/(nuclear+cytoplasmic)) for each group of genes whose promoters were occupied by different RBPs.

(nuclear/(nuclear+cytoplasmic)) need to correct to [(nuclear/(nuclear+cytoplasmic)]

It is ok. No need to change. People can figure it out.

Such a negative correlation might result from selective roles of XRCC5 in inducing less stable RNAs and/or repressing more stable RNAs, possibilities that would be interesting to follow up.

Should we add "and" before "possibilities"?

No need to change.

Using the resultant chromatin association and gene expression data, we were particularly interested in testing the so-called promoter loading model, in which promoter association events are thought to instruct downstream RNA processing events, such as RNA stability, export, or translation, as reported on a few specific cases

Do we need to remove comma here?

It is optional. You decide.

In the e-Extra Content

Statistical parameters were reported either in individual figures or corresponding figure legends. Quantification data are in general presented as bar/line plots, with the error bar representing mean ± SEM, or boxplot, showing the median (middle line), first and third quartiles (box boundaries), and furthest observation or 1.5 times of the interquartile (end of whisker). All statistical analyses were done in R. Whenever asterisks are used to indicate statistical significance, *stands for $p < 0.05$; $^{**}p < 0.01$, and $^{***}p < 0.001$.

Should be “mean ± SD” here.

If you are sure, change it. Check all other places and confirm with Jiayu.

And I need your confirmation on these typos, and then I will include all these including yours in the eProof.

Fu

Thanks,

Rui

> -----原**始**邮**件**-----
> 发**件人:**"Fu, Xiang-Dong" <xdfu@ucsd.edu>
> 发**送**时间**:**2019-06-14 02:25:41 (**星期五**)
> **收件人:** "**肖**锐" <00031889@whu.edu.cn>, "Chen, Jiayu" <jic386@ucsd.edu>
> 抄**送:**
> 主题**:** Re: I didn't receive any information about proofread of the paper
>
> While you are doing the proofing, I have also read through the main text and legends to spot potential mistakes:
>
> 1. Legend for Fig. 5F: Should be Spearman’s, not Pearson's
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Rui: If possible, can you include these information in the eProof? Once you and Jiayu are done, I can take a final look and click to submit.

Fu

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George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

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>
> Yes, I just received. Thanks!
>
> Rui
>
> > -----原始邮件-----
> > 发件人: "Fu, Xiang-Dong" <xdfu@ucsd.edu>
> > 发送时间: 2019-06-13 22:04:53 (星期四)
> > 收件人: "肖锐" <xiaorui9@whu.edu.cn>
> > 抄送:
> > 主题: Re: I didn't receive any information about proofread of the paper
> >
> > Just forward it to you. Please confirm.

Sent from my iPhone

> On Jun 13, 2019, at 6:57 AM, 肖锐 <xiaorui9@whu.edu.cn> wrote:
>
> Dear Prof. Fu,
>
> I didn't receive any information about proofread of the paper, even in junk mail. Could you forward the email to me? Thank you!
>
> Best,
> Rui

From: Fu, Xiang-Dong
To: 肖锐
Subject: Re: I didn"t receive any information about proofread of the paper
Date: Thursday, June 13, 2019 7:04:53 AM

Just forward it to you. Please confirm.

Sent from my iPhone

> On Jun 13, 2019, at 6:57 AM, 肖锐 <xiaorui9@whu.edu.cn> wrote:
>
> Dear Prof. Fu,
>
> I didn't receive any information about proofread of the paper, even in junk mail. Could you forward the email to me? Thank you!
>
> Best,
> Rui

From: Fu, Xiang-Dong
To: xiaorui9@whu.edu.cn
Subject: Fwd: [CELL_10894] Proof of your article for Cell
Date: Thursday, June 13, 2019 7:03:17 AM

Sent from my iPhone

Begin forwarded message:

From: <cell.djs@sheridan.com>
Date: June 13, 2019 at 5:30:08 AM PDT
To: <xdfu@ucsd.edu>
Cc: <blueproofs@cell.com>
Subject: [CELL_10894] Proof of your article for Cell
Reply-To: <blueproofs@cell.com>

If you reply to this e-mail, please do not alter the manuscript number in the subject line.

Dear Dr. Fu,

Thank you for publishing with *Cell*. We are pleased to inform you that the proof of your upcoming publication is ready for review via the link below. On the proof landing page, you will find instructions on how to make corrections directly online or in the PDF.

1. DEADLINE:

- Please return all necessary corrections within **24 hours (or on the next business day)**, and please limit your changes to only those that are necessary to correct scientific meaning or editorial error. **Additional changes may delay publication**. Furthermore, the online publication will be the final publication--there will not be an opportunity to make changes between the times of online and print publication.

2. IMPORTANT NOTES:

- Please carefully review the **title, author list, affiliations, and Acknowledgments**. Changes may not be made to these sections after publication except in rare circumstances, and any exceptions would require an accompanying Correction.
- You are welcome to save and return to your article at any time during the correction process. However, once you hit the Submit button, you **will not** be able to make further corrections. If multiple authors make corrections, please **do not** click the Submit button at the end of each session.

3. SUPPLEMENTAL FILES:

- Please **do not** annotate or otherwise request changes to the supplemental file(s). Instead, if any changes are necessary, **please create a new file by editing your local version of the file, and then upload that new file into the system**. (We are unable to edit any supplemental files, with the exception of creating a title page for some of them; see note below.) *Please note: If we receive an annotated file, we will need to request a new file from you, which could delay publication.*
- Please do not include a title page on any revised supplemental files that you upload into the system. Such pages will be generated automatically before publication.
- Capacity per file is **40 MB**.

https://live1.elsevierproofcentral.com/authorproofs/7289ee3b71836d96df37d2608229551c

Lastly, if your article included a STAR Methods section, we kindly ask that you take this short survey. This is not a mandatory step, but your responses will help us to refine and improve STAR Methods and are greatly appreciated.

Yours sincerely,

The *Cell* production team

From:	Campbell, Tracy (ELS-CMA)
To:	Fu, Xiang-Dong
Cc:	xiaorui9@whu.edu.cn; Chen, Jiayu
Subject:	RE: Cell article queries
Date:	Tuesday, June 11, 2019 6:46:03 AM

Dear Fu,

Thanks very much for the clarification. I have incorporated your changes and sent your manuscript to our printer for layout. Please expect your proofs to arrive in a few business days, and feel free to reach out to me with any questions.

Best wishes,
Tracy

Tracy Campbell
Deputy Production Editor, *Cell*
(617) 386-2168

From: Fu, Xiang-Dong <xdfu@ucsd.edu>
Sent: Tuesday, June 11, 2019 9:13 AM
To: Campbell, Tracy (ELS-CMA) <tcampbell@cell.com>
Cc: xiaorui9@whu.edu.cn; Chen, Jiayu <jic386@ucsd.edu>
Subject: Re: Cell article queries

Indeed, I attached a wrong file. Sorry. Here is the right one.
Fu

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

> On Jun 11, 2019, at 6:06 AM, Campbell, Tracy (ELS-CMA) <tcampbell@cell.com> wrote:
>
> Dear Fu,

The file you sent seems to be a letter to your editor, which I assume you didn't intend to attach. Could you please clarify?

Thanks,
Tracy

Tracy Campbell
Deputy Production Editor, *Cell*
(617) 386-2168

From: Fu, Xiang-Dong <xdfu@ucsd.edu>
Sent: Monday, June 10, 2019 5:32 PM
To: Campbell, Tracy (ELS-CMA) <tcampbell@cell.com>
Cc: xiaorui9@whu.edu.cn; Chen, Jiayu <jic386@ucsd.edu>
Subject: Re: Cell article queries

Dear Tracy,

Please use this file in which we have finalized all answers to your queries.

Best regards,
Fu

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

> On Jun 7, 2019, at 10:22 AM, Fu Xiang-Dong <xdfu@ucsd.edu> wrote:
>
> Dear Tracy,
>
> Here are my answers to your queries. I am pretty sure that all of the information I provide is correct, but I will has my co-workers to double check.

Best and have a nice weekend.
<cell10894_query.docx>
Fu

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

> On Jun 7, 2019, at 9:23 AM, Campbell, Tracy (ELS-CMA) <tcampbell@cell.com> wrote:
>
> Dear Drs. Xiao and Fu,
>
> Good afternoon. Please find my queries regarding your manuscript attached. If you could please review and respond by Monday, June 10, I would greatly appreciate it.
>
> Please let me know if you have any questions.
>
> Thank you,
> Tracy
>
> **Tracy Campbell**
> Deputy Production Editor, *Cell*
> (617) 386-2168
>
> <cell10894_query.docx>

From:	Fu, Xiang-Dong
To:	Campbell, Tracy (ELS-CMA)
Cc:	xiaorui9@whu.edu.cn; Chen, Jiayu
Subject:	Re: Cell article queries
Date:	Monday, June 10, 2019 2:32:02 PM
Attachments:	Cover letter.doc ATT00001.htm

Dear Tracy,

Please use this file in which we have finalized all answers to your queries.

Best regards,

From: 肖锐
To: Fu, Xiang-Dong
Subject: Re: Re: Cell article queries
Date: Monday, June 10, 2019 1:15:56 AM

Dear Prof. Fu,

I got the response from Jerry and Zhengyu for the Cell article queries:

6. ChIA-PET should be chromatin interaction analysis by paired-end tag sequencing.

Please replace "DNA repair/recombination" with "DNA repair and recombination"
Please replace GG/CC sites with GG^CC sites
Please replace "TF/RBP co-occupancies" with "TF and RBP co-occupancies" I think it can be "TF-RBP co-occupancies" as well.
Please replace all "YY1/RBM25" with "YY1-RBM25"

Thanks,

Rui

> -----原始邮件-----
> 发件人:"Fu, Xiang-Dong" <xdfu@ucsd.edu>
> 发送时间:2019-06-08 01:22:04 (星期六)
> 收件人: "Campbell, Tracy (ELS-CMA)" <tcampbell@cell.com>
> 抄送: "xiaorui9@whu.edu.cn" <xiaorui9@whu.edu.cn>, "Chen, Jiayu" <jic386@ucsd.edu>
> 主题: Re: Cell article queries
>
> Dear Tracy,
>
> Here are my answers to your queries. I am pretty sure that all of the information I provide is correct, but I will has my co-workers to double check.
>
> Best and have a nice weekend.
> Fu
>
> Xiang-Dong Fu, Professor
> Dept. of Cellular and Molecular Medicine
> University of California, San Diego
> George Palade Laboratories
> 9500 Gilman Drive, Room 217
> La Jolla, CA 92093-0651
>
> Phone: 858-534-4937
> Fax: 858-822-6692
> Email: xdfu@ucsd.edu

On Jun 7, 2019, at 9:23 AM, Campbell, Tracy (ELS-CMA) <tcampbell@cell.com> wrote:

Dear Drs. Xiao and Fu,

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Please let me know if you have any questions.

Thank you,
Tracy

Tracy Campbell
Deputy Production Editor, *Cell*
(617) 386-2168

<cell10894_query.docx>

From:	Fu, Xiang-Dong
To:	Campbell, Tracy (ELS-CMA)
Cc:	xiaorui9@whu.edu.cn; Chen, Jiayu
Subject:	Re: Cell article queries
Date:	Friday, June 7, 2019 10:22:05 AM
Attachments:	cell10894_query.docx ATT00001.htm

Dear Tracy,

Here are my answers to your queries. I am pretty sure that all of the information I provide is correct, but I will has my co-workers to double check.

Best and have a nice weekend.

From: Fu, Xiang-Dong
To: Bing Zhou
Cc: Xiao Li; Zhou Yu; 罗大极
Subject: Re: Proofs for your article in Nature Protocols (172)
Date: Wednesday, May 15, 2019 11:44:19 AM

Thanks, Bing. You are very generous. At this point, we hope that the publication is free of charge.

Fu

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

> On May 15, 2019, at 9:01 AM, Bing Zhou <zhoubing@ioz.ac.cn> wrote:
>
> Dear Fu,
>
> Glad to hear the final submission has been made. I have the funding to cover this publication and am happy to pay for this paper. Let me know if the bill is available.
>
> Best,
>
> Bing
>
> ---------- Original ----------
>
> **From:** Fu, Xiang-Dong <xdfu@ucsd.edu>
> **Date:** Wed,May 15,2019 11:34 PM
> **To:** Xiao Li <lixiao5128@gmail.com>, Bing Zhou <zhoubing@ioz.ac.cn>, Zhou Yu <yu.zhou@whu.edu.cn>, 罗大极 <luodaji@whu.edu.cn>
> **Subject:** Re: Proofs for your article in Nature Protocols (172)

Dear Xiao and Bing,

Thanks for careful checking of the proof. I went through your changes. I only made one change for Q15 from your original 'produce" to 'are of'. I have submitted it to the journal.

It is unclear whether we will be charged for this paper. Chen Liang promised to pay for his paper at the journal, but so far, we never saw the request to pay. In case we need to pay, I wonder if any of you have grant fund to cover it, as I am in funding gap now.

Fu

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

On May 15, 2019, at 4:25 AM, Xiao Li <lixiao5128@gmail.com> wrote:

Dear Fu,

Thanks for the timely contribution from Bing and all other authors, we have completed the proof reading. It hasn't been submitted so you can take a final look.

Yu's UCSD affiliation has now been removed. No other change was made to the authorship.

Best,
Xiao

p.s. In case you didn't know, one of the reviewers turned out to be XiaoHua Shen from Tsinghua.

On May 14, 2019, at 11:14 PM, Fu, Xiang-Dong <xdfu@ucsd.edu> wrote:

Great! I trust you can take care of it. Bing and Xiao should work with one another on this. Please let me know if you need to discuss anything.

Fu

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
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Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

On May 14, 2019, at 8:09 AM, Bing Zhou <zhoubing@ioz.ac.cn> wrote:

Dear Fu,

The link of the eproof works for me.

Best,
Bing

Bing Zhou
Principal Investigator
State Key Laboratory of Stem Cell and Reproductive Biology,
Institute of Zoology, Chinese Academy of Sciences.
1 Beichen West Road, Chaoyang District,
Beijing 100101, P.R.China
+86 10 82619908

---------- Original ----------

From: "Fu, Xiang-Dong"<xdfu@ucsd.edu>;
Date: Tue, May 14, 2019 10:22 PM
To: "Xiao Li"<lixiao5128@gmail.com>; "zhoubing@ioz.ac.cn" <zhoubing@ioz.ac.cn>;
Subject: Fwd: Proofs for your article in Nature Protocols (172)

Here is the eproof. Please rely this email to indicate you have received it.

Fu

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

Begin forwarded message:

From:<Jprod.UKRJ@mpslimited.com>
Subject:Proofs for your article in Nature Protocols (172)
Date: May 14, 2019 at 4:35:13 AM PDT
To:<xdfu@ucsd.edu>
Cc:<rjsproduction@springernature.com>,
<SNauthorproofemails@mpslimited.com>

<9379F8EA@050AE262.44DADA5C>

<A27D4331@839C0B49.44DADA5C>

Article Title : GRID-seq for comprehensive analysis of global RNA–chromatin interactions
DOI : 10.1038/s41596-019-0172-4
NP-PI180235

Dear Author,

We are pleased to inform you that your paper is nearing publication. Your article proofs are available at:

https://eproofing.springer.com/journals_v2/index.php?token=TjHAkWcWh6llcRJY5OasNYRsP_E0GJH7

The URL is valid only until your paper is published online. It is for proof purposes only and may not be used by third parties. You may share the link with co-authors, but please ensure only one person edits at a

time to avoid changes being lost

You can help us facilitate quick and accurate publication by using our e.Proofing system. The system will show you an HTML version of the article that you can correct online. In addition, you can view/download a PDF version for your reference.

As you are reviewing the proofs, please keep in mind the following:

- This is the only set of proofs you will see prior to publication.
- Only errors introduced during production process or that directly compromise the scientific integrity of the paper may be corrected.
- Any changes that contradict journal style will not be made.
- Any changes to scientific content (including figures) will require editorial review and approval.

Please check the author/editor names very carefully to ensure correct spelling, correct sequence of given and family names and that the given and family names have been correctly designated (NB the family name is highlighted in blue).

Please submit your corrections within 2 working days and make sure you fill out your response to any AUTHOR QUERIES raised during typesetting. Without your response to these queries, we will not be able to continue with the processing of your article for Online Publication.

Should you encounter difficulties with the proofs, please contact me.

Thank you very much.

Sincerely yours,

Springer Nature Corrections Team

MPS Limited,
HMG Ambassador, 137 Residency Road,
Bangalore - 560025, INDIA
e-mail: Jprod.UKRJ@mpslimited.com
P: +91 (0)80 4178 4179

<9E0AD136@FC849060.44DADA5C>

From: Fu, Xiang-Dong
To: 肖锐
Cc: Chen, Jiayu; Zhou Yu
Subject: Re: The correction for the paper from Rui
Date: Thursday, May 9, 2019 12:53:45 PM

Dear Xiao Rui,

Congratulations! It is a major milestone in your career. However, we cannot alter the affiliation as you requested for the following reason:

Accordingly to rules of our school and NIH, any uncertain issues must be disclosed and in certain situations get approval. In this case, I asked for advice from my department chair Don Cleveland. He said if the majority of the work was done at UCSD, UCSD should be listed first. I explained to him that you contributed additional work in China during revision, and he indicated it was ready more than generous to put you as a co-corresponding author. Therefore, changing the order of affiliation would not be consistent with the general practice of academia.

Sorry for this. I need to be extra careful in fulfilling the rules here. Jiayu will upload the final file today after correcting a few minor mistakes spotted by you and other co-authors.

Cheers,

Fu

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

> On May 9, 2019, at 10:41 AM, 肖锐 <xiaorui5757@163.com> wrote:
>
> Dear Prof. Fu and Jerry,
>
> My main corrections on the following points:
> 1. My affiliation: I'd like to use my current affiliation (Department of Hematology, Zhongnan Hospital of Wuhan University, Medical Research Institute, Wuhan University, Wuhan, Hubei, China) as my first affiliation in order to apply the acdamic titles this year for survival.

BTW, should we include postal code in the affiliation as mentioned in the checklist?

2. Include one of my student (Siyu Zhou) into the authorship since she helped on the ChIP-qPCR upon DRB treatment.

3. Correct some typos and some incorrect description on the detail.

Cheers! We are in the endgame now! Thank you for your support!
Rui

<RBP ChIP-seq MS 03_21_2019_XR.docx>

From:	Fu, Xiang-Dong
To:	Evans, Allyson E. (ELS-HBE)
Cc:	Zhou Yu; xinxinzuo2012; ZhouJie
Subject:	Appeal to your decision on D-19-00399
Date:	Monday, May 6, 2019 3:14:40 PM
Attachments:	Response to review on TDP43.docx ATT00001.htm

Dear Allyson,

We received your decision letter, and after fully digesting the information over the weekend, we decide to appeal to your decision against further consideration.

The bottom line is that all three reviewers praised the novel mechanistic insight into the link of TDP-43 aggregation to mitochondrial imbalance. Although each reviewer raised a seemly large set of questions, which might have caused you to feel that there are a lot of holes in our current manuscript, we feel that all criticisms are in fact quite minor, and importantly, all addressable in a reasonable time frame.

The single most important issue is to extend our analysis to iPSC-derived neurons to further strengthen the physiological relevance of our mechanistic insights. We feel that his suggestion is highly constructive, and naturally, we plan to design a series of experiments on the iPSC model. Other than this, all issues raised are minor and easy to address.

To simplify your consideration, I send this email to emphasize the most important issue. If you wish to see our response to all other issues, please see the attached file containing our point-to-point response to all issues/concerns raised and our plan to address them in full.

Given the conceptual advance from our studies, I hope you will decide to afford us an opportunity to revise the manuscript for you and your reviewers to consider, especially after you have the chance to glance through our revision plan.

Please let me know either way so that we can plan accordingly. Thanks in advance for your consideration of this appeal.

From:	xinxinzuo2012
To:	Fu, Xiang-Dong
Cc:	Zhou Yu; undefined
Subject:	2019-05-05 point to point response of TDP43
Date:	Sunday, May 5, 2019 6:38:27 AM
Attachments:	2019-05-05 point to point response of TDP43.docx

Dear Fu,

It is a bit disappointing to be refused by molecular cell. I have discussed with ZhouJie about the comments of reviewers and tried to response some of them. And the necessary experiments we summarized are listed below without priority:

1. Co-IP of TDP43 to provide experimental confirmation of TDP-43 co-aggregated proteins (one RBP and one nuclear-encoded mitochondria proteins)
2. Using another RRM-containing protein or mutated RRM1-TDP43 as negative control to confirm the miRNA binding function or specificity of RRM1 domain of TDP43.
3. Profile the expression of target genes of the TDP-43 target miRNAs in the overexpression of the mutated RRM1 vs nonmutated TDP-43
4. We can perform Ago2-CLIP(RIP) to profile the binding of miRNA before/ after the overexpression of TDP43 if necessary
5. Use antagomiRs to block miRNA let-7c to test the ROS production
6. Use antisense LNA GapmeRs to instead of siRNA to knockdown endogenous TDP-43
7. GSEA (gene set enrichment analysis) of TDP43-CTF RNA-seq data

Besides, I am wondering if we should perform all the key experiments with primary neurons or iPSC-derived neurons (according to the comments reviewer 2&3)? That could be a quite tough problem.

Looking forward to your suggestions!

Xinxin

From: Yu Zhou
To: Fu, Xiang-Dong; xinxinzuo2012@aliyun.com
Subject: TDP43
Date: Saturday, May 4, 2019 11:52:00 PM
Attachments: TDP43.docx

Dear All,

Here is the decision letter in Mol Cell. Let's digest first.

Best regards,
Yu

From: Fu, Xiang-Dong
To: Zhou Yu
Subject: Re: Letter To Editor draft
Date: Thursday, April 18, 2019 10:38:39 AM
Attachments: LetterToEditor190418.docx
ATT00001.htm

Here is revised letter to editor.

From: Yu Zhou
To: Fu, Xiang-Dong
Subject: GRID-seq Yu Zhou affiliation
Date: Wednesday, April 3, 2019 6:14:02 PM

The way below may be better, 7,8. Thank you!

[7]State Key Laboratory of Virology, Hubei Key Laboratory of Cell Homeostasis, College of Life Sciences, 8Institute for Advanced Studies, Wuhan University, Wuhan, China

---

Best regards,
Yu

> -----原始邮件-----
> 发件人:yu.zhou@whu.edu.cn
> 发送时间:2019-04-04 08:59:01 (星期四)
> 收件人: "Xiang-Dong Fu" <xdfu@ucsd.edu>
> 抄送:
> 主题: Fwd: Urgent message from Nature Protocols about your Manuscript #NP-P180235C
>
> Dear Fu,
>
> At paper proof stage, could you please remove my affiliation 3 on UCSD? And you may also remove from 7 the “Institute for Advanced Studies” as below.
>
> [7]State Key Laboratory of Virology, Hubei Key Laboratory of Cell Homeostasis, College of Life Sciences, Wuhan University, Wuhan, China
>
> Thanks a lot! See you soon!
>
> Best,
> Yu
>
> > 下面是被转发的邮件:
> >
> > 发件人: protocols@nature.com
> > 主题: **Urgent message from Nature Protocols about your Manuscript #NP-P180235C**
> > 日期: 2019年4月3日 GMT+8下午9:13:00
> > 收件人: yu.zhou@whu.edu.cn

回复-收件人: protocols@nature.com

3rd Apr 2019

Dear Dr Zhou,

As you will be aware, the protocol "GRID-seq for Comprehensive Analysis of Global RNA-Chromatin Interactions", on which you are an author, has now been accepted for publication in Nature Protocols.

As we prepare the manuscript for publication, we would like to confirm that your address details are correct. Could you please click on the link at the bottom of this message to verify your profile and correct it as needed? Your prompt attention to this will help us to avoid delays in publication of your manuscript. Please also take a look at the Nature Journals policy on financial and non-financial competing interests (http://www.nature.com/authors/editorial_policies/competing.html). If any of these situations apply to you please make sure they are declared in the Competing Interests statement within the manuscript.

If you wish to order reprints of your article or have any questions about reprints please send an email to author-reprints@nature.com.

Please contact the corresponding author, Dr Fu, directly with any queries you may have related to the content and publication of this paper.

Kind regards,

Beata Ghavimi
Editorial Assistant, Nature Protocols

Please verify your address details promptly and correct them as needed by clicking here:
https://mts-np.nature.com/cgi-bin/main.plex?el=A6P6EGK4D4fmZ6Z2A9ftdRgfhuBQAw6U174FmONEAZ

Details of the confidentiality and pre-publicity policy may be found here
http://www.nature.com/authors/policies/confidentiality.html

From:	liang chen
To:	Fu, Xiang-Dong
Cc:	Chen, Jiayu; liang_chen@whu.edu.cn
Subject:	Re: Proofs for your article in Nature Protocols (154)
Date:	Friday, March 29, 2019 5:08:26 PM
Attachments:	Learn_Discover_Achieve.png SN_logo.png SN_brand_strip.png

---

Dear Fu,

Thanks for forwarding the proof and we will get it done in the weekend.

Best,

Liang

Sent from my iPhone

On Mar 30, 2019, at 3:01 AM, Fu, Xiang-Dong <xdfu@ucsd.edu> wrote:

> The proof of your paper is here. Please work on this and get it off in the weekend.
>
> Fu
>
> Xiang-Dong Fu, Professor
> Dept. of Cellular and Molecular Medicine
> University of California, San Diego
> George Palade Laboratories
> 9500 Gilman Drive, Room 217
> La Jolla, CA 92093-0651
>
> Phone: 858-534-4937
> Fax: 858-822-6692
> Email: xdfu@ucsd.edu
>
> Begin forwarded message:
>
> **From:** <Jprod.UKRJ@mpslimited.com>
> **Subject: Proofs for your article in Nature Protocols (154)**
> **Date:** March 29, 2019 at 11:35:11 AM PDT
> **To:** <xdfu@ucsd.edu>
> **Cc:** <rjsproduction@springernature.com>,
> <SNauthorproofemails@mpslimited.com>

<Learn_Discover_Achieve.png>

<SN_logo.png>

Article Title : R-ChIP for genome-wide mapping of R-loops by using catalytically inactive RNASEH1
DOI : 10.1038/s41596-019-0154-6
NP-PI180234

Dear Author,

We are pleased to inform you that your paper is nearing publication. Your article proofs are available at:

https://eproofing.springer.com/journals_v2/index.php?token=RCxmVbKeEIcSst51fCB8aPMnHWjcI-NX

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P: +91 (0)80 4178 4179

<SN_brand_strip.png>

From: Fu, Xiang-Dong
To: Zhou Yu
Subject: Re: China trip
Date: Tuesday, March 12, 2019 7:15:54 PM
Attachments: Mol Cell review on CLEF2 in APA.pdf
ATT00001.htm

Thanks for your quick action. Here is the ms from Mol Cell.

From:	Fu, Xiang-Dong
To:	aevans@cell.com
Cc:	Zhou Yu
Subject:	MOLECULAR-CELL-D-19-00301
Date:	Thursday, March 7, 2019 9:12:52 AM

Dear Allyson,

I am pleased to learn that you have decided to send our paper out for review. As you know, we initially sent this manuscript to Cell, as we feel that we have established an unprecedented link between TDP-43 aggregation and mitochondrial imbalance, which appears to create a feed-forward cycle to further enhance TDP-43 pathology. This has a critical implication in age-dependent onset of ALS.

John Pham felt that while the concept is appealing and the mechanistic insights are interesting, we would need to establish a mouse model to directly establish the disease relevance, which we fully agree. However, John also stated that it would be a whole different project based on the current foundation, which we also agree. We thus decided to seek publication of our initial mechanistic insights first elsewhere, such as Mol Cell, which places a greater emphasis on mechanisms. I am glad that you seem to agree with this approach, as creating a mouse model that couples TDP-43 mutations with mitochondrial imbalance is itself a huge undertaking, and in fact, we are still strategizing how to precede with this important direction.

Because of your busy schedule, you do not need to reply this email. I just want to drop a note to establish the initial contact and we work together once the reviews are back.

Best regards,

Fu

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

From: Fu, Xiang-Dong
To: Zhou Yu
Cc: xinxinzuo2012@aliyun.com
Subject: Re: Cell Editorial Decision CELL-D-19-00535
Date: Sunday, March 3, 2019 11:30:17 AM

It is fine. Let's hope it will be worked out at Mol Cell.

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

On Mar 2, 2019, at 5:01 AM, Yu Zhou <yu.zhou@whu.edu.cn> wrote:

Dear Fu,

We have transferred our manuscript to Mol Cell, and modified a little bit on the Cover letter as enclosed.

Best regards,
Yu

> -----Original Messages-----
> **From:**"Fu, Xiang-Dong" <xdfu@ucsd.edu>
> **Sent Time:**2019-03-02 00:36:39 (Saturday)
> **To:** "Yu Zhou" <yu.zhou@whu.edu.cn>, "xinxinzuo2012@aliyun.com" <xinxinzuo2012@aliyun.com>
> **Cc:**
> **Subject:** Fwd: Cell Editorial Decision CELL-D-19-00535
>
> Let's transfer it to Mol Cell. Please do it from your computer as I am still traveling.
>
> Fu
>
> Sent from my iPhone

Begin forwarded message:

From: "Pham, John W. (ELS-CMA)" <jpham@cell.com>
Date: March 1, 2019 at 8:09:53 AM PST
To: "xdfu@ucsd.edu" <xdfu@ucsd.edu>
Cc: CELL PRESS Cell Manuscripts <cellms@cell.com>
Subject: Re: Cell Editorial Decision CELL-D-19-00535

Dear Fu,

Since I'm not on the Mol Cell team anymore, I don't feel it is my place to make recommendations for them, and I want to give space to the new Editor-in-Chief to make the decisions that are right for the journal. But I'm happy to make myself available to discuss your paper with the editors of Mol Cell if you transfer your paper there.

I understand your point about making the connection between TDP-43 aggregation and mitochondrial imbalance, but I still think that more work is needed to show the relevance of the proposed mechanisms to that imbalance, and to disease pheontypes. It seems like you have some tools to look into that (for example the TDP-43 cleavage fragment that does not bind miRNAs). I imagine that even for Mol Cell, the reviewers would ask for that kind of insight, although perhaps they wouldn't require an animal model. Again, the editors of Mol Cell would be in the best position to discuss what they would be looking for.

If you have any questions, or feel there's anything else you want to discuss, feel free to contact me.

Best,

John

From: Fu, Xiang-Dong <xdfu@ucsd.edu>
Sent: Thursday, February 28, 2019 6:27 PM
To: CELL PRESS Cell Manuscripts <cellms@cell.com>
Cc: xinxinzuo2012 <xinxinzuo2012@aliyun.com>; Zhou Yu <yu.zhou@whu.edu.cn>
Subject: Re: Cell Editorial Decision CELL-D-19-00535

Dear John,

I am a bit disappointed by your assessment because the main message of our manuscript is the first established link between TDP-43 aggregation and mitochondrial imbalance, which provides a new

concept to account for the adult onset and progression of ALS, and because of this novel concept, we thought that the manuscript represents a strong candidate for Cell.

Instead, your editorial concern seems to focus on TDP-43 aggregation and resultant consequence on gene expression in the nucleus to cause the disease, which is NOT what we intend to address in this manuscript. You mentioned to develop a potential animal model to determine whether mitochondrial imbalance would induce early onset of ALS in mice bearing a knock-in disease causing mutation. This would be a whole different project, as you indicated.

Given your advice to get this important work published in a timely manner, do you think that this paper represents a strong candidate for Mol Cell?

Best,

Fu

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

> On Feb 28, 2019, at 1:25 PM, Cell Editorial Office <em@editorialmanager.com> wrote:
>
> Dr. Xiang-Dong Fu
> Div Of Cellular And
> Molecular Medicine Ucsd
> 9500 Gilman Dr.
> La Jolla, CA 92093 0651
> UNITED STATES

Oxidative Stress Induces TDP-43 Aggregation to Cause Global Mitochondrial Imbalance in ALS
CELL-D-19-00535

Feb 28, 2019

Dear Fu,

Thank you for submitting your paper to Cell. As always, it's good to hear from you. I have now had a chance to read your paper and to discuss it with the team. We find the topic interesting, and we can see the potential of the work. At the same time, we have concerns that lead us to believe that the paper would not likely make it through the review process for Cell. Part of our concern relates to the breadth of the work in terms of mechanisms that might be responsible for the disease-related effects of TDP-43 aggregation. Tackling both RNA and protein contributors, and the different mechanisms through which they might contribute, is a lot for one paper. It doesn't leave much space for exploring the core questions to the degree that is probably needed for us, including whether TDP-43 aggregation impairs its functions in the nucleus in regulating gene expression, as you mention in your paper. The finding that TDP-43 can sequester miRNAs has potential, although as you note, such interaction has been reported before. What remains to be seen is whether that sequestration is actually causative for TDP-43 related disease phenotypes. At this point, from our reading of your paper, that remains an outstanding question. Without some clear insights into this, we feel that the functional relevance of the findings are not well established, at least to the degree that we think would be needed to make the paper a strong candidate for Cell. While I'm not that up to date on the TDP-43 literature, I'm aware that there are animal models, and this might be a potential avenue to explore. But as that represents a lot more work, I can't suggest that you add that to your paper, and it might be in your best interest to focus the work and publish it more quickly elsewhere.

I'm sorry I can't be more positive, and I wish you all the best at finding a good home for the paper.

You have the option of transferring your paper to another Cell Press journal. If you would like to take advantage of this option, please use this link:
Agree to Transfer
After your files have been transferred, you will be given an opportunity to update your materials before they are delivered to the editors at your new journal. You will be able to make any desired revisions or additions at this stage, so feel free to select a transfer option now and work on your revisions after that. For more details on the transfer process, please click here or contact the editors at your new target journal.

Please note that the above link will expire 90 days after receipt of this letter. However, if you still wish to transfer after that period, you may submit directly to the journal of your choice and reference your original manuscript number in the cover letter.

We hope that this option may be helpful for you, however if you decide not to transfer this manuscript, please click here: Decline to Transfer

Declining to transfer will officially close out the manuscript in our system. If you do not accept or decline by May 29, 2019, the system will automatically decline on your behalf. If you prefer, you do have the choice of submitting this manuscript or a revised version of it to another Cell Press journal as a regular new submission, in which case you can decline the transfer.

Best wishes,
John

John Pham, Ph.D.
Editor-in-Chief, Cell

<Cover letter TDP43ms MolCell.doc>

From: bzhou
To: Fu, Xiang-Dong; Xiao Li
Cc: 罗大极
Subject: Re: Decision on Nature Protocols submission NP-P180235B
Date: Saturday, March 2, 2019 8:04:23 AM
Attachments: NP-P180235B Fu - LXedit-Luo-Zhou.docx

Dear Fu,

The attached is my revision of the main text. I did not modify any figures and you may use the lasted version from Xiao.

It should pay more attention to the "bivalent linker" definition, where I found that only our protocol use ssRNA-dsDNA while ChAR-seq and MARGI use ssDNA-dsDNA as their linker.

Best,
Bing

---------- Original ----------

From: "Fu, Xiang-Dong"<xdfu@ucsd.edu>;
Date: Fri, Mar 1, 2019 10:54 PM
To: "Xiao Li"<lixiao5128@gmail.com>; "**周兵**"<bzhou@iozlab.ac.cn>;
Cc: "罗大极"<luodaji@whu.edu.cn>;
Subject: Re: Decision on Nature Protocols submission NP-P180235B

We need to get this done as soon as possible.

Bing: I need you to get your part done and send the package to me tonight at the latest! I will go through it and send it off tomorrow.

Fu

Sent from my iPhone

On Feb 28, 2019, at 1:18 AM, Xiao Li <lixiao5128@gmail.com> wrote:

> Dear Fu,
>
> I just noticed today that Aaron Straight at Stanford, the core inventor of ChAR-seq, published their detailed protocol in the journal Current Protocols last week.
>
> Interestingly, we have previously estimated the number of usable reads in ChAR-seq data to be ~20% and have written in in our NP paper (page 6). Now in their paper, they specifically stated that "...about 15% to 30% of the sequenced reads remain as "highquality" reads for analysis".
> They also mentioned that they had successfully tested EcoP15I, a type III RE that generates 27 bp DNA fragments, as a replacement of MmeI to enhance mappability of the library. We had this idea before I left the lab but too bad they got it done first.
>
> Anyways, they cited our work with nice wording. Here's the link to the paper if you would like to cite it in our paper as well.
> https://doi.org/10.1002/cpmb.87

Best,
Xiao

On Feb 28, 2019, at 10:00 AM, 罗大极 <luodaji@whu.edu.cn> wrote:

Dear Xiao,

That is great. I have checked all your replies except computational analysis part and changed 3 places in your text.

Regards,

Daji

Daji Luo, PhD.
Associate Professor
Department of Genetics, School of Basic Medical Sciences, Wuhan University
Address:No.185 Donghu Road, Wuchang distrcit, Wuhan, Hubei, PR China.
(Tel) +86 189 8628 1862
(Lab) +86 27 6875 9702

> -----原**始**邮**件**-----
> 发**件人:**"Xiao Li" <lixiao5128@gmail.com>
> 发**送**时间**:**2019-02-27 19:43:10 (**星期三**)
> **收件人:** "**周兵**" <bzhou@iozlab.ac.cn>, "罗大极" <luodaji@whu.edu.cn>
> 抄**送:** "Xiang-Dong Fu" <xdfu@ucsd.edu>
> 主题**:** Re: Decision on Nature Protocols submission NP-P180235B
>
> Dear Bing and Daji,
>
> I have addressed almost every comments by the editor, except a few regarding details of our computational pipeline. I tracked all my changes in the text for you to review.
> Figures are accordingly modified. The 2 Supplementary Figures are pasted into the word template as requested by the editor.
>
> Daji, please comb through the equipment/protocol parts one more time to ensure that I didn’t miss anything.
>
> Best,
> Xiao

On Feb 26, 2019, at 1:39 AM, Fu, Xiang-Dong <xdfu@ucsd.edu> wrote:

The editor has made some changes or comments. Please go through the documents to address the questions raised. Please keep your changes tracked. After I am done with the Keystone meeting. I will go through all of the changes and then submit it.

Bing is here with me in the meeting. I suggest Xiao and Daji go through it first and then ask Bing to take a look, add his changes, and then give me the document containing all of your revision for me to work on.

Fu

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

Begin forwarded message:

From: <protocols@nature.com>
Subject: Decision on Nature Protocols submission NP-P180235B
Date: February 25, 2019 at 6:14:43 AM PST
To: <xdfu@ucsd.edu>
Reply-To: <protocols@nature.com>

25th Feb 2019

Dear Dr. Fu,

Your Protocol entitled "GRID-seq for Comprehensive Analysis of Global RNA-Chromatin Interactions in 3D Genome" has now been seen by our referees, and in the light of their advice, I am delighted to say that we can in principle offer to publish it. First, however, we would like you to revise your protocol to address the points made by the referees below and to make some editorial changes to your paper so that it complies with our

Protocol format instructions.

I have edited your manuscript so that it conforms to our house style. My edits can be seen using 'track changes' in the attached doc. I have also requested some additional information and clarification regarding some sections. These requests can be viewed using 'comments'. Please review my edits and, if they are acceptable to you, accept them and make any further revisions to this file (also using 'track changes' and 'commenting' functionality). Please be aware that, after these revisions, you may not see your protocol again until it is laid out as a proof, at which point only minor changes can be made. If you have any problem reading the attached file, please let me know so I can send you a PDF version with the comments highlighted.

Please upload your revised text (in Microsoft Word format) and figures using the link provided below. Please save your text file as (NP-P180235B) plus the corresponding author name, for example "NP22 smith".

https://mts-np.nature.com/cgi-bin/main.plex?el=A5P7CbC4A1GSN1J1A9ftdUIgZaFrIjsXRiwUh0zpLgZ

Please also re-upload any checklists you have completed (e.g. Reporting Summary, Code and Software supplement) along with your revised manuscript and indicate whether these have been revised since the previous submission.

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Please see further information on preparing your figures on our website https://www.nature.com/nprot/for-authors/preparing-your-submission#figure.

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(maximum size of 30 MB) so that they can be downloaded quickly. The combined total size of all files must not exceed 150 MB. Unless there is a good reason not to (for example, the SI file is a Supplementary Video or Excel file), we provide SI to our readers as PDF files. We also integrate supplementary figures into the main article, to make it easier for readers to access them in the HTML version of the article. Please place any supplementary figures and their associated titles and legends in our Integrated Supplementary Figures template.
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Before resubmitting the final version of the manuscript, if you are a corresponding author on the manuscript, please follow the steps below to link your account on our MTS with your ORCID. If you don't have an ORCID yet, you will be able to create one in minutes. If you are not listed as a corresponding author, please ensure that the corresponding author(s) comply.

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2. In the '**Personal profile**' tab, click on '**ORCID Create/link an Open Researcher Contributor ID(ORCID)**'. This will re-direct you to the ORCID website.
3a. If you already have an ORCID account, enter your ORCID email and password and click on '**Authorize**' to link your ORCID with your account on the MTS.
3b. If you don't yet have an ORCID, you can easily create one by providing the required information and then click on '**Authorize**'. This will link your newly created ORCID with your account on the MTS.

IMPORTANT: All authors identified as 'corresponding authors' on the manuscript must follow these instructions. Non-corresponding authors do not have to link their ORCIDs, but please encourage them to do so now. Note that it will not be possible to add/modify ORCIDs at proof. Thus, if they wish to have their ORCID added to the paper, they must also follow the above procedure prior to acceptance.

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We hope that you will support this initiative and supply the required information. Should you have any query or comments, please do not hesitate to contact me.

COVER SUGGESTION: If you would like to make a suggestion for our monthly cover image, please upload this as a 'Related File' with your revised manuscript files and notify the editor in your cover letter. If chosen, we will need a high resolution version of the image at a minimum of 300 dpi. It will also need to be at least 216 mm tall by 285 mm wide. Please note that the cover image is chosen by the editorial team via a democratic process.

We hope to receive your revised manuscript as soon as possible, ideally within 2 weeks. Do let us know as soon as possible if you need to extend this deadline or if you have any further questions.

Sincerely,

Ivanka Kamenova, PhD
Associate Editor, Nature Protocols
Nature Research

Springer Nature
4 Crinan Street, London N1 9XW, UK
ivanka kamenova@nature.com
https://www.nature.com/nprot/
ORCID iD 0000-0003-2645-9031
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Reviewers' Comments:

<Fu_NP-20181230_AIPedit_1551104051_5.docx><11138_2_attach_10_3216.docx>

<NP-P180235B Fu - LX edit-Luo.docx>

From: xinxinzuo2012
To: Fu, Xiang-Dong; yu.zhou@whu.edu.cn
Subject: Re:Fwd: Cell Editorial Decision CELL-D-19-00535
Date: Friday, March 1, 2019 2:58:48 PM

Dear Fu,
Ok. I will help ZhouYou to complete it together.

Xinxin

发自我的小米手机
在 "Fu, Xiang-Dong" <xdfu@ucsd.edu>,2019年3月2日 上午12:36写道:

> Let's transfer it to Mol Cell. Please do it from your computer as I am still traveling.
>
> Fu
>
> Sent from my iPhone
>
> Begin forwarded message:
>
> **From:** "Pham, John W. (ELS-CMA)" <jpham@cell.com>
> **Date:** March 1, 2019 at 8:09:53 AM PST
> **To:** "xdfu@ucsd.edu" <xdfu@ucsd.edu>
> **Cc:** CELL PRESS Cell Manuscripts <cellms@cell.com>
> **Subject: Re: Cell Editorial Decision CELL-D-19-00535**
>
> Dear Fu,
>
> Since I'm not on the Mol Cell team anymore, I don't feel it is my place to make recommendations for them, and I want to give space to the new Editor-in-Chief to make the decisions that are right for the journal. But I'm happy to make myself available to discuss your paper with the editors of Mol Cell if you transfer your paper there.
>
> I understand your point about making the connection between TDP-43 aggregation and mitochondrial imbalance, but I still think that more work is needed to show the relevance of the proposed mechanisms to that imbalance, and to disease pheontypes. It seems like you have some tools to look into that (for example the TDP-43 cleavage fragment that does not bind miRNAs). I imagine that even for Mol Cell, the reviewers would ask for that kind of insight, although perhaps they wouldn't require an animal model. Again, the editors of Mol Cell would be in the best position to discuss what they would be looking for.
>
> If you have any questions, or feel there's anything else you want to discuss, feel free

to contact me.

Best,

John

From: Fu, Xiang-Dong <xdfu@ucsd.edu>
Sent: Thursday, February 28, 2019 6:27 PM
To: CELL PRESS Cell Manuscripts <cellms@cell.com>
Cc: xinxinzuo2012 <xinxinzuo2012@aliyun.com>; Zhou Yu <yu.zhou@whu.edu.cn>
Subject: Re: Cell Editorial Decision CELL-D-19-00535

Dear John,

I am a bit disappointed by your assessment because the main message of our manuscript is the first established link between TDP-43 aggregation and mitochondrial imbalance, which provides a new concept to account for the adult onset and progression of ALS, and because of this novel concept, we thought that the manuscript represents a strong candidate for Cell.

Instead, your editorial concern seems to focus on TDP-43 aggregation and resultant consequence on gene expression in the nucleus to cause the disease, which is NOT what we intend to address in this manuscript. You mentioned to develop a potential animal model to determine whether mitochondrial imbalance would induce early onset of ALS in mice bearing a knock-in disease causing mutation. This would be a whole different project, as you indicated.

Given your advice to get this important work published in a timely manner, do you think that this paper represents a strong candidate for Mol Cell?

Best,

Fu

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937

Fax: 858-822-6692
Email: xdfu@ucsd.edu

On Feb 28, 2019, at 1:25 PM, Cell Editorial Office <em@editorialmanager.com> wrote:

Dr. Xiang-Dong Fu
Div Of Cellular And
Molecular Medicine Ucsd
9500 Gilman Dr.
La Jolla, CA 92093 0651
UNITED STATES

Oxidative Stress Induces TDP-43 Aggregation to Cause Global Mitochondrial Imbalance in ALS
CELL-D-19-00535

Feb 28, 2019

Dear Fu,

Thank you for submitting your paper to Cell. As always, it's good to hear from you. I have now had a chance to read your paper and to discuss it with the team. We find the topic interesting, and we can see the potential of the work. At the same time, we have concerns that lead us to believe that the paper would not likely make it through the review process for Cell. Part of our concern relates to the breadth of the work in terms of mechanisms that might be responsible for the disease-related effects of TDP-43 aggregation. Tackling both RNA and protein contributors, and the different mechanisms through which they might contribute, is a lot for one paper. It doesn't leave much space for exploring the core questions to the degree that is probably needed for us, including whether TDP-43 aggregation impairs its functions in the nucleus in regulating gene expression, as you mention in your paper. The finding that TDP-43 can sequester miRNAs has potential, although as you note, such interaction has been reported before. What remains to be seen is whether that sequestration is actually causative for TDP-43 related disease phenotypes. At this point, from our reading of your paper, that remains an outstanding question. Without some clear insights into this, we feel that the functional relevance of the findings are not well established, at least to the degree that we think would be

needed to make the paper a strong candidate for Cell. While I'm not that up to date on the TDP-43 literature, I'm aware that there are animal models, and this might be a potential avenue to explore. But as that represents a lot more work, I can't suggest that you add that to your paper, and it might be in your best interest to focus the work and publish it more quickly elsewhere.

I'm sorry I can't be more positive, and I wish you all the best at finding a good home for the paper.

You have the option of transferring your paper to another Cell Press journal. If you would like to take advantage of this option, please use this link:
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Best wishes,
John

John Pham, Ph.D.
Editor-in-Chief, Cell

---

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Please contact the publication office if you have any questions.

From: Fu, Xiang-Dong
To: Xiao Li; 周兵
Cc: 罗大极
Subject: Re: Decision on Nature Protocols submission NP-P180235B
Date: Friday, March 1, 2019 6:54:14 AM

We need to get this done as soon as possible.

Bing: I need you to get your part done and send the package to me tonight at the latest! I will go through it and send it off tomorrow.

Fu

Sent from my iPhone

On Feb 28, 2019, at 1:18 AM, Xiao Li <lixiao5128@gmail.com> wrote:

> Dear Fu,
>
> I just noticed today that Aaron Straight at Stanford, the core inventor of ChAR-seq, published their detailed protocol in the journal Current Protocols last week.
>
> Interestingly, we have previously estimated the number of usable reads in ChAR-seq data to be ~20% and have written in in our NP paper (page 6). Now in their paper, they specifically stated that "...about 15% to 30% of the sequenced reads remain as "highquality" reads for analysis".
> They also mentioned that they had successfully tested EcoP15I, a type III RE that generates 27 bp DNA fragments, as a replacement of MmeI to enhance mappability of the library. We had this idea before I left the lab but too bad they got it done first.
>
> Anyways, they cited our work with nice wording. Here's the link to the paper if you would like to cite it in our paper as well.
> https://doi.org/10.1002/cpmb.87
>
> Best,
> Xiao
>
> On Feb 28, 2019, at 10:00 AM, 罗大极 <luodaji@whu.edu.cn> wrote:
>
> Dear Xiao,
>
> That is great. I have checked all your replies except computational analysis part and changed 3 places in your text.

Regards,

Daji

Daji Luo, PhD.
Associate Professor
Department of Genetics, School of Basic Medical Sciences, Wuhan University
Address:
No.185 Donghu Road, Wuchang distrcit, Wuhan, Hubei, PR China.
(Tel) +86 189 8628 1862
(Lab) +86 27 6875 9702

> -----原始邮件-----
> 发件人:"Xiao Li" <lixiao5128@gmail.com>
> 发送时间:2019-02-27 19:43:10 (星期三)
> 收件人: "周兵" <bzhou@iozlab.ac.cn>, "罗大极" <luodaji@whu.edu.cn>
> 抄送: "Xiang-Dong Fu" <xdfu@ucsd.edu>
> 主题: Re: Decision on Nature Protocols submission NP-P180235B
>
> Dear Bing and Daji,
>
> I have addressed almost every comments by the editor, except a few regarding details of our computational pipeline. I tracked all my changes in the text for you to review.
> Figures are accordingly modified. The 2 Supplementary Figures are pasted into the word template as requested by the editor.
>
> Daji, please comb through the equipment/protocol parts one more time to ensure that I didn't miss anything.
>
> Best,
> Xiao
>
>
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>
>
>
>
> > On Feb 26, 2019, at 1:39 AM, Fu, Xiang-Dong <xdfu@ucsd.edu> wrote:
> >
> > The editor has made some changes or comments. Please go through the documents to address the

questions raised. Please keep your changes tracked. After I am done with the Keystone meeting. I will go through all of the changes and then submit it.

Bing is here with me in the meeting. I suggest Xiao and Daji go through it first and then ask Bing to take a look, add his changes, and then give me the document containing all of your revision for me to work on.

Fu

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

Begin forwarded message:

From: <protocols@nature.com>
Subject: Decision on Nature Protocols submission NP-P180235B
Date: February 25, 2019 at 6:14:43 AM PST
To: <xdfu@ucsd.edu>
Reply-To: <protocols@nature.com>

25th Feb 2019

Dear Dr. Fu,

Your Protocol entitled "GRID-seq for Comprehensive Analysis of Global RNA-Chromatin Interactions in 3D Genome" has now been seen by our referees, and in the light of their advice, I am delighted to say that we can in principle offer to publish it. First, however, we would like you to revise your protocol to address the points made by the referees below and to make some

editorial changes to your paper so that it complies with our Protocol format instructions.

I have edited your manuscript so that it conforms to our house style. My edits can be seen using ‘track changes’ in the attached doc. I have also requested some additional information and clarification regarding some sections. These requests can be viewed using ‘comments’. Please review my edits and, if they are acceptable to you, accept them and make any further revisions to this file (also using ‘track changes’ and ‘commenting’ functionality). Please be aware that, after these revisions, you may not see your protocol again until it is laid out as a proof, at which point only minor changes can be made. If you have any problem reading the attached file, please let me know so I can send you a PDF version with the comments highlighted.

Please upload your revised text (in Microsoft Word format) and figures using the link provided below. Please save your text file as (NP-P180235B) plus the corresponding author name, for example "NP22 smith".

https://mts-np.nature.com/cgi-bin/main.plex?el=A5P7CbC4A1GSN1J1A9ftdUIgZaFrIjsXRiwUh0zpLgZ

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We hope to receive your revised manuscript as soon as possible, ideally within 2 weeks. Do let us know as soon as possible if you need to extend this deadline or if you have any further questions.

Sincerely,

Ivanka Kamenova, PhD
Associate Editor, Nature Protocols
Nature Research

Springer Nature
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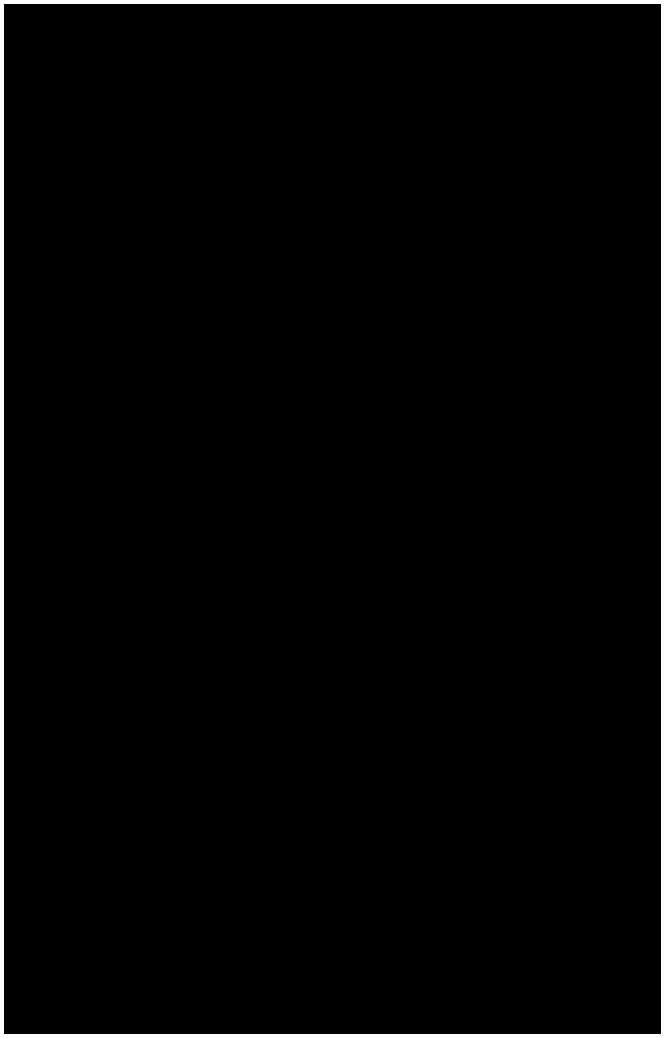
ivanka.kamenova@nature.com
https://www.nature.com/nprot/
ORCID iD 0000-0003-2645-9031
Connecting Research and Researchers

Reviewers' Comments:



> <Fu_NP-20181230_AIPedit_1551104051_5.docx><11138_2_attach_10_3216.docx>

<NP-P180235B Fu - LX edit-Luo.docx>

From: Xiao Li
To: 罗大极
Cc: 周兵; Fu, Xiang-Dong
Subject: Re: Decision on Nature Protocols submission NP-P180235B
Date: Thursday, February 28, 2019 1:18:26 AM

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Anyways, they cited our work with nice wording. Here's the link to the paper if you would like to cite it in our paper as well.
https://doi.org/10.1002/cpmb.87

Best,
Xiao

> On Feb 28, 2019, at 10:00 AM, 罗大极 <luodaji@whu.edu.cn> wrote:
>
> Dear Xiao,
>
> That is great. I have checked all your replies except computational analysis part and changed 3 places in your text.
>
> Regards,
>
> Daji

Daji Luo, PhD.
Associate Professor
Department of Genetics, School of Basic Medical Sciences, Wuhan University
Address:No.185 Donghu Road, Wuchang distrcit, Wuhan, Hubei, PR China.

(Tel) +86 189 8628 1862
(Lab) +86 27 6875 9702

-----原始邮件-----
发件人:"Xiao Li" <lixiao5128@gmail.com>
发送时间:2019-02-27 19:43:10 (星期三)
收件人: "周兵" <bzhou@iozlab.ac.cn>, "罗大极" <luodaji@whu.edu.cn>
抄送: "Xiang-Dong Fu" <xdfu@ucsd.edu>
主题: Re: Decision on Nature Protocols submission NP-P180235B

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I have addressed almost every comments by the editor, except a few regarding details of our computational pipeline. I tracked all my changes in the text for you to review.
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Daji, please comb through the equipment/protocol parts one more time to ensure that I didn't miss anything.

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Xiao

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>
> Fu
>
> Xiang-Dong Fu, Professor
> Dept. of Cellular and Molecular Medicine
> University of California, San Diego

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9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
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Email: xdfu@ucsd.edu

Begin forwarded message:

From: <protocols@nature.com>
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Date: February 25, 2019 at 6:14:43 AM PST
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Reply-To: <protocols@nature.com>

25th Feb 2019

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highlighted.

Please upload your revised text (in Microsoft Word format) and figures using the link provided below. Please save your text file as (NP-P180235B) plus the corresponding author name, for example "NP22 smith".

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<NP-P180235B Fu - LX edit-Luo.docx>

From: 罗大极
To: xiao li
Cc: 周兵; Fu, Xiang-Dong
Subject: Re: Re: Decision on Nature Protocols submission NP-P180235B
Date: Wednesday, February 27, 2019 6:02:31 PM
Attachments: NP-P180235B Fu - LX edit-Luo.docx

Dear Xiao,

That is great. I have checked all your replies except computational analysis part and changed 3 places in your text.

Regards,

Daji

Daji Luo, PhD.
Associate Professor
Department of Genetics, School of Basic Medical Sciences, Wuhan University
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(Tel) +86 189 8628 1862
(Lab) +86 27 6875 9702

> -----原始邮件-----
> 发件人:"Xiao Li" <lixiao5128@gmail.com>
> 发送时间:2019-02-27 19:43:10 (星期三)
> 收件人: "周兵" <bzhou@iozlab.ac.cn>, "罗大极" <luodaji@whu.edu.cn>
> 抄送: "Xiang-Dong Fu" <xdfu@ucsd.edu>
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Email: xdfu@ucsd.edu

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Cc: 周兵; 罗大极
Subject: Re: Decision on Nature Protocols submission NP-P180235B
Date: Wednesday, February 27, 2019 7:22:00 AM

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Thanks a lot.

Fu

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9500 Gilman Drive, Room 217
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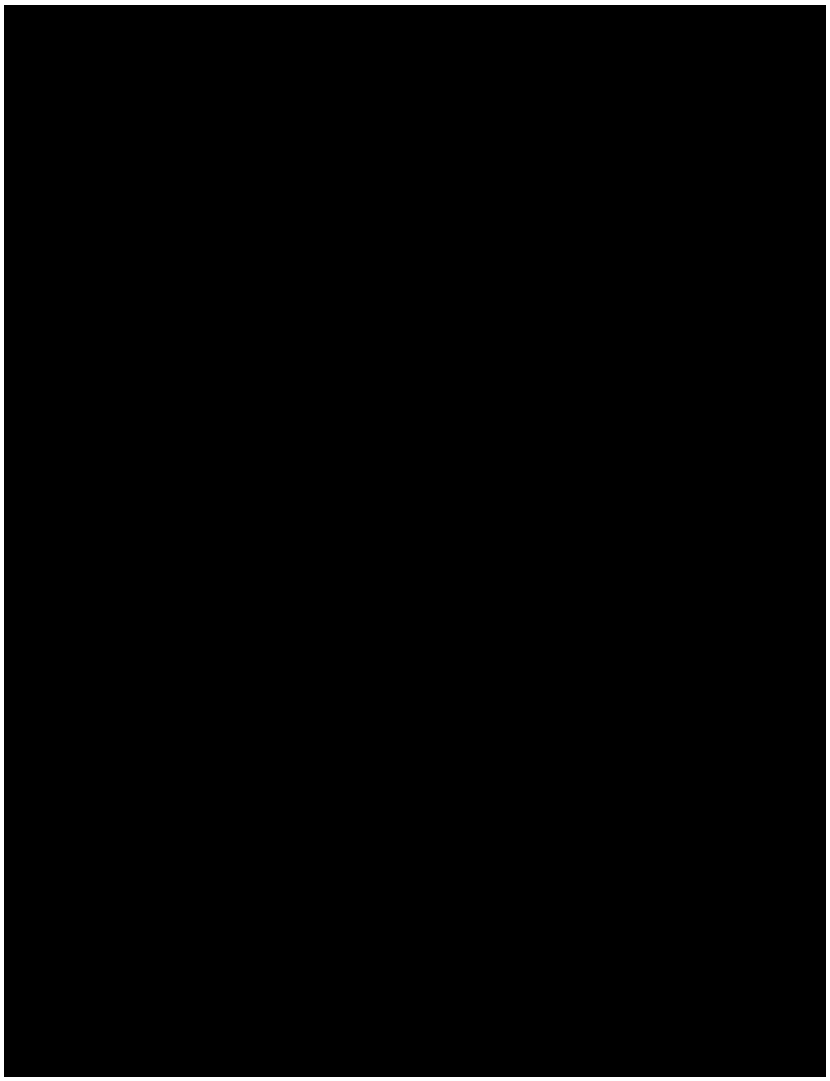

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For any PDF-able SI that are not integrated figures (e.g. tables, notes, manual, methods, etc.), please create a single, combined PDF. Please submit any SI that are not PDF-able (e.g. videos, podcasts, Excel docs, etc.) separately, but remember to include the SI titles and legends at the end of the manuscript.

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Before resubmitting the final version of the manuscript, if you are a corresponding author on the manuscript, please follow the steps below to link your account on our MTS with your ORCID. If you don't have an ORCID yet, you will be able to create one in minutes. If you are not listed as a corresponding author, please ensure that the corresponding author(s) comply.

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3a. If you already have an ORCID account, enter your ORCID email and password and click on '**Authorize**' to link your ORCID with your account on the MTS.
3b. If you don't yet have an ORCID, you can easily create one by providing the required information and then click on '**Authorize**'. This will link your newly created ORCID with your account on the

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IMPORTANT: All authors identified as ‘corresponding authors’ on the manuscript must follow these instructions. Non-corresponding authors do not have to link their ORCIDs, but please encourage them to do so now. Note that it will not be possible to add/modify ORCIDs at proof. Thus, if they wish to have their ORCID added to the paper, they must also follow the above procedure prior to acceptance.

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We hope that you will support this initiative and supply the required information. Should you have any query or comments, please do not hesitate to contact me.

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We hope to receive your revised manuscript as soon as possible, ideally within 2 weeks. Do let us know as soon as possible if you need to extend this deadline or if you have any further questions.

Sincerely,

Ivanka Kamenova, PhD
Associate Editor, Nature Protocols
Nature Research

Springer Nature
4 Crinan Street, London N1 9XW, UK
ivanka.kamenova@nature.com
https://www.nature.com/nprot/
ORCID iD 0000-0003-2645-9031
Connecting Research and Researchers

Reviewers' Comments:

<Fu_NP-20181230_AIPedit_1551104051_5.docx><11138_2_attach_10_3216.docx>

From: Chen, Jiayu
To: Fu, Xiang-Dong; liang_chen@whu.edu.cn
Subject: RE: Urgent message from Nature Protocols about your Manuscript #NP-P180234D
Date: Tuesday, February 26, 2019 10:45:38 AM

I have done it early this morning.

I also asked Xuan. She didn't receive that e-mail. Perhaps they do not need any confirmation from her.

From: Fu, Xiang-Dong
Sent: Tuesday, February 26, 2019 7:13 AM
To: liang_chen@whu.edu.cn
Cc: Chen, Jiayu
Subject: Re: Urgent message from Nature Protocols about your Manuscript #NP-P180234D

Yes. I am done with mine.

Fu

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

> On Feb 26, 2019, at 4:00 AM, Liang Chen <liang_chen@whu.edu.cn> wrote:
>
> Hi Fu and Jerry,
>
> Just in case you did not receive it, I forwarded the message from Nature Protocols asking for confirmation of the contact address. I just did mine. Thank you!
>
> Have a good day!
>
> Best,
>
> Liang

Begin forwarded message:

From: protocols@nature.com
Subject: Urgent message from Nature Protocols about your Manuscript #NP-P180234D
Date: February 26, 2019 at 7:17:02 PM GMT+8
To: liang_chen@whu.edu.cn
Reply-To: protocols@nature.com

26th Feb 2019

Dear Prof Chen,

As you will be aware, the protocol "R-ChIP for Genome-wide Mapping of R-loops by Using Catalytically Inactive RNASEH1", on which you are an author, has now been accepted for publication in Nature Protocols.

As we prepare the manuscript for publication, we would like to confirm that your address details are correct. Could you please click on the link at the bottom of this message to verify your profile and correct it as needed? Your prompt attention to this will help us to avoid delays in publication of your manuscript. Please also take a look at the Nature Journals policy on financial and non-financial competing interests (http://www.nature.com/authors/editorial_policies/competing.html). If any of these situations apply to you please make sure they are declared in the Competing Interests statement within the manuscript.

If you wish to order reprints of your article or have any questions about reprints please send an email to author-reprints@nature.com.

Please contact the corresponding author, Dr Fu, directly with any queries you may have related to the content and publication of this paper.

Kind regards,

Beata Ghavimi
Editorial Assistant, Nature Protocols

Please verify your address details promptly and correct them as needed by clicking here:
https://mts-np.nature.com/cgi-bin/main.plex?

el=A7P5EGJ5E6fWp3Z5A9ftdD15XV2WUCJsjIOUwG27gZ

This email has been sent through the Springer Nature Tracking System NY-610A-NPG&MTS

From: Fu, Xiang-Dong
To: 周兵; Xiao Li; 罗大极
Subject: Fwd: Decision on Nature Protocols submission NP-P180235B
Date: Monday, February 25, 2019 9:39:27 AM
Attachments: Fu_NP-20181230_AIPedit_1551104051_5.docx
ATT00001.htm
11138_2_attach_10_3216.docx
ATT00002.htm

The editor has made some changes or comments. Please go through the documents to address the questions raised. Please keep your changes tracked. After I am done with the Keystone meeting. I will go through all of the changes and then submit it.

Bing is here with me in the meeting. I suggest Xiao and Daji go through it first and then ask Bing to take a look, add his changes, and then give me the document containing all of your revision for me to work on.

Fu

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

Begin forwarded message:

From: <protocols@nature.com>
Subject: Decision on Nature Protocols submission NP-P180235B
Date: February 25, 2019 at 6:14:43 AM PST
To: <xdfu@ucsd.edu>
Reply-To: <protocols@nature.com>

25th Feb 2019

Dear Dr. Fu,

Your Protocol entitled "GRID-seq for Comprehensive Analysis of Global RNA-Chromatin Interactions in 3D Genome" has now been seen by our referees, and in the light of their advice, I am delighted to say that we can in principle offer to publish it. First, however, we would like you to revise your protocol to address

the points made by the referees below and to make some editorial changes to your paper so that it complies with our Protocol format instructions.

I have edited your manuscript so that it conforms to our house style. My edits can be seen using 'track changes' in the attached doc. I have also requested some additional information and clarification regarding some sections. These requests can be viewed using 'comments'. Please review my edits and, if they are acceptable to you, accept them and make any further revisions to this file (also using 'track changes' and 'commenting' functionality). Please be aware that, after these revisions, you may not see your protocol again until it is laid out as a proof, at which point only minor changes can be made. If you have any problem reading the attached file, please let me know so I can send you a PDF version with the comments highlighted.

Please upload your revised text (in Microsoft Word format) and figures using the link provided below. Please save your text file as (NP-P180235B) plus the corresponding author name, for example "NP22 smith".

https://mts-np.nature.com/cgi-bin/main.plex?el=A5P7CbC4A1GSN1J1A9ftdUIgZaFrIjsXRiwUh0zpLgZ

Please also re-upload any checklists you have completed (e.g. Reporting Summary, Code and Software supplement) along with your revised manuscript and indicate whether these have been revised since the previous submission.

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We hope to receive your revised manuscript as soon as possible, ideally within 2 weeks. Do let us know as soon as possible if you need to extend this deadline or if you have any further questions.

Sincerely,

Ivanka Kamenova, PhD
Associate Editor, Nature Protocols
Nature Research

Springer Nature
4 Crinan Street, London N1 9XW, UK
ivanka.kamenova@nature.com
https://www.nature.com/nprot/
ORCID iD 0000-0003-2645-9031
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Reviewers' Comments:

From: Liang Chen
To: Fu, Xiang-Dong
Cc: Chen, Jiayu
Subject: Re: Update on manuscript NP-P180234D
Date: Thursday, February 21, 2019 4:07:16 PM

Hi Fu,

Thank you very much for forwarding the decision letter from NP! It looks that we need to wait a little longer for the proof.

Best,

Liang

> On Feb 22, 2019, at 3:25 AM, Fu, Xiang-Dong <xdfu@ucsd.edu> wrote:
>
> Xiang-Dong Fu, Professor
> Dept. of Cellular and Molecular Medicine
> University of California, San Diego
> George Palade Laboratories
> 9500 Gilman Drive, Room 217
> La Jolla, CA 92093-0651
>
> Phone: 858-534-4937
> Fax: 858-822-6692
> Email: xdfu@ucsd.edu
>
> Begin forwarded message:
>
> **From:** <protocols@nature.com>
> **Subject: Update on manuscript NP-P180234D**
> **Date:** February 21, 2019 at 10:37:27 AM PST
> **To:** <xdfu@ucsd.edu>
> **Reply-To:** <protocols@nature.com>
>
> Dear Dr. Fu,
>
> I am pleased to inform you that your protocol, "R-ChIP for Genome-wide Mapping of R-loops by Using Catalytically Inactive

RNASEH1", has now been accepted and sent to our Production department and should soon be published in Nature Protocols. This message is intended to let you know what to expect from us next and where to address any further questions.

Your protocol will now be copyedited to ensure that it conforms to Nature Protocols style. Assuming there are no major problems, you will be asked to view a set of proofs once your protocol has been laid out into the final PDF format. Once proofs are generated, they will be sent to you electronically and you will be asked to send a corrected version within 24 hours. We realise this is a very tight turnaround but there is usually some flexibility in the system, so please get in touch if you require extra time. It is extremely important that you let us know now if you will be difficult to contact over the next three months. If this is the case, please send us the contact information (email and phone number) of someone who will be able to check the proofs and deal with any last-minute problems.

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Please feel free to contact me at any time with any questions.

Best regards,

Ivanka Kamenova, PhD
Associate Editor, Nature Protocols
Nature Research

Springer Nature
4 Crinan Street, London N1 9XW, UK
ivanka.kamenova@nature.com
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****

please click here.**

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From: Fu, Xiang-Dong
To: xinxinzuo2012
Cc: Zhou Yu
Subject: Re: Manuscript number for your Cell submission
Date: Thursday, February 21, 2019 2:24:02 PM

Excellent plan!

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

> On Feb 21, 2019, at 2:18 PM, xinxinzuo2012 <xinxinzuo2012@aliyun.com> wrote:
>
> Dear Fu,
> I have already obtained the necessary antibody and mito UPR related experiments can be readily carried out.
> Besides, I am also considering to do additonal experimental tests related to mitochondrial imbalance, such as mass spectrometry analysis of purified mitochondria which may provide a global infomation of mito protein change level.
>
> Xinxin
>
> 发自我的小米手机
> 在 "Fu, Xiang-Dong" <xdfu@ucsd.edu>,2019年2月22日 上午4:58写道:
>
> > See below. If the paper is sent out for review, we may need to consider performing mito UPR related experiments while waiting for reviews.
> >
> > Fu
> >
> > Xiang-Dong Fu, Professor
> > Dept. of Cellular and Molecular Medicine
> > University of California, San Diego
> > George Palade Laboratories
> > 9500 Gilman Drive, Room 217

La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

Begin forwarded message:

From: Cell Editorial Office <em@editorialmanager.com>
Subject: Manuscript number for your Cell submission
Date: February 21, 2019 at 12:27:46 PM PST
To: Xiang-Dong Fu <xdfu@ucsd.edu>
Reply-To: Cell Editorial Office <cellms@cell.com>

Dear Dr. Fu,

Thank you again for your submission to Cell. The manuscript "Oxidative Stress Induces TDP-43 Aggregation to Cause Global Mitochondrial Imbalance in ALS", has been assigned the following manuscript number: **CELL-D-19-00535**. Your paper will now be assigned to a handling editor who will read it and discuss it with the rest of the editorial team to evaluate if it is a strong candidate for peer review.

Best,

Jennifer Estrompa
Journal Associate, Cell
50 Hampshire Street
Cambridge, MA 02139
cellms@cell.com

Sneak Peek 2.0: Now it's even easier to preview Cell Press papers under review

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Go on, satisfy your curiosity! Visit Sneak Peek.

From: Liang Chen
To: Fu, Xiang-Dong
Subject: Re: nature protocol ms status
Date: Wednesday, February 20, 2019 2:16:17 AM

Hi Fu,

Thank you for your reply and it is wonderful to know that it is all done!

Have a good trip back.

Best,

Liang

> On Feb 20, 2019, at 4:45 PM, Fu, Xiang-Dong <xdfu@ucsd.edu> wrote:
>
> I wrote to yhe editor a few days ago. She told me it was all done. They are checking with their art editor and we should receive their final notice soon.
>
> Fu
>
> 发自我的华为手机
>
> -------- 原始邮件 --------
> 主题:nature protocol ms status
> 发件人:Liang Chen
> 收件人:"Fu, Xiang-Dong"
> 抄送:
>
> Hi Fu,
>
> Sorry that I missed the lunch with you and Jing Hu last time, as I was in Xinjiang. Jing told me you will go back to SD today, safe fly.
>
> I checked the status for our nature protocol manuscript today and it is still under consideration. I wonder if we shall wait a little longer before contacting the editor?
>
> Thank you.
>
> Best,
>
> Liang

From: Fu, Xiang-Dong
To: Xiao Li; 周兵; 罗大极
Subject: Fwd: NP: NP-P180235B Request for manuscript Word document
Date: Tuesday, February 19, 2019 3:37:51 PM

Hi Xiao,

The GRIP-seq manuscript has been accepted in principle. The editor needs to make some editorial changes, but she could not find the word file of the text. Can you please send her the file?

Fu

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

Begin forwarded message:

From: <ivanka.kamenova@nature.com>
Subject: NP: NP-P180235B Request for manuscript Word document
Date: February 20, 2019 at 1:38:29 AM GMT+8
To: <xdfu@ucsd.edu>
Reply-To: <ivanka.kamenova@nature.com>

Dear Dr. Fu,

Apologies for not noticing this sooner, but it appears that your file is missing the Word document version of the manuscript. Would you be able to send this to me at ivanka.kamenova@nature.com so that I can edit the file using track changes? Thank you very much.

Best,
Ivanka

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Confidentiality Statement:

From: 罗大极
To: Fu, Xiang-Dong
Subject: Re: Fwd: NP-P180234D and NP-180235B
Date: Tuesday, February 19, 2019 1:54:38 AM

Dear Prof FU,

Thank you very much.

Happy Lantern Festival.

Sincerely,

Daji

Daji Luo, PhD.
Associate Professor
Department of Genetics, School of Basic Medical Sciences, Wuhan University
Address:No.185 Donghu Road, Wuchang distrcit, Wuhan, Hubei, PR China.
(Tel) +86 189 8628 1862
(Lab) +86 27 6875 9702

> -----Original Messages-----
> **From:**"Fu, Xiang-Dong" <xdfu@ucsd.edu>
> **Sent Time:**2019-02-19 17:23:34 (Tuesday)
> **To:** "罗大极" <luodaji@whu.edu.cn>
> **Cc:**
> **Subject:** Fwd: NP-P180234D and NP-180235B

From: Fu, Xiang-Dong
To: 罗大极
Subject: Fwd: NP-P180234D and NP-180235B
Date: Tuesday, February 19, 2019 1:23:36 AM

From: Ivanka Kamenova <ivanka.kamenova@nature.com>
Subject: RE: NP-P180234D and NP-180235B
Date: February 19, 2019 at 4:04:02 AM GMT+8
To: "Fu, Xiang-Dong" <xdfu@ucsd.edu>

Dear Fu,

I am very sorry for not updating you on the status of your manuscripts. I have sent R-ChIP (NP-P180234D) for figures to be checked by the art editors and should be able to accept the manuscript formally upon hearing back from the art editors – I would expect this to happen in the next few days. You will then receive further updates from our Production department regarding the next stage, i.e. getting proofs.

GRID-seq (NP-P180235B) came back from re-review recently and I am happy to say that all the reviewers were pleased with the changes. I will therefore send you the accepted-in-principle, edited version by the end of this week. Please let me know if you have any other questions.

All the best,
Ivanka

From: Fu, Xiang-Dong [mailto:xdfu@ucsd.edu]
Sent: 17 February 2019 00:27
To: Ivanka Kamenova; Nature Protocols, Info
Subject: NP-P180234D and NP-180235B

Dear Ivanka,

I send this email to find out the status of our manuscripts at Nature Protocols.

The first is on R-ChIP (NP-P180234D), which was accepted in principle from you last email and you have made extensive editorial changes. We have essentially followed all of your instructions to load this “final” manuscript. It has been 44 days since we loaded the file. I imagine that it should be ready to go to the printer at this point.

The second is on GRID-seq (NP-P180235B). This fully revised manuscript has been loaded 47 days ago. I thus wonder whether we are supposed to hear back from you.

I would be greatly appreciated if you could just drop a simple note on the status of

these manuscripts.

Thanks,

Fu

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

From: Fu, Xiang-Dong
To: xinxinzuo2012; Zhou Yu
Subject: Revised cover letter for TDP-43
Date: Sunday, February 17, 2019 11:07:31 PM
Attachments: Cover letter TDP43 story.doc
ATT00001.htm

Dear Xinxin and Zhou Yu,

Here is the revised cover letter. Xinxin highlights a phase with yellow, which reads fine to me. I still removed “sub” from subset because we refer to a specific set of microRNAs. When all data are generated, please go ahead submitting it.

From: Fu, Xiang-Dong
To: Zhou Yu; xinxinzuo2012; ZhouJie
Subject: draft cover letter
Date: Sunday, February 17, 2019 6:18:31 PM
Attachments: Cover letter for TDP43 storyi.doc
ATT00001.htm

Here is the draft cover letter. You may make additional modifications, as you see fit.

I may stop by Wuda tomorrow morning.

Fu

From: 罗大极
To: Fu, Xiang-Dong
Subject: About Nature Protocols submission NP-P180235A
Date: Wednesday, February 13, 2019 5:30:10 AM

Dear Prof Fu,

Happy New Year~

I feel sorry to trouble you. I am preparing for the NSFC project which the deadline is 10th Mar, 2019. This NP paper is one of the most important support material. Would you please tell me the desision of NP? or could do me a favor to help us to contact editor to inquire about the status of NP? Thank you very much.

Best wishes.

Daji

Daji Luo, PhD.
Associate Professor
Department of Genetics, School of Basic Medical Sciences, Wuhan University
Address:No.185 Donghu Road, Wuchang distrcit, Wuhan, Hubei, PR China.
(Tel) +86 189 8628 1862
(Lab) +86 27 6875 9702

From:	Fu, Xiang-Dong
To:	xinxinzuo2012; ZhouJie; Zhou Yu
Cc:	Liang Yi; Zhang Xiaorong
Subject:	Re: The updated figures
Date:	Tuesday, February 12, 2019 12:58:17 AM
Attachments:	TDP43 ms 2_12_2019.docx ATT00001.htm

Dear All,

This is the most updated manuscript on TDP-43. I have largely re-written the legends for both main and supplementary figures. I have also gone through the methods sections, which by way you guys did not great job!. We now need to do the following:

1. Create a Resources Table. You can find any cell paper as a guide. You can get specific from Chen Liang if you have questions.

2. Fill in all references. Note that there are a few I do not the sources. I listed others in red. If you are not clear, I will help out when we meet in person.

3. Xiaorong has a number of questions and comments, which he will send us. You may directly incorporate his comments into the text. If you are not clear, we can wait until we meet in person.

4. We need to remove current Fig. 5E, as the data is part of Fig. 6B. This will change the current Fig. 5F to 5E, and Fig. 5G to 5F.

5. It would be ideal to add wt TDP-43 to Fig. 6C.I know Xinxin is pushing to generating a few more data to improve one or two other figure panels.

6. Read through the text and fill in all missing information to your best ability.

Please let me know when I should come over to Wuda so that we can seat together to brush through the manuscript word by word and sentence by sentence. Liang Yi will also join us for this exercise. If all possible, let's try to submit it before I return to the US.

From:	Fu, Xiang-Dong
To:	xinxinzuo2012; ZhouJie; Zhou Yu; Liang Yi; Zhang Xiaorong
Subject:	ms update
Date:	Monday, February 11, 2019 1:06:47 AM
Attachments:	TDP43 ms 2_11_2019.docx ATT00001.htm

Hi all,

Here is the latest update of the TDP-43 manuscript in which I have largely completed the Discussion section. I have also made various minor changes in other parts.

I have received the Methods fro Xinxin, but have not yet been able to actively work on it. I suggest you take a close look at what I have done and I will work on the remaining parts tomorrow. We may meet to read through the manuscript in person Wednesday or Thursday if my father's condition permits me to come over to Wuda.

Xiaorong: Please read it and send your comments over via email.

From:	xinxinzuo2012
To:	Fu, Xiang-Dong
Cc:	Zhou Yu; undefined
Subject:	2019-02-11 TDP43 Methods
Date:	Sunday, February 10, 2019 10:25:56 PM
Attachments:	2019-02-11 Materials & Methods.docx

Dear Fu,

Here is the material & methods!

After proofreading with zhou jie, I will send you the updated figure and the figure legends later. And I have been in Wuda lab already, to complete the necessary data as soon as possible.

Xinxin

From: Yu Zhou
To: Fu, Xiang-Dong
Cc: xinxinzuo2012; zhoujie
Subject: Re: Re: another update on the TDP-43 ms
Date: Thursday, February 7, 2019 1:01:44 AM
Attachments: TDP43 ms 2_5_2019YZ.docx

Dear Fu,

Please find enclosed version with minor revisions on typos and mis-citations of figures. Thanks a lot to your reorganization which is clear and fluent.

Best regards,
Yu

-----Original Messages-----
From:"Fu, Xiang-Dong" <xdfu@ucsd.edu>
Sent Time:2019-02-05 15:20:36 (Tuesday)
To: xinxinzuo2012 <xinxinzuo2012@aliyun.com>, ZhouJie <1532459932@qq.com>, "Zhou Yu" <yu.zhou@whu.edu.cn>
Cc:
Subject: Re: another update on the TDP-43 ms

Dear all,

Here is a further update on the ms. In this version, I have largely finished the results section through re-arranging various figure panels. Specifically:

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S6D: Previous S8D
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Fu

Xiang-Dong Fu, Professor
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La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

> On Feb 4, 2019, at 2:38 PM, Yu Zhou <yu.zhou@whu.edu.cn> wrote:
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> Dear Fu,
> Thank you very much! Happy new year!
>
> Best,
> Yu
> **在** 2019-02-04 12:15:55,"Fu, Xiang-Dong" <xdfu@ucsd.edu> **写道**:
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From: ZhouJie
To: Fu, Xiang-Dong
Cc: 小欣翼翼; yu.zhou
Subject: 回复: another update on the TDP-43 ms
Date: Wednesday, February 6, 2019 3:33:55 AM
Attachments: tableS4.xlsx
tableS3.xlsx
tableS2.xlsx
tableS1.xlsx
method_of_data_analysis.docx
TDP43 ms_zhoujie_modifucation.docx

Dear Fu:
I attached Supplementary Tables and the method part of data analysis. And did some modifications and supplements to the ms.Hoping that will be useful.

zhoujie

---------- 原始邮件 ----------

发件人: "付老师"<xdfu@ucsd.edu>;
发送时间: 2019年2月5日(星期二) 下午3:20
收件人: "xinxinzuo2012"<xinxinzuo2012@aliyun.com>;"ZhouJie"<1532459932@qq.com>;"Zhou Yu"<yu.zhou@whu.edu.cn>;
主题: Re: another update on the TDP-43 ms

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S6E: Previous S8F
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> Yu
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From: xinxinzuo2012
To: Fu, Xiang-Dong; undefined; Zhou Yu
Subject: 回复:another update on the TDP-43 ms
Date: Tuesday, February 5, 2019 1:12:27 AM

Dear Fu,

Thank you very much for your effort and efficiency on updating this manuscript. I will update all the present figures according to this latest version and send the packaged figure to you as soon as I finished!

Wish you a Happy New Year and all the best.

Xinxin

> ---
> 发**件人**:Fu Xiang-Dong <xdfu@ucsd.edu>
> 发**送**时间:2019**年**2**月**5**日**(**星期二**) 15:20
> **收件人**:xinxinzuo2012 <xinxinzuo2012@aliyun.com>; undefined <1532459932@qq.com>; Zhou Yu <yu.zhou@whu.edu.cn>
> 主 题:Re: another update on the TDP-43 ms
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From:	Fu, Xiang-Dong
To:	xinxinzuo2012; ZhouJie; Zhou Yu
Subject:	Re: another update on the TDP-43 ms
Date:	Monday, February 4, 2019 11:20:40 PM
Attachments:	TDP43 ms 2_5_2019.docx ATT00001.htm

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From:	Yu Zhou
To:	Fu, Xiang-Dong
Cc:	xinxinzuo2012; ZhouJie
Subject:	Re:another update on the TDP-43 ms
Date:	Sunday, February 3, 2019 10:39:16 PM

Dear Fu,
Thank you very much! Happy new year!

Best,
Yu
在 2019-02-04 12:15:55,"Fu, Xiang-Dong" <xdfu@ucsd.edu> 写道:

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From:	ZhouJie
To:	Fu, Xiang-Dong; Zhou Yu; xinxinzuo2012
Subject:	Re: another update on the TDP-43 ms
Date:	Sunday, February 3, 2019 9:24:54 PM

Thank your for the update, I will read it carefully.Happy new year!

---Original---
From: "Fu, Xiang-Dong"<xdfu@ucsd.edu>
Date: Mon, Feb 4, 2019 12:18 PM
To"Zhou Yu"<yu.zhou@whu.edu.cn>;"xinxinzuo2012"<xinxinzuo2012@aliyun.com>;
Subject: another update on the TDP-43 ms

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From: "Fu, Xiang-Dong"<xdfu@ucsd.edu>
Date: Mon, Feb 4, 2019 12:18 PM
To: "ZhouJie"<1532459932@qq.com>;"Zhou Yu"<yu.zhou@whu.edu.cn>;"xinxinzuo2012"<xinxinzuo2012@aliyun.com>;
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From: xinxinzuo2012
To: Fu, Xiang-Dong; undefined; Zhou Yu
Subject: 回复:another update on the TDP-43 ms
Date: Sunday, February 3, 2019 8:47:26 PM

Got it! I will carefully read the manuscript and update the packaged figure at the same time!

Will you all a happy new year!

Xinxin

发件人:Fu Xiang-Dong <xdfu@ucsd.edu>
发送时间:2019年2月4日(星期一) 12:18
收件人:xinxinzuo2012 <xinxinzuo2012@aliyun.com>; undefined <1532459932@qq.com>; Zhou Yu <yu.zhou@whu.edu.cn>
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This morning, I have spent a serious of efforts in re-organizing the data corresponding to your previous Fig. 5 and 6. I essentially combined the two figures to convey the message that TDP-43 mutants and oxidative stress synergistically trap miRNAs. You should see the re-arranged figure panels by reading the largely written text. Specifically,

4A: Previous S6A (what is M3?)
4B: Previous S6C
4C: Previous 6A
4D: Previous 5A
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4F: Top panel: previous 5B; middle panel: previous 5C; bottom panel: Previous S5D (only the data on NG108-15 cells)
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4H: Previous 5D
4I: Previous 5G
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S4A: Previous S5B
S4B: Previous S5E
S4C: Previous 5E

Xiang-Dong Fu, Professor
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9500 Gilman Drive, Room 217
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Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

From: Fu, Xiang-Dong
To: xinxinzuo2012; ZhouJie; Zhou Yu
Subject: another update on the TDP-43 ms
Date: Sunday, February 3, 2019 8:16:17 PM
Attachments: TDP43 ms 2_4_2019.docx
ATT00001.htm

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From: Fu, Xiang-Dong
To: xinxinzuo2012; ZhouJie; Zhou Yu
Subject: ms update
Date: Saturday, February 2, 2019 12:16:55 AM
Attachments: TDP43 ms.docx
ATT00001.htm

Dear Xinxin, Zhou Jie, and Zhou Yu,

This is what I have gone through so far (till the end of Fig. 3). Xinxin sent me the modified figures, but the file is too big to transit through the slow internet in the local coffee shop. It would be more productive if Xinxin sends me your corrections,comments, and updated references on the parts I have gone through, which would allow me to polish what we have gone so far.

From: xinxinzuo2012
To: Fu, Xiang-Dong; undefined
Cc: Zhou Yu
Subject: 回复:progress in revising the TDP-43 ms
Date: Thursday, January 31, 2019 12:47:38 AM
Attachments: 2019-01-31 Packaged figures.zip
2019-01-31 Figure legends.docx

Dear Fu,

Welcome back to Wuhan!

I am really grateful for your effort and efficiency in pushing this project. And I will carefully read the revised essay you send us and communicate with you after that.

By the way, here are the newly updated figures and figure legends which may be helpful when you get to the results part. I made several modifications according to your comments in last letter, including the newly obtained “UG” motif of TDP43-enriched miRNAs from Zhou Jie. And we also unified all the histogram analysis as previously suggested by Zhou Yu.

These days I have been working on experiments related to “TDP43-aggregation” and “mitochondrial imbalance”, the preliminary results are listed:

a) To rule out the sediment mitochondria into the pellet, VDAC and COXIV were used as mitochondria marker protein which were not detect in pellet fraction. I added three other mitochondrial-encoded proteins (ND1, ND6 and ATP6) as negative control.

b) Besides LRPPRC, the recent western blot data show that Ndufa9 was also depleted form mitochondria under TDP43 aggregation. And I am working on probing more proteins especially those up-regulated ones.

c) To prove the co-aggregation between mito-proteins and TDP-43, I first purified the pellet and perform Co-IP with TDP43-specific antibody. WB show that mitochondria protein LRPPRC was associated with TDP43. And I planned to test more proteins with available antibodies.

All these results can be packaged as soon as I finished!

xinxin

发**件人**:Fu Xiang-Dong <xdfu@ucsd.edu>
发**送**时间:2019**年**1**月**31**日**(**星期四**) 12:06
收件人:xinxinzuo2012 <xinxinzuo2012@aliyun.com>; undefined <1532459932@qq.com>
抄 **送**:Zhou Yu <yu.zhou@whu.edu.cn>
主 题:progress in revising the TDP-43 ms

Dear Xinxin and Zhou Jie,

I arrived in Wuhan yesterday afternoon after spending 2 and half days in Beijing. As you know, I have started working on your TDP-43 manuscript. As I will spend most time in Wuhan, this is my main goal to push it as much as I can [redacted]

I have spent a lot of time in thinking and developing a strategy to convey our ideas and findings. Here is the update in which I have extensively revised the title, abstract, and introduction. As you can see, I have tried to enlarge the scope a bit to place our findings in the general framework of ALS etiology.

Once I get into the results section, my speed should be faster. I suggest you to take a look at what I have done so far and make notes on anything I have missed or potential mistakes I have introduced. Let me work on the results for one or two more days before we meet to discuss the manuscript. You may call me any time ([redacted]) if you wish to talk to me before we meet. If Zhou Jie needs to go home for the new year, please do so. We may communicate via phone, email, or WeChat.
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Email: xdfu@ucsd.edu

On Jan 29, 2019, at 6:09 PM, ZhouJie <1532459932@qq.com> wrote:

Dear Fu:

Zuo xinxin and me keep updating figures these days. I want to stay here to do anything that can push forward this work. But the Chinese new year is coming, [redacted]. So, may I ask about your arrangement, please?

Sorry for any incovenience that could cause.

Zhoujie

From: ZhouJie
To: Fu, Xiang-Dong; xinxinzuo2012
Cc: Zhou Yu
Subject: Re: progress in revising the TDP-43 ms
Date: Thursday, January 31, 2019 12:38:39 AM

Dear Fu:

Thank you for paying attention to this project, I will read the updated manuscript carefully. The analysis part has been done and Xinxin will send you the lastest updated figures soon. I have to go home for a few days and will come back to Wuhan as soon as possible. I have brought my computer with me so I can do something if necessary. I saved your phone number, we can communicate in any way.
Wish you a happy new year!

Zhou Jie
---Original---

From: "Fu, Xiang-Dong"<xdfu@ucsd.edu>
Date: Thu, Jan 31, 2019 12:06 PM
To: "ZhouJie"<1532459932@qq.com>;"xinxinzuo2012"<xinxinzuo2012@aliyun.com>;
Cc: "Zhou Yu"<yu.zhou@whu.edu.cn>;
Subject: progress in revising the TDP-43 ms

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To: xinxinzuo2012; ZhouJie
Cc: Zhou Yu
Subject: progress in revising the TDP-43 ms
Date: Wednesday, January 30, 2019 8:06:43 PM
Attachments: TDP43 ms.docx
ATT00001.htm

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From: Fu, Xiang-Dong
To: ZhouJie
Cc: Zhou Yu; 小欣翼翼
Subject: Re: 2019-01-18 newly updated figures
Date: Tuesday, January 22, 2019 8:42:41 AM

Dear Zhou Jie,

Thanks for your email. Below I address your questions.

> On Jan 22, 2019, at 5:53 AM, ZhouJie <1532459932@qq.com> wrote:
>
> Dear Fu,
> Maybe it will be helpful to add some informations about the motif issue and somes points you mentioned.
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I communicated with Xinxin last night about how to make a reasonable cut-off for motif analysis. In microarray analysis, you previously detected enriched UG motif. This is because microarray used Cy3-labeled input and Cy5-labeled IPed samples to cohybridize on the array. The readout will have IPed microRNAs normalized against input. In RNA-seq, you need to make similar normalization, as probably you did with input control. A simple cut-off is not ideal. In this case, you need to first rank order all detected microRNAs according to the enrichment ratio. Most likely you will a progressive increase in a linear fashion and then a sharp increase. This turning point would be your cut-off. However, I could be wrong, as there might not be such turning point. In your current Fig. 2A, you detected a large number of enriched microRNAs. How many of them? You may test several more stringent fold change cut-offs to see if you detect the expected motif. You may not want to see highly expressed microRNAs. I would imagine that the fold-enrichment is more important.

> I checked SOD1 and FUS in our seqenceing data, try to link SOD1 or FUS to our stroy. There are some informations:
> 1) SOD1 and FUS shows no significant change in RNA level or translation level when kd TDP43 or transfect CTF35.
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According to ALS pathology, there is little relationship between SOD, TLS and TDP-43. However, I think there are reports about TDP43 regulation of FUS expression, which would be consistent with your point 3. I will check it out and you may check the literature with Xinxin about this. If it is true, we should include the description in our paper.

zhoujie

---------- 原始邮件 ----------

发件人: "付老师"<xdfu@ucsd.edu>;
发送时间: 2019年1月22日(星期二) 中午11:16
收件人: "xinxinzuo2012"<xinxinzuo2012@aliyun.com>;
抄送: "Zhou Yu"<yu.zhou@whu.edu.cn>; "ZhouJie"<1532459932@qq.com>;
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I will need to pay attention to a number of pressing issues here before I fly back to China this coming Saturday. I will thus pause here a bit, although I will continue to think about the overall strategy to write this important paper.

Best regards,
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> On Jan 20, 2019, at 3:13 AM, xinxinzuo2012 <xinxinzuo2012@aliyun.com> wrote:
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发件人:Fu Xiang-Dong <xdfu@ucsd.edu>
发送时间:2019年1月20日(星期日) 02:52
收件人:xinxinzuo2012 <xinxinzuo2012@aliyun.com>; undefined <1532459932@qq.com>
抄 送:Zhou Yu <yu.zhou@whu.edu.cn>
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<xinxinzuo2012@aliyun.com> wrote:

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<2019-01-18 newly updated figures.zip>

<2019-01-20 TDP43-manuscript.docx>

<motifs.png><barplot.png>

From: ZhouJie
To: Fu, Xiang-Dong
Cc: yu.zhou; 小欣翼翼
Subject: 回复: 2019-01-18 newly updated figures
Date: Tuesday, January 22, 2019 5:53:32 AM
Attachments: motifs.png
barplot.png

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发送时间: 2019年1月22日(星期二) 中午11:16
收件人: "xinxinzuo2012"<xinxinzuo2012@aliyun.com>;
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发**送**时间:2019**年**1**月**20**日**(**星期日**) 02:52
收件人:xinxinzuo2012 <xinxinzuo2012@aliyun.com>; undefined <1532459932@qq.com>
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From:	Fu, Xiang-Dong
To:	xinxinzuo2012
Cc:	Zhou Yu; ZhouJie
Subject:	Re: 2019-01-18 newly updated figures
Date:	Monday, January 21, 2019 7:16:24 PM
Attachments:	Abstract for the TDP43 paper.docx ATT00001.htm

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7. Mitochondrial proteins and RBPs were co-aggregated in TDP-43-positive aggregates (mass spectrometric analysis)
8. Mitochondrial imbalance induced by TDP-43 proteinopathy (down-regulated by co-aggregated with TDP43 and up-regulated gene expression through miRNA sponge)

After reading the points your listed, I realized that I was limited to the data at hand. And it might be necessary to think further or develop a general mechanism (including FUS &SOD1) to make our story more profound. I need to read more relevant literature and also discuss with zhou Jie to make further supplements based

on the notes you send us.

xinxin

发件人:Fu Xiang-Dong <xdfu@ucsd.edu>
发送时间:2019年1月20日(星期日) 02:52
收件人:xinxinzuo2012 <xinxinzuo2012@aliyun.com>; undefined <1532459932@qq.com>
抄 送:Zhou Yu <yu.zhou@whu.edu.cn>
主 题:Re: 2019-01-18 newly updated figures

Dear Xinxin and Zhou Jie,

I have started to systematically read TDP-43 related papers in order to develop a good conceptual framework for describing your results. The following facts mayl be important for us to formulate our ideas:

1. Because ALS is linked to aggregate formation, which is accompanied by nuclear clearance, the main hypothesis for the diseases is the combinatory contribution of loss-of-function in the nucleus and gain-of-function in the cytoplasm. Because TDP-43 and FUS have roles in both transcription and RNA processing, deletion of either causes embryonic lethality, it is easy to imagine some contributions of their nuclear clearance to cell death in ALS, but the question is what type of gain-of-function by their cytoplasmic aggregates is relevant to the disease.

2. It has been reported that overexpression of wt SOD1 does not cause ALS, but overexpression of TDP-43 and FUS does. Given SOD1 has no role in the nucleus, it appears that cytoplasmic aggregation is a common feature among these disease genes. In addition, mutations in a number of genes involved in protein quality controls have been identified in ALS.

3. Variations in SOD1 enzymatic activity are not linked to ALS, but mutant SOD1 co-aggregates with endogenous wt SOD1. Importantly, mutant SOD1 causes mitochondrial dysfunction. I need to read more about whether and how mutations in TDP-43 and FUS cause abnormalities in the mitochondria.

4. ALS is associated with mutations in SOD1, TDP-43 and FUS, but each is linked to distinct pathologies. For example, in SOD1 mutant cells, there is no TDP-43 aggregates. Interestingly, however, TDP-43 aggregates have been detected in some AD, PD, and HD

patients, and some alpha-synuclein aggregates, which is the hallmark of PD, were detected in ALS.

5. Oxidative stress has been a popular idea when SOD1 was first linked to ALS. However, I have not heard much about such link to mutations in TDP-43 or FUS. Our data now suggest a comeback of oxidative stress as a key theme of ALS etiology and/or progression.

If possible, can you help extend this list of facts in case I have missed some important ones. Additionally, you may common on some of these points to indicate that how you think these are related to your story. It is time to do some major intellectual exercise to develop your paper.

Fu

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

On Jan 18, 2019, at 2:45 AM, xinxinzuo2012 <xinxinzuo2012@aliyun.com> wrote:

Dear Fu,

Here are the newly updated figures. We reorganized the data according to Zhou Yu's suggestion mainly in pages' layout, including image and words' size, unifying labeling and colors. And it does look better as well as more formal than before. I've saved these figures in JPG format which will be easier for you to download and read.

Looking forward to meeting you in Wuhan!

xinxin

<2019-01-18 newly updated figures.zip>

From: Fu, Xiang-Dong
To: xinxinzuo2012; ZhouJie
Cc: Zhou Yu
Subject: Re: 2019-01-18 newly updated figures
Date: Saturday, January 19, 2019 10:52:25 AM

Dear Xinxin and Zhou Jie,

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1. Because ALS is linked to aggregate formation, which is accompanied by nuclear clearance, the main hypothesis for the diseases is the combinatory contribution of loss-of-function in the nucleus and gain-of-function in the cytoplasm. Because TDP-43 and FUS have roles in both transcription and RNA processing, deletion of either causes embryonic lethality, it is easy to imagine some contributions of their nuclear clearance to cell death in ALS, but the question is what type of gain-of-function by their cytoplasmic aggregates is relevant to the disease.

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Looking forward to meeting you in Wuhan!

xinxin

<2019-01-18 newly updated figures.zip>

From:	Fu, Xiang-Dong
To:	liang_chen@whu.edu.cn; Zhou Yu
Subject:	This paper shows a negative role of DOT1 in gene expression
Date:	Wednesday, January 2, 2019 6:35:01 AM

Cecere, G., Hoersch, S., Jensen, M.B., Dixit, S., and **Grishok, A.** (2013) ZFP-1(AF10)/DOT-1 Complex Opposes H2B Ubiquitination to Reduce Pol II Transcription. *Mol Cell,* 50(6): 894-907.

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
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9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

From:	Kevin Murach
To:	XR Zhang
Cc:	Fu, Xiang-Dong; yu.zhou@whu.edu.cn
Subject:	Re: 2014 Cell Manuscript
Date:	Friday, August 28, 2020 8:42:50 AM

Hello,

Thank you so much for responding so quickly! I really appreciate it.

I do not see the miRACE results in the supplementary info. I only see the a portion of the CLIP-seq data:

https://www.cell.com/cms/10.1016/j.cell.2014.05.047/attachment/4fa54116-4277-4ca1-b911-0c0e8c5b4c5a/mmc1.pdf

I personally lack the expertise to analyze the GEO dataset, so I was hoping for an excel sheet, but I understand if that is not tenable.

Thank you in advance for your time. I do not mean to inconvenience you.

Be well and take care.

Regards,

Kevin

Kevin A. Murach, PhD
Postdoctoral Fellow
University of Kentucky College of Health Sciences
Charles T. Wethington, Jr. Building,
Room 401
Lexington, KY 40536-0200
Office: (859) 218-0872
Fax: (859) 257-2375
kmu236@g.uky.edu

> On Aug 28, 2020, at 11:33 AM, XR Zhang <xrzhang@ibp.ac.cn> wrote:
>
> Dear Kevin,
>
> You can access the CLIP-seq raw data from GEO datasets (GSE57596), the miRACE results was included in the supplementary information.
>
> Please feel free to get in touch if any additional information is needed.
>
> Best,

Xiaorong

From:	xinxinzuo2012
To:	Fu, Xiang-Dong
Cc:	Yu Zhou
Subject:	The update for ROS data
Date:	Monday, August 17, 2020 4:48:14 AM
Attachments:	ROS production.pptx

Dear Fu,

In our last discussion, you raised questions related to ROS data. In fact, the testing was a little unstable (Sometimes it even decreases compared to the negative control).

Therefore, we tried to modulate the cell to a better state to keep the background ROS level normal. The positive controls were added in each assay. Compared with the negative control, the ROS production was induced in either treatment. We also test additional candidate genes such as the components of mitochondria respiratory chain complex as suggested by Xiaorong. The related data is in the attachment.

Now I am working on the data packaging of Fig3 (Integrating the newly obtained miRNAs data with existing data of let-7/eIF4G2), and hope to send it for your perusal before this weekend.

Best wishes,

Xinxin

From: 肖锐
To: xdfu@ucsd.edu
Subject: Greetings from Rui
Date: Thursday, March 19, 2020 9:29:05 AM

Dear Prof. Fu,

It's quite encouraging that the COVID-19 epidemic will be put out soon in Wuhan, but the news, the COVID-19 cases in the US steeply increase to over 9000 today, just shocked me and I heard that the researchers in the UCSD were told to work from home a few days days ago. In this case, the epidemic situation in the US is awful now. I hope you and your family are fine, as well as all the colleagues in the lab. Please be careful and safe!

During the time sealed at home in Shashi, I read a lot of papers, seriously thought about how to organize the story on the molecular mechanism of RBM22 in 5q- syndrome as we talked about last time and listed out the figures and panels required in a logical way for the story, finding we still need several key experiments to do and elevate the conceptual points. My students are putting the figures in order now and we are looking forward discussing with you after the epidemic. Another interesting and promising project we are pursuing is to figure out the human recursive splicing profiling by developing a new technique since the global map of recursive splicing (RS) is inexplicit, and we have generated some preliminary data which can better reveal potential RS in comparison with rRNA-depleted RNA-seq. And we are working on global inspection of the sequencing data, what conclusions we can make, the structure of this story, how to illustrate our data, the conceptual points and biological/physiological functions of these events. Although the project is immature now, I think we are going to have a clue soon. Hope my students could make presentations on these two stories when we meet next time. Wish you can visit my lab by then and my students will definitely get very excited and encouraged. :)

And congratulations to you again for the great paper just published in Cell. It's undoubtedly a fundamental and textbook discovery.

Best,
Rui

From:	Yu Zhou
To:	alan.herbert@insideoutbio.com
Cc:	Fu, Xiang-Dong; Li Jiang; Shao, Changwei
Subject:	Re: Data from your NEAT1 paper
Date:	Friday, February 14, 2020 9:43:49 PM
Attachments:	1mirfc_group3.xlsx 2mir_clipbound.xlsx

Dear Alan,

Thanks a lot for your interests in our work! The data you requested are provided in the two Excel files.

Please let us know if you have further questions.

Best regards,
Yu

Yu Zhou, Ph.D.
Principal Investigator
College of Life Sciences, Room 6109
Wuhan University, China

> 在 2020年2月15日,上午2:42,Shao, Changwei <c8shao@health.ucsd.edu> 写道:
>
> Hi all,
>
> I have no these data in my hand, Do we have these data for sharing?
>
> Thanks.
>
> Best,
> Changwei
>
> > Begin forwarded message:
> >
> > **From:** "Fu, Xiang-Dong" <xdfu@health.ucsd.edu>
> > **Subject: Fwd: Data from your NEAT1 paper**
> > **Date:** February 14, 2020 at 09:55:54 PST
> > **To:** "Shao, Changwei" <c8shao@ucsd.edu>
> >
> > Do we have such information to provide?
> >
> > Xiang-Dong Fu,

Distinguished Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

Begin forwarded message:

From: Alan Herbert <alan.herbert@insideoutbio.com>
Subject: Data from your NEAT1 paper
Date: February 14, 2020 at 9:39:06 AM PST
To: xdfu@ucsd.edu

Hi Dr. Fu,

I found your recent paper "NEAT1 scaffolds RNA binding proteins and the microprocessor to globally enhance pri-miRNA processing." of great interest. Great work!

I was wondering whether you could provide some additional data that is mentioned in the paper but is not in the supplementary data files. I was interested in more information on the names of the miRNAs you mention in these two statements"

"64–80% of a total of 532 expressed miRNAs with a read number >30 in control siRNA-treated HeLa cells were down regulated upon knockdown of NONO, PSF, and NEAT1 (both V1 and V2)"

and

"we found that both NONO and PSF bound 263 transcribed pri-miRNAs"

Do you have an Excel file with the data that you can send me?

The request is not related to anything that InsideOutBio is doing (we work on complement in cold tumors) but is more of an academic nature.

Thanks,

Alan

Alan Herbert
President and Founder
InsideOutBio.com
Charlestown, MA 02129
617.584.0360
https://www.linkedin.com/in/dralanherbert/

From: miguel
To: Fu, Xiang-Dong
Cc: 陈亮
Subject: Re: Re: Mail from miguel
Date: Friday, November 8, 2019 8:26:08 PM

Many thanks, Fu!

> -----Original Messages-----
> **From:**"Fu, Xiang-Dong" <xdfu@health.ucsd.edu>
> **Sent Time:**2019-11-09 06:20:06 (Saturday)
> **To:** miguel <miguel@gibh.ac.cn>, "陈亮" <00031945@whu.edu.cn>
> **Cc:**
> **Subject:** Re: Mail from miguel
>
> Dear Miguel and Liang,
>
> I have been tied up badly, and as a result, I was able to glance your manuscript during my flight to Beijing yesterday and continued this morning because of a degree of jetleg.
>
> I made some editions and comments along the way. I am unclear about your logic for focusing on BRD4 and CDK9, as your result of screen showed many with similar differential effects in 2i versus 2L conditions. One way to improve the logic and the overall quality of the paper is to perform RNA-seq under each kd condition and perform t-SNE to deduce regulatory networks. This may allow you to deduce transcription responses controlled by a set of TFs and chromatin remodelers that are similar to those induced by BRD4 and CDK9.
>
> I realize that you may want to get out this paper, rather than further extending it. In any case, hope my comments are useful.
>
> Good luck with the submission,
> Fu
>
> Xiang-Dong Fu, Professor
> Dept. of Cellular and Molecular Medicine
> University of California, San Diego
> George Palade Laboratories
> 9500 Gilman Drive, Room 217
> La Jolla, CA 92093-0651
>
> Phone: 858-534-4937
> Fax: 858-822-6692
> Email: xdfu@ucsd.edu

On Nov 6, 2019, at 2:15 AM, miguel <miguel@gibh.ac.cn> wrote:

Dear Fu,

It would be great if you could check our paper, it is a nice (or so we think) but complex story and your comments would help us make sure we don't make any mistake interlacing concepts.

All the best,
Miguel

-----Original Messages-----
From:"陈亮" <00031945@whu.edu.cn>
Sent Time:2019-11-06 02:00:35 (Wednesday)
To: "Xiang-Dong Fu" <xdfu@ucsd.edu>
Cc: miguel <miguel@gibh.ac.cn>
Subject: Fwd: Mail from miguel

Hi Fu,

Hope everything goes well.

As you may know, we recently helped Dr. Miguel Esteban with several GRO-seq experiments for his ES cell maintenance study, which found that b-catenin is critical to maintain mouse ES cell identity in 2i condition by promoting transcription initiation. Now a manuscript “beta-catenin safeguards ground state pluripotency by reinforcing the transcriptional apparatus” is prepared for submission to Science Advances and I am a co-author.

Before submission, we wonder if you have time to briefly go through the manuscript and give us a few comments to improve the manuscript? Any suggests will be greatly appreciated.

Thank you very much for your consideration!

Best,

Liang

Begin forwarded message:

From: miguel <miguel@gibh.ac.cn>
Subject: Mail from miguel <miguel@gibh.ac.cn>.
Date: November 5, 2019 at 2:37:44 PM GMT+8
To: liang_chen@whu.edu.cn

Please see attached.

From: 陈亮
To: Fu, Xiang-Dong
Cc: miguel
Subject: Fwd: Mail from miguel
Date: Tuesday, November 5, 2019 10:08:43 AM
Attachments: FIGURE LEGENDS_draft.docx
Main and Sup Figures.pdf
BRD4 SAdvances_draft.docx

Hi Fu,

Hope everything goes well.

As you may know, we recently helped Dr. Miguel Esteban with several GRO-seq experiments for his ES cell maintenance study, which found that b-catenin is critical to maintain mouse ES cell identity in 2i condition by promoting transcription initiation. Now a manuscript “beta-catenin safeguards ground state pluripotency by reinforcing the transcriptional apparatus” is prepared for submission to Science Advances and I am a co-author.

Before submission, we wonder if you have time to briefly go through the manuscript and give us a few comments to improve the manuscript? Any suggests will be greatly appreciated.

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Liang

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> **Subject: Mail from miguel <miguel@gibh.ac.cn>.**
> **Date:** November 5, 2019 at 2:37:44 PM GMT+8
> **To:** liang_chen@whu.edu.cn
>
> Please see attached.

From: Yu Zhou
To: Fu, Xiang-Dong
Subject: APA talk slides
Date: Monday, October 28, 2019 8:29:32 AM
Attachments: 201809APAtalk.pdf

From: Yongzhen Xu
To: Fu, Xiang-Dong
Cc: yongzhen.xu@whu.edu.cn
Subject: Follow-up: Invitation to Review for Science Bulletin
Date: Saturday, October 12, 2019 2:40:01 PM

13-Oct-2019

Dear Prof. Fu:

Thank you for replying to my invitation to review for Science Bulletin.

It is unfortunate that you are unable to review this manuscript at this time. Looking forward to your next attribution when future manuscripts come in that fall under your area of expertise.

Sincerely,
Dr. Yongzhen Xu
Science Bulletin Associate Editor
yongzhen.xu@whu.edu.cn

From: 肖锐
To: Fu, Xiang-Dong
Subject: Re: Re: Could help me to take a look at our paper and give a leture when you visit Wuhan?
Date: Monday, September 30, 2019 6:57:41 PM

Dear Prof. Fu,

We very appreciate your quick reponse. It's enough to get your input on the title and abstract and I will take care of the manuscript.

And congratulate you to be Distinguished Professor! Awesome!

Thanks,

Rui

> -----原始邮件-----
> 发件人:"Fu, Xiang-Dong" <xdfu@ucsd.edu>
> 发送时间:2019-10-01 09:30:55 (星期二)
> 收件人: "肖锐" <xiaorui9@whu.edu.cn>
> 抄送:
> 主题: Re: Could help me to take a look at our paper and give a leture when you visit Wuhan?
>
> Dear Xiao Rui,
>
> I really do not have time to seriously edit the manuscript before my trip to China next week. I have mountains of things to take care before the trip. I have thus focused on modifying the title and abstract for your consideration, as in the attached file.
>
> Good luck and best wishes.
>
> Fu
>
> Xiang-Dong Fu,
> Distinguished Professor
> Dept. of Cellular and Molecular Medicine
> University of California, San Diego
> George Palade Laboratories
> 9500 Gilman Drive, Room 217
> La Jolla, CA 92093-0651
>
> Phone: 858-534-4937
> Email: xdfu@ucsd.edu
>
> > On Sep 29, 2019, at 7:42 PM, 肖锐 <xiaorui9@whu.edu.cn> wrote:

>
> Dear Prof. Fu,
>
> Do you have time to take a look at a revised paper at Nature Communication which I participated? The paper is entitled "Igf2bp3 maintains maternal RNA stability at pre-MZT and enables early embryo development" and we are going to resubmit it before the deadline for revision (10/4). The comments of the Reviewers are positive, but we still need your input on the rebuttal letter which I drafted and the revised manuscript before resubmission.
>
> I want to invite you to give a leture in our institute as I mentioned in my last email. Do you have time when we you visit Wuhan this time? It's also OK at your next visit and we are flexible.
>
> Thank you and have a great day!
> Rui <Figure+supp Fig-MJ.pdf><manuscript-revised-MJ.docx><Rebuttal letter-MJ.docx>

From:	Fu, Xiang-Dong
To:	肖锐
Subject:	Re: Could help me to take a look at our paper and give a leture when you visit Wuhan?
Date:	Monday, September 30, 2019 6:43:24 PM
Attachments:	manuscript-revised-MJ.docx ATT00001.txt

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Good luck and best wishes.

From:	肖锐
To:	Fu, Xiang-Dong
Subject:	Could help me to take a look at our paper and give a leture when you visit Wuhan?
Date:	Sunday, September 29, 2019 7:50:55 PM
Attachments:	Figure+supp Fig-MJ.pdf manuscript-revised-MJ.docx Rebuttal letter-MJ.docx

---

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I want to invite you to give a leture in our institute as I mentioned in my last email. Do you have time when we you visit Wuhan this time? It's also OK at your next visit and we are flexible.

Thank you and have a great day!
Rui

From: yongzhen.xu@whu.edu.cn
To: Fu, Xiang-Dong
Subject: Re: Re: Liang"s manuscript
Date: Wednesday, September 25, 2019 4:42:01 PM

Thank you very much.

See you on October. Charles will be Wuhan in the last two weeks on October (not 100% sure, he just sent visa application yesterday).
Best regards,

Yongzhen

> -----Original Messages-----
> **From:**"Fu, Xiang-Dong" <xdfu@ucsd.edu>
> **Sent Time:**2019-09-26 00:00:13 (Thursday)
> **To:** "yongzhen.xu@whu.edu.cn" <yongzhen.xu@whu.edu.cn>
> **Cc:**
> **Subject:** Re: Liang's manuscript
>
> Hi Yongzhen,
>
> I do not have time to carefully go through the entire manuscript. I have thus paid specially attention to your title and abstract to make sure that they are appealing to editor, reviewers, and general audience.
>
> I thought your title is a bit too long. Why not just emphasize the role of minor spliceosome to SMA?
>
> Defective Minor Spliceosome Induces Spinal Muscular Atrophy in Drosophila
>
> I have also further polished your abstract:
>
> Minor (U12-type) spliceosome is evolutionarily conserved, but its biological significance remains poorly understood. Here, by CRISPR/Cas9-mediated disruption of the minor spliceosome, we report that defective minor spliceosome is responsible for spinal muscular atrophy (SMA) in *Drosophila*. Using a newly developed bioinformatic approach, we identify a large set of minor spliceosome-sensitive splicing events and demonstrate that three evolutionarily conserved minor intron-containing neural genes directly contribute to disease development as evidenced by the ability of their cDNAs to rescue the SMA phenotypes. Interestingly, many individual splice sites are recognizable by both minor and major

spliceosomes, but only compatible splice sites simultaneously targeted by either the minor or major spliceosome can lead to productive splicing. This mechanism suggests a new mode of splicing regulation through non-productive competition between minor and major spliceosomes. These findings reveal a vital contribution of minor spliceosome to SMA and to regulated splicing in animals.

Please note that I added “evoluationarily conserved”, but please make sure this is the case by confirming that the 3 genes contain minor introns in their animal counterparts. If not, you have carefully reword the general message. Hope these are helpful.

FU

Xiang-Dong Fu,
Distinguished Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@ucsd.edu

> On Sep 25, 2019, at 1:42 AM, yongzhen.xu@whu.edu.cn wrote:
>
> Hi, Prof. Fu,
> Could you give us more comments and suggestions?
> We plan to submit to Mol Cell before the Chinese National Holiday, what do you think?
> Best,
> Yongzhen
> BTW, below is the last email I sent to you.
>
> -----Original Messages-----
> From: yongzhen.xu@whu.edu.cn
> Sent Time: 2019-09-21 11:32:47 (Saturday)
> To: xdfu@ucsd.edu
> Cc:
> Subject: Liang's manuscript
>
> Hi, Prof. Fu,

According to your comments and discussions, I modified our manuscript as in the attached text and figure files.
1) Title: I changed, but feel not good and too long;
2) Abstract: I modified some places based on your suggested alternative abstract;
3) Introdcution: I switched the order, move introduction of SMA to after minor splicing;
4) Results: modified and added new about the competition
5) Discussion: A new figure (fig. 7) was made to show our competition model

Answers to your questions and comments, and new writings are shown in the "modification mode". To keep clarity, small changes what I made are accepted .

Thanks a lot.

Yongzhen <Li et al 2019-09-21.docx><all figures 2019-09-20.pdf>

From: Fu, Xiang-Dong
To: yongzhen.xu@whu.edu.cn
Subject: Re: Liang"s manuscript
Date: Wednesday, September 25, 2019 9:00:14 AM

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FU

Xiang-Dong Fu,
Distinguished Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@ucsd.edu

> On Sep 25, 2019, at 1:42 AM, yongzhen.xu@whu.edu.cn wrote:
>
> Hi, Prof. Fu,
> Could you give us more comments and suggestions?
> We plan to submit to Mol Cell before the Chinese National Holiday, what do you think?
> Best,
> Yongzhen
> BTW, below is the last email I sent to you.
>
> -----Original Messages-----
> From: yongzhen.xu@whu.edu.cn
> Sent Time: 2019-09-21 11:32:47 (Saturday)
> To: xdfu@ucsd.edu
> Cc:
> Subject: Liang's manuscript
>
> Hi, Prof. Fu,
>
> According to your comments and discussions, I modified our manuscript as in the attached text and figure files.
> 1) Title: I changed, but feel not good and too long;
> 2) Abstract: I modified some places based on your suggested alternative abstract;
> 3) Introdcution: I switched the order, move introduction of SMA to after minor splicing;
> 4) Results: modified and added new about the competition
> 5) Discussion: A new figure (fig. 7) was made to show our competition model
>
> Answers to your questions and comments, and new writings are shown in the "modification mode". To keep clarity, small changes what I made are accepted .
>
> Thanks a lot.
>
> Yongzhen <Li et al 2019-09-21.docx><all figures 2019-09-20.pdf>

From:	yongzhen.xu@whu.edu.cn
To:	Fu, Xiang-Dong
Subject:	Fw: Liang"s manuscript
Date:	Wednesday, September 25, 2019 1:50:22 AM
Attachments:	Li et al 2019-09-21.docx all figures 2019-09-20.pdf

---

Hi, Prof. Fu,
Could you give us more comments and suggestions?
We plan to submit to Mol Cell before the Chinese National Holiday, what do you think?
Best,
Yongzhen
BTW, below is the last email I sent to you.

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1) Title: I changed, but feel not good and too long;
2) Abstract: I modified some places based on your suggested alternative abstract;
3) Introdcution: I switched the order, move introduction of SMA to after minor splicing;
4) Results: modified and added new about the competition
5) Discussion: A new figure (fig. 7) was made to show our competition model

Answers to your questions and comments, and new writings are shown in the "modification mode". To keep clarity, small changes what I made are accepted .

Thanks a lot.

Yongzhen

From: yongzhen.xu@whu.edu.cn
To: Fu, Xiang-Dong
Subject: Re: Re: our manuscript of SMA and minor splicing
Date: Wednesday, September 18, 2019 5:10:04 PM

Hi,Prof. Fu,

I noticed that about half of the classical U12-type introns are partially spliced in L3 larvae of *U12*$^{\Delta/\Delta}$ and *U6atac*$^{\Delta/\Delta}$ strains, which I thought this could be due to remaining of maternal minor spliceosome, because the two homozygous strains are lethal, they were obtained by cross of their heterozygous. However, I doubt the maternal could last into L3 larvae stage (compare to the major spliceosome, level of the minor spliceosome is very low), at the same time, splicing of the other half of U12-type introns are fully inhibited.

I think it is possible that both of intron splice sites of some minor introns (not all) can be recognized by the major spliceosome, but so far I don't know how prove this. In this manuscript, we find single splice site that could be recognized by both spliceosomes are due to the advantage of splice site Unused index analyses.I was thinking about CLIP assays, but hard to imagine it will work.

In the discussion, I will add possible explantations, but so far need to think more.

Best,

Yongzhen

> -----Original Messages-----
> **From:**"Fu, Xiang-Dong" <xdfu@ucsd.edu>
> **Sent Time:**2019-09-18 23:41:07 (Wednesday)
> **To:** "yongzhen.xu@whu.edu.cn" <yongzhen.xu@whu.edu.cn>
> **Cc:**
> **Subject:** Re: our manuscript of SMA and minor splicing
>
> Hi Yongzhen,
>
> I am still puzzled by partial minor intron splicing even in cells which the minor spliceosome is inactivated. Do you feel it is possible that both intron splice sites can be recognized by the major spliceosome? In some cases, one minor splice site is recognized by the major spliceosome, which is paired with an alternative major site. This is a new mechanism for alternative splicing. However, it is difficult to imagine all minor sites have similar behavior. You will need to come up with good explanation for these questions.
>
> Fu
>
> Xiang-Dong Fu,
> Distinguished Professor
> Dept. of Cellular and Molecular Medicine
> University of California, San Diego
> George Palade Laboratories
> 9500 Gilman Drive, Room 217

La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@ucsd.edu

On Sep 17, 2019, at 4:55 PM, yongzhen.xu@whu.edu.cn wrote:

Hi,Prof. Fu,

Thank you very much for quick response and very helpful modifications,comments and editions.

The alternative abstract is much better than mine, I will think about your new directions and adjust our manuscript.
See you on October.

Best regards,

Yongzhen

-----Original Messages-----
From:"Fu, Xiang-Dong" <xdfu@ucsd.edu>
Sent Time:2019-09-18 01:25:33 (Wednesday)
To: "yongzhen.xu@whu.edu.cn" <yongzhen.xu@whu.edu.cn>
Cc:
Subject: Re: our manuscript of SMA and minor splicing

Hi Yongzhen,

I have quickly gone through your ms, which is very interesting. However, I believe that you can make story sound more interesting. I have suggested an alternative abstract for your consideration. I have also made various comments and editions in the text. If you agree with my strategy to emphasize the significance of your findings from a slightly different angle, you may further modify your text and title to follow the logic in the abstract.

I will come to Wuhan between Oct. 15-18 and hope to catch you up.

Best wishes,

Fu

Xiang-Dong Fu,
Distinguished Professor
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University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@ucsd.edu

> On Sep 16, 2019, at 12:02 AM, yongzhen.xu@whu.edu.cn wrote:
>
> Hi, Prof. Fu,
>
> How are you?
>
> Finally, we finished the manuscript about SMA and minor splicing in Drosophila. I am wondering whether you have time to read it and give us comments and modifications.
>
> Attaches include a Word text file and a PDF figure file. So far, I am not sure which journal we will submit.
>
> Many thanks!
>
> Best regards,
>
> Yongzhen<all figures 2019-09-16.pdf><Li et al 2019-09-16.docx>

From:	Fu, Xiang-Dong
To:	yongzhen.xu@whu.edu.cn
Subject:	Re: our manuscript of SMA and minor splicing
Date:	Tuesday, September 17, 2019 10:25:34 AM
Attachments:	Li et al 2019-09-16.docx ATT00001.txt

Hi Yongzhen,

I have quickly gone through your ms, which is very interesting. However, I believe that you can make story sound more interesting. I have suggested an alternative abstract for your consideration. I have also made various comments and editions in the text. If you agree with my strategy to emphasize the significance of your findings from a slightly different angle, you may further modify your text and title to follow the logic in the abstract.

From: yongzhen.xu@whu.edu.cn
To: Fu, Xiang-Dong
Subject: our manuscript of SMA and minor splicing
Date: Monday, September 16, 2019 12:07:22 AM
Attachments: all figures 2019-09-16.pdf
Li et al 2019-09-16.docx

Hi, Prof. Fu,

How are you?

Finally, we finished the manuscript about SMA and minor splicing in Drosophila. I am wondering whether you have time to read it and give us comments and modifications.

Attaches include a Word text file and a PDF figure file. So far, I am not sure which journal we will submit.

Many thanks!

Best regards,

Yongzhen

From: Vartak, Supriya (NIH/NIAMS) [F]
To: 肖锐
Cc: Chen, Jiayu; Fu, Xiang-Dong
Subject: Re: Fwd: TAF15 antibody - how much to use
Date: Friday, September 13, 2019 6:34:24 AM

Thank you, Rui.
A single vial of the catalogue number that I mentioned has a concentration of 0.074 mg/ml (100 ul). Not sufficient for even one ChIP-seq!
Do you use some other vial type (concentrated) or just buy several vials of the same catalogue?
Thank you so much for your time.
Best,
Supriya

From: 肖锐 <xiaorui9@whu.edu.cn>
Sent: Friday, September 13, 2019 8:02 AM
To: Vartak, Supriya (NIH/NIAMS) [F] <supriya.vartak@nih.gov>
Cc: chen, jiayu <jic386@ucsd.edu>; xdfu@ucsd.edu <xdfu@ucsd.edu>
Subject: Re: Fwd: TAF15 antibody - how much to use

Dear Supriya,
Thank you for your attention to our work!
8-10 ug of anti-TAF15 is sufficient to perform one ChIP-seq.

Best,
Rui

Rui Xiao, Professor
Medical Research Institute
Wuhan University
115 Donghu Road
Wuhan 430071, Hubei, China

Email: xiaorui9@whu.edu.cn

> -----原始邮件-----
> 发件人:"Fu, Xiang-Dong" <xdfu@ucsd.edu>
> 发送时间:2019-09-13 05:36:39 (星期五)
> 收件人: "Chen, Jiayu" <jic386@ucsd.edu>, "肖锐" <xiaorui9@whu.edu.cn>
> 抄送:
> 主题: Fwd: TAF15 antibody - how much to use
>
> Can one of you address this question?

Fu

Xiang-Dong Fu,
Distinguished Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@ucsd.edu

Begin forwarded message:

From: "Vartak, Supriya (NIH/NIAMS) [F]" <supriya.vartak@nih.gov>
Subject: TAF15 antibody - how much to use
Date: September 12, 2019 at 2:04:35 PM PDT
To: "xdfu@ucsd.edu" <xdfu@ucsd.edu>

Dear Xiang-Dong,
I am a post doc with Rafael Casellas at NIH.
I am writing to enquire about the TAF15 antibody you guys used for ChIp-seq in your recent paper.
I got the same catalogue antibody (ab134916) for TAF15 - how much antibody (ug) did you guys use?
Thank you so much.
Best,
Supriya

From: Hao, Yajing
To: yu.zhou@whu.edu.cn
Cc: Fu, Xiang-Dong; Shao, Changwei
Subject: Re: Question about the splicing screen data
Date: Thursday, August 15, 2019 4:55:59 PM

Hi, Yu!

I still have some question about the second run (plate58 to plate69).

So can we schedule a meeting at your convenience through we-chat?

Bests!

Yajing

> On Aug 15, 2019, at 4:11 PM, yu.zhou@whu.edu.cn wrote:
>
> <raslgkd-YuZhou.pdf>

From:	yu.zhou@whu.edu.cn
To:	Hao, Yajing
Cc:	Fu, Xiang-Dong; Shao, Changwei
Subject:	Re: Question about the splicing screen data
Date:	Thursday, August 15, 2019 4:18:54 PM
Attachments:	RASL20131006featureData.txt raslgkd-YuZhou.pdf

Hi Yajing,

Please find one of my progress reports in Fu Lab about analyzing genome-wide RNAi screening data. I think the slides and the .txt data file will solve your problems. If anything is not clear, we can arrange further discussions.

Best,
Yu

> **在** 2019**年**8**月**14**日**,**上午**11:12,Yu Zhou <yu.zhou@whu.edu.cn> **写道**:
>
> Hi Yajing, I will send you the information within two days.
> Best,
> Yu
>
>> **在** 2019**年**8**月**13**日**,**上午**9:03,Hao, Yajing <yahao@ucsd.edu> **写道**:
>>
>> Hi, Yu Zhou!
>>
>> I still have some questions about the splicing data. Please find the attached file.
>>
>> Thanks very much!
>>
>> Bests!
>>
>> Yajing
>>
>>
>> <Question about splicing data.docx>
>

From: Yu Zhou
To: Hao, Yajing
Cc: Fu, Xiang-Dong; Shao, Changwei
Subject: Re: Question about the splicing screen data
Date: Tuesday, August 13, 2019 8:13:07 PM

Hi Yajing, I will send you the information within two days.
Best,
Yu

> 在 2019年8月13日,上午9:03,Hao, Yajing <yahao@ucsd.edu> 写道:
>
> Hi, Yu Zhou!
>
> I still have some questions about the splicing data. Please find the attached file.
>
> Thanks very much!
>
> Bests!
>
> Yajing
>
>
> <Question about splicing data.docx>

From: Hao, Yajing
To: yu.zhou@whu.edu.cn
Cc: Fu, Xiang-Dong; Shao, Changwei
Subject: Question about the splicing screen data
Date: Monday, August 12, 2019 6:03:05 PM
Attachments: Question about splicing data.docx

Hi, Yu Zhou!

I still have some questions about the splicing data. Please find the attached file.

Thanks very much!

Bests!

Yajing

From: Xiao-Fan Wang, Ph.D.
To: Fu, Xiang-Dong
Subject: Re: help
Date: Tuesday, July 23, 2019 8:03:07 PM

Thank you so much!

[redacted]. Best regards, XF

> On Jul 23, 2019, at 3:10 PM, Fu, Xiang-Dong <xdfu@ucsd.edu> wrote:
>
> Hi Xiaofan,
>
> [redacted]
>
> I took a look at the dispute. In my view, there is no serious problem with the published work. Gene promoters are defined as sequences from ~1.5kb upstream to ~0.5kb downstream of transcription start sites (TTSs). Many key promoter elements in fact reside downstream of TTSs. Therefore, meta gene alignment showing a peak that is slightly downstream of TSSs is no surprising. Many RNA binding proteins we have profiled on chromatin show such distribution.
>
> That said, the complainer pointed out a few loci where the signals appear similar to background. This is a common problem in genomic profiling experiments, as promoter proximal regions are often associated with open chromatin, which is much easy to be disrupted during sonication. As a result, some promoters show peak, even without antibody enrichment. Thus, it is important to have total input control from the same material used for ChIP-seq and identified peaks have to be analyzed against control. I am not sure whether the authors have done that. The meta gene analysis should show both input and antibody-enriched signals to be convincing for such general trend.
>
> Hope this helps.
>
> Fu
>
> Xiang-Dong Fu,
> Distinguished Professor
> Dept. of Cellular and Molecular Medicine
> University of California, San Diego
> George Palade Laboratories
> 9500 Gilman Drive, Room 217
> La Jolla, CA 92093-0651
>
> Phone: 858-534-4937
> Email: xdfu@ucsd.edu
>
> > On Jul 19, 2019, at 11:55 AM, Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu> wrote:

Hi XD:

We received this complaint on a paper that was published back in 2016: http://www.jbc.org/content/291/49/25553. Unfortunately, I do not have the expertise to analyze the complaint even though I was the Editor who handled its review. It's about some ChIP-Seq data in this paper. The images are fine based on our internal analysis, so can you tell me if the complaint is valid?

Thanks, XF

<Pan-ppr.pdf>

From:	Xiao-Fan Wang, Ph.D.
To:	Fu, Xiang-Dong
Subject:	help
Date:	Friday, July 19, 2019 11:55:37 AM
Attachments:	Pan-ppr.pdf

Hi XD:

We received this complaint on a paper that was published back in 2016: http://www.jbc.org/content/291/49/25553. Unfortunately, I do not have the expertise to analyze the complaint even though I was the Editor who handled its review. It's about some ChIP-Seq data in this paper. The images are fine based on our internal analysis, so can you tell me if the complaint is valid?

Thanks, XF

From: Fu, Xiang-Dong
To: Huang, Gang
Cc: liang_chen@whu.edu.cn
Subject: Re: Request for RNASEH1 and R-loop reporter plasmids
Date: Wednesday, July 10, 2019 2:58:25 PM

You can obtain the plasmids from Addgene and R-loop reporters from my former postdoc Liang Chen, as he has taken the reagents to his own lab at Wuhan University.

Fu

Xiang-Dong Fu,
Distinguished Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@ucsd.edu

> On Jul 10, 2019, at 2:53 PM, Huang, Gang <Gang.Huang@cchmc.org> wrote:
>
> Dear Dr. Fu,
>
> Hope all well!
>
> This is Gang Huang, a PI at Cincinnati Children's Hospital Medical Center, writing to request for RNASEH1 and R-loop reporter plasmids. I met you when you visited here 2 yr ago. Inspired by your excellent work on R-loops biology, we started to explore the R-loop issue in SETD2-mutated cells. Would you please share some of your valuable plasmids listed below for our study?
>
> (1) three ppyCAG-based RNASEH1 expression plasmids with V5 tag, containing human WT, D210N-mutant, and WKKD-mutant RNASEH1;
>
> (2) four pcDNA5-based R-loop reporter plasmids, containing WT hepatitis d ribozyme, mutant ribozyme without any R-loop-promoting sequence, mutant ribozyme with a G-rich R-loop-promoting sequence, and mutant ribozyme with a R-loop-promoting sequence from CPSF7.
>
> Please find my address and FedEx account information below my signature.
>
> Best regards,
>
> Gang Huang, PhD

Phone: (513) 636-3214
FedEx delivery address:
Gang Huang, PhD
Room S7.224
Cincinnati Children's Hospital Medical Center
240 Albert Sabin Way
Cincinnati, OH 45229
FedEx account # 743203844
(Internal billing # F30210)

From:	Fu, Xiang-Dong
To:	xinxinzuo2012
Cc:	Zhou Yu
Subject:	Fwd: TDP-43
Date:	Monday, July 8, 2019 8:52:25 AM
Attachments:	TDP43 mutations in C elegans.pdf ATT00001.htm

Dear Xinxin,

Thanks for the email sharing your latest advances. It appears that things are moving well.

I was talking with Yishi Jin who is a C. elegans-Neuron expect in our campus, wondering whether we can even push for the C. elegans model for mito imbalance and neurodegeneration.

She has a related paper:

A Select Subset of Electron Transport Chain Genes Associated with Optic Atrophy Link Mitochondria to Axon Regeneration in *Caenorhabditis elegans*.

Knowlton WM[1], Hubert T[1], Wu Z[2], Chisholm AD[1], Jin Y[1,2,3].

I also found a relevant paper, as attached. She asked for the names for worm homologs. Can you help find out?

From:	Kathy Lin
To:	Yu Zhou
Cc:	Fu, Xiang-Dong; david bartel
Subject:	Re: Re: A novel class of microRNA-recognition elements that function only within open reading frames
Date:	Friday, June 7, 2019 8:52:33 AM

Dear Yu,

We really appreciate you providing the data and responding so quickly. We are excited to work with this data in our analyses, and we'll let you know if we have any questions.

Best wishes,
Kathy

On Fri, Jun 7, 2019 at 11:32 AM Yu Zhou <yu.zhou@whu.edu.cn> wrote:

> Dear Kathy,
>
> Thanks a lot for your interests in our work. Please find enclosed zipped file with 3 Excel tables for CLIP-seq peaks, RNA-seq fold-changes, and gene information, respectively. If you have any further questions, please don't hesitate to contact us. Hoping the data will be helpful for your project.
>
> ---
> Best regards,
> Yu
>
> Yu Zhou, Ph.D.
> Principal Investigator
> College of Life Sciences, Room 6109
> Wuhan University, China
>
> -----Original Messages-----
> **From:**"Fu, Xiang-Dong" <xdfu@ucsd.edu>
> **Sent Time:**2019-06-06 23:39:50 (Thursday)
> **To:** "Kathy Lin" <klin85@mit.edu>, "Zhou Yu" <yu.zhou@whu.edu.cn>
> **Cc:** "David Bartel" <dbartel@wi.mit.edu>
> **Subject:** Re: A novel class of microRNA-recognition elements that function only within open reading frames
>
> Dear Kathy,
>
> I have forwarded your email to my co-worker Dr. Yu Zhou of Wuhan University where the Ago2 CLIP was performed. He should be able to address your question in full and providing the data.

Fu

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
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9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

On Jun 6, 2019, at 7:27 AM, Kathy Lin <klin85@mit.edu> wrote:

Dear Professor Fu,

I am a graduate student in David Bartel's laboratory at MIT, and I am very interested in the AGO2 eCLIP data you all generated for this work. In particular, I would like to compare our miRNA targeting predictions to CLIP peak enrichments you observe. Would it be possible to obtain the CLIP peak signals +/- miR-20a, along with the corresponding RNA-Seq fold-changes (as shown in Figures 6a and 6e, respectively)? At the moment, the "Source data" section for Figure 6 on the Nature website does not seem to link to Figure 6 data.

Thanks,
Kathy

From:	Yu Zhou
To:	kathy lin
Cc:	Fu, Xiang-Dong; david bartel
Subject:	Re: Re: A novel class of microRNA-recognition elements that function only within open reading frames
Date:	Friday, June 7, 2019 8:47:49 AM
Attachments:	miR20a.zip

Dear Kathy,

Thanks a lot for your interests in our work. Please find enclosed zipped file with 3 Excel tables for CLIP-seq peaks, RNA-seq fold-changes, and gene information, respectively. If you have any further questions, please don't hesitate to contact us. Hoping the data will be helpful for your project.

Best regards,
Yu

Yu Zhou, Ph.D.
Principal Investigator
College of Life Sciences, Room 6109
Wuhan University, China

> -----Original Messages-----
> **From:**"Fu, Xiang-Dong" <xdfu@ucsd.edu>
> **Sent Time:**2019-06-06 23:39:50 (Thursday)
> **To:** "Kathy Lin" <klin85@mit.edu>, "Zhou Yu" <yu.zhou@whu.edu.cn>
> **Cc:** "David Bartel" <dbartel@wi.mit.edu>
> **Subject:** Re: A novel class of microRNA-recognition elements that function only within open reading frames
>
> Dear Kathy,
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> I have forwarded your email to my co-worker Dr. Yu Zhou of Wuhan University where the Ago2 CLIP was performed. He should be able to address your question in full and providing the data.
>
> Fu
>
> Xiang-Dong Fu, Professor
> Dept. of Cellular and Molecular Medicine
> University of California, San Diego
> George Palade Laboratories
> 9500 Gilman Drive, Room 217
> La Jolla, CA 92093-0651

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Thanks,
Kathy

From: Fu, Xiang-Dong
To: Kathy Lin; Zhou Yu
Cc: David Bartel
Subject: Re: A novel class of microRNA-recognition elements that function only within open reading frames
Date: Thursday, June 6, 2019 8:39:50 AM

Dear Kathy,

I have forwarded your email to my co-worker Dr. Yu Zhou of Wuhan University where the Ago2 CLIP was performed. He should be able to address your question in full and providing the data.

Fu

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
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Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

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> Dear Professor Fu,
>
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>
> Thanks,
> Kathy

From: Fu, Xiang-Dong
To: valeiras@mrc-lmb.cam.ac.uk
Cc: Zhou Yu
Subject: Re:
Date: Friday, May 17, 2019 9:04:48 AM

Thanks for your interest. I have forwarded your email to my co-worker to find out the information for you.

Fu

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

> On May 17, 2019, at 8:58 AM, valeiras@mrc-lmb.cam.ac.uk wrote:
>
> Dear Dr.Fu,
>
> I'm contacting you regarding your publication entitled "NEAT1 Scaffolds RNA Binding Proteins and the Microprocessor to Globally Enhance Pri-miRNA Processing". I woudl like to start some work looking into regulation of miRNAs and was really interested in your approach ussing the Luciferase reported plasmid particularly for the mir17-92 cluster. Was wondering if I could get the complete sequence of the final plasmid used, which is tye actual insert sequence, is it the polycistronic miRNA or the separeted products. In the figures it woudl appear as if it was one vector with the policistronic insert for pri-miRNA 17-92. However when I looked into the supplementary information, the primers used are for separate miRNAs. if you could clarify this it woudl be of great help for me to make the same cobstruct!
>
> Thank you very much in advance,
>
> Best wishes
>
> Brenda
>
> Brenda Valeiras, Ph.D.

MRC Laboratory of Molecular Biology
Francis Crick Avenue
Cambridge Biomedical Campus
Cambridge CB2 0QH
UK

From:	xinxinzuo2012
To:	Fu, Xiang-Dong
Cc:	Zhou Yu
Subject:	Work plans for TDP43 project and the culture of iPSC and neurons
Date:	Sunday, May 12, 2019 6:27:02 PM
Attachments:	List of experiments.docx

Dear Fu,

Thank you very much for your information of Met. And I will read the paper carefully and try to test it in our study.

Here is the list of necessary experiments which I summarized from your “point to point response” several days ago. I have been prepared to carried out them, such as the of biotin-labeled miRNAs (motif mutant) and antibodies for immunostaining.

Last Friday, I came to the Miguel lab in Guangzhou with ZhouYu. And I have already stayed here for two days to learn how to culture the human iPS cells and how to differentiae them into neurons. They are very nice to give all the protocol to me and suggest me to stay a few more days to learn the key steps of picking rosettes.

Besides, After discussion with several postdoc from their lab, I think there may be three strategies to obtain neurons.

1. Induce iPS cells to neurons (take nearly one month)
2. Isolate the primary neurons form mouse brain (quickly and easier)
3. shPTB to direct conversion of fibroblasts to neurons

Xinxin

From: Fu, Xiang-Dong
To: xinxinzuo2012; Zhou Yu
Subject: You may want to read these papers
Date: Sunday, May 12, 2019 4:27:38 PM
Attachments: SAM paper.pdf
ATT00001.htm
SAM and PP2A.pdf
ATT00002.htm

Hi Xinxin and Yu,

I was helping interviewing a candidate for Zheda. The attached papers suggest that we may test using Met to obligate oxidative stress in neurons, which would be of therapeutic values in treating ALS and other neurodegenerative diseases.

From: Fu, Xiang-Dong
To: Wani, Sajad A.
Cc: Zhou Yu
Subject: Re: A Novel Class of MicroRNA Recognition Elements That Function Only in Open Reading Frames
Date: Thursday, April 18, 2019 1:13:30 PM

Here are the answers to your questions

> On Apr 17, 2019, at 5:12 PM, Wani, Sajad A. <wani.16@osu.edu> wrote:
>
> Hi Drs. Yu Zhou and Xiang-Dong Fu
>
> My name is Sajad and i am working as a Post Doctoral Researcher at Ohio State University, OH, United States.i had read your paper entitled " A Novel Class of MicroRNA Recognition Elements That Function Only in Open Reading Frames ". It's indeed a great paper.
>
> The article mentions that " CDS-targeted miRNAs require extensive base pairings in the 3' side rather than the 5' seed; cause gene silencing in an Argonaute-dependent, but GW182-independent manner; and repress translation by inducing transient ribosome stalling instead of mRNA destabilization. ".
>
> i am performing an experiment called identification of MRES by pull-down and alignment of captive transcripts—sequencing to identify the microRNA recognition elements of a miRNA.
>
> Can you provide your scientific opinion on below queries?
>
> Can we say that mRNAs which have target sites against a miRNA in 3' UTR sites are down-regulated at the transcript levels which we can measure by RNA seq /qPCR assays?

True, but the miRNA targeting 3'UTR may also affect translation.

> While as mRNAs which have target sites against a miRNA in CDS are not down-regulated at the transcript levels but at protein levels which can be measured by MS-MS/ Western blot.

True, if the CDS-targeted miRNA is sufficiently stable.

> Moreover, mRNAs which have target sites against a miRNA in both 3' UTR and CDS sites are down-regulated at the transcript levels as well as protein levels or are downregulated to a higher extent.

I would expect so.

> Also, do some mRNAs with miRNA binding sites in coding regions lead to upregulation of transcript/protein upon miRNA mimic transfection.

Yes.

> I am looking forward to hearing from you.
> Thanks
> Sajad

<Outlook-zjg1o3ei.png>
Sajad Ahmad Wani, PhD
Pelotonia Post Doctoral Researcher
The Ohio State University
Columbus, Ohio, USA, 43210

From: 陈亮
To: HU Jing
Cc: Fu, Xiang-Dong
Subject: Re: Sum of comments for V2 PPT from Liang
Date: Sunday, April 14, 2019 11:54:59 PM

Jing,

You are welcome. Please send me the revised version once it is ready and we can discuss it later. Good luck!

Liang

Sent from Cormail Lunkr

----- 原始邮件 -----
发件人: hujingbio@hotmail.com
收件人: xdfu@ucsd.edu,liang_chen@whu.edu.cn
发送时间: 2019-04-15 13:22:33
主 题: Sum of comments for V2 PPT from Liang

Dear Profs. Fu and Chen,

Thanks Liang for your comments and suggestions for my job talk V2 PPT. I summarized them as below and I will resend you my V3 PPT later soon.

Main Problems (revised plans):

1) Major logic line within each part is not clear and transitions are not smooth. Especially, significance of big question(s) in the field and how I try to answer it in my research are not highlighted (which could be used as transitions as well). And put outline/diagram at beginning may lose to inspire curiosity for audiences (just show background before related points).

2) Too much information/too many figures in each slide (simplify to one or two panels for one most critical point per slide, get rid of anything unnecessary).

3) Future research plan is too superficial and didn't show meanings and significances (expand with more details and emphasize the research potential).

4) Too many slides for overtime (8-10 slides for RBFox2 and 15-17 slides for PTB).

Thanks,
Jing

From: Yu Zhou
To: Fu, Xiang-Dong
Subject: Re: Re: my traveling schedule
Date: Monday, March 25, 2019 5:51:43 PM
Attachments: ng.765.pdf
Pericentric-heterochromatin-RNA.pdf
RepeatRNA.pdf

Tang Peng said he didn't know the paper on that conclusion. He suggested following relevant papers.

https://www.nature.com/articles/ng.765
https://www.nature.com/articles/ng843z

https://www.sciencedirect.com/science/article/pii/S0092867417305901?via%3Dihub

https://www.sciencedirect.com/science/article/pii/S0092867414001354

Best regards,
Yu

> -----原始邮件-----
> 发件人:"Fu, Xiang-Dong" <xdfu@ucsd.edu>
> 发送时间:2019-03-26 08:26:02 (星期二)
> 收件人: "Zhou Yu" <yu.zhou@whu.edu.cn>
> 抄送:
> 主题: Re: my traveling schedule
>
> Hi Zhou Yu,
>
> Could you help me check a literature information showing that heterochromatin contains twice much RNA than euchromatin? I think Tang Peng told me this.
>
> Thanks.
>
> Fu
>
> Xiang-Dong Fu, Professor
> Dept. of Cellular and Molecular Medicine
> University of California, San Diego
> George Palade Laboratories
> 9500 Gilman Drive, Room 217
> La Jolla, CA 92093-0651
>
> Phone: 858-534-4937

Fax: 858-822-6692
Email: xdfu@ucsd.edu

On Mar 25, 2019, at 5:18 PM, Yu Zhou <yu.zhou@whu.edu.cn> wrote:

Got it! Thanks for the detailed schedule.

Best regards,
Yu

-----原始邮件-----
发件人:"Fu, Xiang-Dong" <xdfu@ucsd.edu>
发送时间:2019-03-26 01:19:51 (星期二)
收件人: "Hao, Yajing" <yahao@ucsd.edu>, "Jin Mingjie" <mjjin@yahoo.com>, "Zhang Xiaorong" <zhangxiaorong52@163.com>, "Zhou Yu" <yu.zhou@whu.edu.cn>, "何顺民" <heshunmin@ibp.ac.cn>
抄送:
主题: my traveling schedule

4/5: Fly UA851 from Chicago (12:55pm) to Beijing (3:24pm); Fly CZ3140 from Beijing (7:15pm) to Wuhan (9:35pm). I will have a gap of ~4hrs at the Beijing airport.

4/9: Fly MU2477 from Wuhan (7:40am) to Shenzhen (9:40am).

4/10: Fly CZ3151 from Shenzhen (8:30am) to Beijing (11:45am).

4/12: Fly CA1843 from Beijing (1:25pm) to Hefei (3:25pm)

4/14: Train D2373 from Hefei (8:14am) to Wuhan (10:14am)

4/16: Fly CA8203 from Wuhan (12:40pm) to Beijing (2:40pm); Fly UA889 from Beijing (4:25pm) to SFO (1:15pm); Fly UA5463 from SFO (4:59pm) to SAN (6:37pm).

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
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9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

From: Liang Chen
To: Fu, Xiang-Dong; Chen, Jiayu
Subject: comments for DRIPc NP MS
Date: Friday, March 8, 2019 1:46:56 AM
Attachments: Chedin_NatProtocol_2019_Final-comments.docx

Hi Fu and Jerry,

I went through the DRIPc NP protocol Jerry sent to me and added a few comments that may be helpful for your discussion.

Please see the attachment. Thank Jerry for finding this MS.

Best,

Liang

Liang Chen, Ph.D.
College of Life Sciences, Wuhan University
Wuhan, Hubei, 430072, P.R.China
Email: liang_chen@whu.edu.cn

From:	Fu, Xiang-Dong
To:	liangyi@whu.edu.cn
Subject:	Re: The updated manuscript on prion protein
Date:	Wednesday, March 6, 2019 6:40:35 PM
Attachments:	Mol Cell ms 2 29 2019.doc ATT00001.htm

Hi Liang Yi,

As I have tones of things to capture up, I really run out of time to do a thorough job on your manuscript. Instead, I have gone through the front part (until page 8) to illustrate how I would modify the text to make your statements more clear. In fact, I do not think these are perfectly polished sentences, and thus, please take or leave some of the modifications. If you like the style, you may use these examples to amend the remaining parts of the paper.

As I do not have direct contribution to this work, I do not think you should add my name to the authorship. In any case, I hope that my editions are helpful in improving the clarity, which you may extend to the rest of the paper.

Best wishes,

From:	山挺
To:	Fu, Xiang-Dong; 周宇
Subject:	Shan Ting project data collection
Date:	Monday, March 4, 2019 4:34:19 AM
Attachments:	Shanting 2019.2.pptx other data.pptx

Dear professor Fu,

Here I have summarized my project data. I think the main topic could be " m6A reader YTHDF2 binding in 3'UTR directly represses translation and regluates DNA repair ". Slides in the first PPT are a series of data of this topic and the other PPT has some other data not included.

Best regards,

Shan Ting

From: liangyi@whu.edu.cn
To: Fu, Xiang-Dong
Subject: Re: The updated manuscript on prion protein
Date: Saturday, March 2, 2019 3:17:50 AM
Attachments: Mol Cell ms 2 29 2019.doc

Dear Prof. Xiang-Dong Fu,

Thank you very much for your critical comments on my manuscript on prion protein (Abstract, Intro, and Result sections).

This is the most updated manuscript on prion protein. I have now revised the manuscript carefully according to your very helpful advice.

Please let me know where I should revise and give me your further critical comments on my manuscript on prion protein.

PS. If you agree, I shall add you as one senior co-author into my manuscript on prion protein.

Yi

Dr. Yi Liang, Professor of Biochemistry
State Key Laboratory of Virology
College of Life Sciences, Wuhan University
Wuhan 430072, China

liangyi@whu.edu.cn

From: Fu, Xiang-Dong
Date: 2019-02-18 17:31
To: liangyi@whu.edu.cn
Subject: Re: The updated manuscript on prion protein

Dear Yi,

I went through your Intro and Result sections with various comments inserted. My overall impressions are:

1. Main messages tend to be berried in experimental details.

2. The style is closer to that of JBC, but not Mol Cell.

3. Some data are insufficiently strong. For example, you did not see much elevated apoptosis. Based on a single marker, you concluded that the cytotoxicity is related to

elevated autophagy. The evidence is relatively thin.

4. The TEM pictures showed altered mito structure, indicative of damaged mito. Is this responsible for increased ROS? How does this happens? It is quite descriptive on this part of the story.

5. Key functional assays are all based on treatment of PrP106-206, which is not associated with any natural prion disease. This raises a question on various functional distinctions between wt and variant PrPs in natural settings. It is also unclear how variant PrPs block the activity of such prion-prone peptide. Through blocking its function as "seed" for inducing aggregation?

Hope these are helpful to you. If you disagree, please ignore my comments. Overall, I feel that the paper was not sharply written for Mol Cell. I will stop by Wuda tomorrow morning if you are round to briefly discuss your paper.
Fu

Xiang-Dong Fu, Professor
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Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

On Feb 17, 2019, at 4:36 PM, liangyi@whu.edu.cn wrote:

Dear Prof. Xiang-Dong Fu,

Thank you very much for your critical comments on my manuscript on prion protein.

This is the most updated manuscript on prion protein.

Yi

Dr. Yi Liang, Professor of Biochemistry
State Key Laboratory of Virology
College of Life Sciences, Wuhan University
Wuhan 430072, China

liangyi@whu.edu.cn

发**件人:** Liang Yi
发**送**时间**:** 2019-02-16 19:25
收件人: Fu, Xiang-Dong
主题**:** Re: **回**复:The updated manuscript on prion protein

付老师,您好!
惊闻您父亲前天去世,请节哀顺变!

文章等您忙完 再讨论。
梁毅

发自我的 iPhone

在 2019年2月16日,19:03,Fu, Xiang-Dong <xdfu@ucsd.edu> 写道:

我父亲前天去世,我这几天都得忙于办后事。

发自我的华为手机

-------- 原始邮件 --------
主题:The updated manuscript on prion protein
发件人:liangyi@whu.edu.cn
收件人:"Fu, Xiang-Dong"
抄送:

Dear Prof. Xiang-Dong Fu,

Thank you very much for your critical comments on my manuscript on prion protein.

I have gone through the manuscript. This is the most updated manuscript on prion protein. I have made some revisions according to your very helpful comments.

Please let me know where I should revise and give me your further critical comments on my manuscript on prion protein.

Thank you! Have a nice weekend!

Yi

Dr. Yi Liang, Professor of Biochemistry
State Key Laboratory of Virology
College of Life Sciences, Wuhan University
Wuhan 430072, China

liangyi@whu.edu.cn

From: Fu, Xiang-Dong
Date: 2019-02-12 16:58
To: xinxinzuo2012; ZhouJie; Zhou Yu
CC: Liang Yi; Zhang Xiaorong
Subject: Re: The updated figures

Dear All,

This is the most updated manuscript on TDP-43. I have largely re-written the legends for both main and supplementary figures. I have also gone through the methods sections, which by way you guys did not great job!. We now need to do the following:

1. Create a Resources Table. You can find any cell paper as a guide. You can get specific from Chen Liang if you have questions.

2. Fill in all references. Note that there are a few I do not the sources. I listed others in red. If you are not clear, I will help out when we meet in person.

3. Xiaorong has a number of questions and comments, which he will send us. You may directly incorporate his comments into the text. If you are not clear, we can wait until we meet in person.

4. We need to remove current Fig. 5E, as the data is part of Fig. 6B. This will change the current Fig. 5F to 5E, and Fig. 5G to 5F.

5. It would be ideal to add wt TDP-43 to Fig. 6C.I know Xinxin is pushing to generating a few more data to improve one or two other figure panels.

6. Read through the text and fill in all missing information to your best ability.

Please let me know when I should come over to Wuda so that we can seat together to brush through the manuscript word by word and sentence by sentence. Liang Yi will also join us for this exercise. If all possible, let's try to submit it before I return to the US.
Fu

Xiang-Dong Fu, Professor
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University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

On Feb 7, 2019, at 8:46 AM, xinxinzuo2012 <xinxinzuo2012@aliyun.com> wrote:

Dear Fu,

Here is the newly packaged figure according to your latest version which is indeed more concise and logical.

Now I am working on modifying the corresponding figure legends as well as completing material & method part. When I was re-arranging the data, I noticed that the description in manuscript may not consistent with the corresponding figures in two or three points and also figures which might be useful was missed, especially in new fig 5 & 6.

I wonder if it would be convenient for you to meet on February 9 (the day after tomorrow), so that we can go through the newly arranged figure together and also determine the specific data that needs to be supplemented in the further. Looking forward to seeing you!

Xinxin

<2019-02-06 packaged figures.zip>

<Mol Cell_ ms 2_16_2019.doc>

From: xinxinzuo2012
To: Fu, Xiang-Dong; yu.zhou@whu.edu.cn
Subject: Re:some thoughts
Date: Thursday, February 28, 2019 6:35:15 PM

Dear Fu,
Thank you for your efforts on pushing this paper! During this whole week waiting, I mainly fouced on mitochondria UPR and tested the marker gene expression. I am also considering to confirm the direct interation between TDP43 and mito-proteins,using co-IP or co-immunostaing just as you mentioned in the last letter.
I have read the letters between you and Cell editor, the experiments they suggested are indeed may not be completed at the present. Hope we will have a chance for Molecular cell or other suitable for us.

Xinxin

发自我的小米手机
在 "Fu, Xiang-Dong" <xdfu@ucsd.edu>,2019年3月1日 上午3:06写道:

> Hi Xinxin and Yu,
>
> I am attending a keystone meeting this week. I have been constantly thinking about potential issues reviewers might raise on your manuscript. One is the need to perform co-immunostaining between TDP-43 and co-aggregated mito proteins. You did nice work on colocalization with let-7b. Co-staining with antibodies should be easier. You may check a few sequestered ones with two unsequestered ones as control. Another area is to characterize the mitochondrial morphology induced by mito imbalance under EM. I wonder if we can consider this direction or wait until the issue is raised.
>
> Like you, I am anxious waiting for words from Cell. I heard that John Pham, the editor-in-chief, is handling the manuscript by himself.
>
> Fu
>
> Xiang-Dong Fu, Professor
> Dept. of Cellular and Molecular Medicine
> University of California, San Diego
> George Palade Laboratories
> 9500 Gilman Drive, Room 217
> La Jolla, CA 92093-0651
>
> Phone: 858-534-4937
> Fax: 858-822-6692
> Email: xdfu@ucsd.edu

From: Fu, Xiang-Dong
To: liangyi@whu.edu.cn
Subject: Re: The updated manuscript on prion protein
Date: Monday, February 18, 2019 1:32:08 AM
Attachments: Mol%20Cell_%20ms%202_16_2019.doc
ATT00001.htm

Dear Yi,

I went through your Intro and Result sections with various comments inserted. My overall impressions are:

1. Main messages tend to be berried in experimental details.

2. The style is closer to that of JBC, but not Mol Cell.

3. Some data are insufficiently strong. For example, you did not see much elevated apoptosis. Based on a single marker, you concluded that the cytotoxicity is related to elevated autophagy. The evidence is relatively thin.

4. The TEM pictures showed altered mito structure, indicative of damaged mito. Is this responsible for increased ROS? How does this happens? It is quite descriptive on this part of the story.

5. Key functional assays are all based on treatment of PrP106-206, which is not associated with any natural prion disease. This raises a question on various functional distinctions between wt and variant PrPs in natural settings. It is also unclear how variant PrPs block the activity of such prion-prone peptide. Through blocking its function as “seed” for inducing aggregation?

Hope these are helpful to you. If you disagree, please ignore my comments. Overall, I feel that the paper was not sharply written for Mol Cell. I will stop by Wuda tomorrow morning if you are round to briefly discuss your paper.

From: Fu, Xiang-Dong
To: liangyi@whu.edu.cn
Subject: Comments on your ms
Date: Tuesday, February 12, 2019 6:47:10 PM

Dear Liang Yi,

I have gone through your manuscript.

First of all, your abstract is too long (>200 words, but the limit for Mol Cell is 150 words). To me, the general message is a bit blurred. You need to find a way to emphasize the novelty of your findings and the conceptual advances.

Here is the alternative abstract for your consideration, which meets the length requirement for Mol Cell.

A naturally occurring mutation G127V in human prion protein (PrP) has recently been found to greatly attenuate prion disease, but the mechanism has remained elusive. We herein report that the long hydrophobic chain introduced in this mutant impairs the intrinsic ability of PrP to complete the required phase transition to form pathological fibrils. We further validate this by introducing an amino acid with a different long hydrophobic chain (Ile) at the same position and obtain similar results. Furthermore, using a strong prion-prone peptide from PrP (aa106-126) to drive a series of pathological features in neuronal cells, we show that both PrP^{G127V} and PrP^{G127I} are more resistant than wild-type PrP to the peptide-induced neurotoxicity that results from the formation of pathological fibrils, elevated ROS production, and damaged mitochondria. These findings elucidate the molecular basis for a neutralizing mutation in PrP, which may be exploited to develop therapeutic strategies against prion disease.

If [redacted] I will come to Wuda to spend a day to polish Zou Xinxin's manuscript tomorrow. If you have time, please join us brushing through the paper, during which we can find time to discuss how to elevate the concept in your paper.

Fu

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

On Feb 12, 2019, at 8:28 PM, liangyi@whu.edu.cn wrote:

From:	Fu, Xiang-Dong
To:	liang_chen@whu.edu.cn
Subject:	Fwd: R-ChIP N9-primer
Date:	Monday, February 4, 2019 7:12:11 PM
Attachments:	Primer.pdf ATT00001.htm

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
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George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

Begin forwarded message:

From: 間野達雄 <tatsuomano@gmail.com>
Subject: R-ChIP N9-primer
Date: February 4, 2019 at 10:46:32 AM GMT+8
To: "xdfu@ucsd.edu" <xdfu@ucsd.edu>

Dear Xiang-Dong Fu,

I've read your paper "R-ChIP Using Inactive RNase H Reveals Dynamic Coupling of R-loops with Transcriptional pausing at Gene Promoters".
I'm very impressed with you cool idea, and would like to try it.

I have a question about N9-primer for random priming in the library preparation.
In your paper, N9-primer contains P7 sequence.
According to my understanding, Illumina's adaptor ligated to 3'-end contains rP7 and P5 sequences, and
The primers for PCR amplifications are P7 and P5 (for example, KAPA library amplification kit),
thus, I think, amplification process should proceed as the figure I attached to this email.

The resultant library has P7 in 5'-end, and rP7 in 3'-end, which might not be compatible Illumina's sequencing?
How can I prepare the library with both P5 and P7 sequence with this primer ?

Thanks in advance,

The University of Tokyo Hospital
Department of Neurology

Tatsuo Mano
tatsuomano@gmail.com

From: Yu Zhou
To: Fu, Xiang-Dong
Subject: Re: Re: Cotton manuscript revision
Date: Saturday, January 5, 2019 4:17:01 PM

Dear Fu, thank you very much!

Best regards,
Yu

-----Original Messages-----
From:"Fu, Xiang-Dong" <xdfu@ucsd.edu>
Sent Time:2019-01-06 00:20:12 (Sunday)
To: "Zhou Yu" <yu.zhou@whu.edu.cn>
Cc:
Subject: Re: Cotton manuscript revision

Here is the revised cover letter.
Fu

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

> On Jan 4, 2019, at 9:08 PM, Yu Zhou <yu.zhou@whu.edu.cn> wrote:
>
> Dear Fu,
>
> Thank you very much for your detailed revisions! I will revise the text and abstract.
>
> What do you think about the cover letter?

Best regards,
Yu

-----Original Messages-----
From:"Fu, Xiang-Dong" <xdfu@ucsd.edu>
Sent Time:2019-01-05 09:54:56 (Saturday)
To: "Zhou Yu" <yu.zhou@whu.edu.cn>
Cc:
Subject: Re: Cotton manuscript revision

Hi Yu,

It is such a long manuscript, which I only had time to quickly go through until the end of the results section. I made various suggestions for your consideration. Overall, the work is quite interesting, but I feel that your abstract is not yet sufficient to reflect those interesting observations.

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

On Jan 4, 2019, at 3:38 AM, Yu Zhou <yu.zhou@whu.edu.cn> wrote:

Dear Fu,

If you have time, please help revise the enclosed Word version of the manuscript by setting tracking mode on. All the figures are in the PDF version. Thank you very much!

Best,
Yu

> -----Original Messages-----
> From: "Yu Zhou" <yu.zhou@whu.edu.cn>
> Sent Time: 2019-01-01 22:08:19 (Tuesday)

> To: xdfu@ucsd.edu
> Cc:
> Subject: Cotton manuscript revision
>
> Dear Fu,
>
> Happy New Year!
>
> Could you please take some time to help revise my manuscript and cover letter for the Cotton project?
>
> Please find enclosed CoverLetter.docx and manuscript cotms.pdf which includes all main figures and supplementary figures.
>
> Due to my writing in Latex, not Word, you can edit the manuscript online through the link below.
>
> https://www.overleaf.com/6236815518dchnfmssxqbb
>
> "Rich Text" mode may be easier for you than "Source" mode.
>
> Thank you very much!
>
> ------------------------------
> Best regards,
> Yu

Best regards,
Yu

Large attachments send from whu.edu.cn

cotms.pdf (28MB, Expiry Date: 2019-01-11 19:36)
View download information

<cotms.docx><CoverLetter.docx>

<CoverLetter.docx>

From: Fu, Xiang-Dong
To: Zhou Yu
Subject: Re: Cotton manuscript revision
Date: Saturday, January 5, 2019 8:20:18 AM
Attachments: CoverLetter.docx
ATT00001.htm

Here is the revised cover letter.

From: Yu Zhou
To: Fu, Xiang-Dong
Subject: Re: Re: Cotton manuscript revision
Date: Friday, January 4, 2019 9:08:11 PM
Attachments: CoverLetter.docx

Dear Fu,

Thank you very much for your detailed revisions! I will revise the text and abstract.

What do you think about the cover letter?

Best regards,
Yu

> -----Original Messages-----
> **From:**"Fu, Xiang-Dong" <xdfu@ucsd.edu>
> **Sent Time:**2019-01-05 09:54:56 (Saturday)
> **To:** "Zhou Yu" <yu.zhou@whu.edu.cn>
> **Cc:**
> **Subject:** Re: Cotton manuscript revision
>
> Hi Yu,
>
> It is such a long manuscript, which I only had time to quickly go through until the end of the results section. I made various suggestions for your consideration. Overall, the work is quite interesting, but I feel that your abstract is not yet sufficient to reflect those interesting observations.
>
> Xiang-Dong Fu, Professor
> Dept. of Cellular and Molecular Medicine
> University of California, San Diego
> George Palade Laboratories
> 9500 Gilman Drive, Room 217
> La Jolla, CA 92093-0651
>
> Phone: 858-534-4937
> Fax: 858-822-6692
> Email: xdfu@ucsd.edu

On Jan 4, 2019, at 3:38 AM, Yu Zhou <yu.zhou@whu.edu.cn> wrote:

Dear Fu,

If you have time, please help revise the enclosed Word version of the manuscript by setting tracking mode on. All the figures are in the PDF version.
Thank you very much!

Best,
Yu

> -----Original Messages-----
> From: "Yu Zhou" <yu.zhou@whu.edu.cn>
> Sent Time: 2019-01-01 22:08:19 (Tuesday)
> To: xdfu@ucsd.edu
> Cc:
> Subject: Cotton manuscript revision
>
> Dear Fu,
>
> Happy New Year!
>
> Could you please take some time to help revise my manuscript and cover letter for the Cotton project?
>
> Please find enclosed CoverLetter.docx and manuscript cotms.pdf which includes all main figures and supplementary figures.
>
> Due to my writing in Latex, not Word, you can edit the manuscript online through the link below.
>
> https://www.overleaf.com/6236815518dchnfmssxqbb
>
> "Rich Text" mode may be easier for you than "Source" mode.
>
> Thank you very much!
>
> ---
> Best regards,
> Yu

Best regards,
Yu

Large attachments send from whu.edu.cn

cotms.pdf (28MB, Expiry Date: 2019-01-11 19:36)
View download information

<cotms.docx><CoverLetter.docx>

From: Fu, Xiang-Dong
To: Zhou Yu
Subject: Re: Cotton manuscript revision
Date: Friday, January 4, 2019 5:57:15 PM
Attachments: cotms.docx
ATT00001.htm

Hi Yu,

It is such a long manuscript, which I only had time to quickly go through until the end of the results section. I made various suggestions for your consideration. Overall, the work is quite interesting, but I feel that your abstract is not yet sufficient to reflect those interesting observations.

From:	Shou, Weinian
To:	Xiao-Fan Wang, Ph.D.; xdfu@ucsd.edu; Guan; Kun-Liang; mhan@colorado.edu; Xi.He@childrens.harvard.edu; Youxing.Jiang@UTSouthwestern.edu; lim@mskcc.org; xin.lu@ludwig.ox.ac.uk; Lin Mei; kangshen@stanford.edu; ltong@columbia.edu
Subject:	Re: [External] final report
Date:	Tuesday, December 10, 2019 1:53:20 PM

Beautifully done, Xiaofan, Best.....Weinian

On 12/10/19, 10:15 AM, "Xiao-Fan Wang, Ph.D." <xiao.fan.wang@duke.edu> wrote:

Dear Committee members:

Attached please find the final report that will be submitted to SHTech after the final editing by all members. I would like to receive any comments/edits by Thursday noon, and if no comments from any of you, I would assume approval of the report. Please go through the main body for the whole school and then pay attention to those evaluations for individual PIs for whom you are responsible as Primary and Secondary Reviewer.

We are almost there, and thank you again for the hard work that will help SHTech in its next phase of development!

Best regards, XF

From:	Xiao-Fan Wang, Ph.D.
To:	Liang Tong
Cc:	xdfu@ucsd.edu; Guan, Kun-Liang; mhan@colorado.edu; Xi.He@childrens.harvard.edu; Youxing.Jiang@UTSouthwestern.edu; lim@mskcc.org; xin.lu@ludwig.ox.ac.uk; Lin Mei; kangshen@stanford.edu; wshou@iu.edu
Subject:	Re: final report
Date:	Tuesday, December 10, 2019 5:44:02 AM

Thanks!

Sent from my iPhone

On Dec 10, 2019, at 8:20 AM, Liang Tong <ltong@columbia.edu> wrote:

> Excellent report! Thank you, Xiao-Fan.
>
> I have a few small edits on the main body, in case you find them useful.
>
> Happy Holidays, everyone!
>
> best regards
> Liang
>
> On Mon, Dec 9, 2019 at 9:15 PM Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu> wrote:
>
> > Dear Committee members:
> >
> > Attached please find the final report that will be submitted to SHTech after the final editing by all members. I would like to receive any comments/edits by Thursday noon, and if no comments from any of you, I would assume approval of the report. Please go through the main body for the whole school and then pay attention to those evaluations for individual PIs for whom you are responsible as Primary and Secondary Reviewer.
> >
> > We are almost there, and thank you again for the hard work that will help SHTech in its next phase of development!
> >
> > Best regards, XF
>
> <Final Report.SLS-LT.docx>

From:	Liang Tong
To:	Xiao-Fan Wang, Ph.D.
Cc:	xdfu@ucsd.edu; Guan, Kun-Liang; mhan@colorado.edu; Xi.He@childrens.harvard.edu; Youxing.Jiang@UTSouthwestern.edu; lim@mskcc.org; xin.lu@ludwig.ox.ac.uk; Lin Mei; kangshen@stanford.edu; wshou@iu.edu
Subject:	Re: final report
Date:	Tuesday, December 10, 2019 5:21:02 AM
Attachments:	Final Report.SLS-LT.docx

Excellent report! Thank you, Xiao-Fan.

I have a few small edits on the main body, in case you find them useful.

Happy Holidays, everyone!

best regards
Liang

On Mon, Dec 9, 2019 at 9:15 PM Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu> wrote:

> Dear Committee members:
>
> Attached please find the final report that will be submitted to SHTech after the final editing by all members. I would like to receive any comments/edits by Thursday noon, and if no comments from any of you, I would assume approval of the report. Please go through the main body for the whole school and then pay attention to those evaluations for individual PIs for whom you are responsible as Primary and Secondary Reviewer.
>
> We are almost there, and thank you again for the hard work that will help SHTech in its next phase of development!
>
> Best regards, XF

From:	lim@mskcc.org
To:	kangshen@stanford.edu
Cc:	lxm387@case.edu; Youxing.Jiang@utsouthwestern.edu; xiao.fan.wang@duke.edu; xdfu@ucsd.edu; kuguan@ucsd.edu; mhan@colorado.edu; Xi.He@childrens.harvard.edu; xin.lu@ludwig.ox.ac.uk; wshou@iu.edu; ltong@columbia.edu
Subject:	Re: Re: final report
Date:	Monday, December 9, 2019 9:01:24 PM

Looks great. Best, Ming

Sent from my iPhone

> On Dec 9, 2019, at 11:41 PM, Kang Shen <kangshen@stanford.edu> wrote:
>
> Looks great. Thanks Xiao-Fan.
> Kang
>> On 12/9/19 8:40 PM, Lin Mei wrote:
>> Second. Thank you, Xiao-Fan for your leadership.
>>
>> -----Original Message-----
>> From: Youxing Jiang [mailto:Youxing.Jiang@UTSouthwestern.edu]
>> Sent: 2019年12月9日 22:06
>> To: Xiao-Fan Wang, Ph.D. <xiao fan.wang@duke.edu>; xdfu@ucsd.edu; Guan;
>> Kun-Liang <kuguan@ucsd.edu>; mhan@colorado.edu;
>> Xi.He@childrens harvard.edu; lim@mskcc.org; xin.lu@ludwig.ox.ac.uk; Lin
>> Mei <lxm387@case.edu>; kangshen@stanford.edu; wshou@iu.edu;
>> ltong@columbia.edu
>> Subject: RE: final report
>>
>> Looks good to me. Quite impressive report and thank Xiao-Fan for all the
>> effort.
>>
>> Youxing
>>
>> -----Original Message-----
>> From: Xiao-Fan Wang, Ph.D. [mailto:xiao.fan.wang@duke.edu]
>> Sent: Monday, December 09, 2019 8:11 PM
>> To: xdfu@ucsd.edu; Guan; Kun-Liang; mhan@colorado.edu;
>> Xi.He@childrens harvard.edu; Youxing Jiang; lim@mskcc.org;
>> xin.lu@ludwig.ox.ac.uk; Lin Mei; kangshen@stanford.edu; wshou@iu.edu;
>> ltong@columbia.edu
>> Subject: final report
>>
>> EXTERNAL MAIL
>>
>> Dear Committee members:
>>
>> Attached please find the final report that will be submitted to SHTech
>> after the final editing by all members. I would like to receive any
>> comments/edits by Thursday noon, and if no comments from any of you, I
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>> the whole school and then pay attention to those evaluations for
>> individual PIs for whom you are responsible as Primary and Secondary
>> Reviewer.
>>
>> We are almost there, and thank you again for the hard work that will help

>> SHTech in its next phase of development!
>>
>> Best regards, XF
>>
>> CAUTION: This email originated from outside UTSW. Please be cautious of
>> links or attachments, and validate the sender's email address before
>> replying.
>>
>> _____
>>
>> UT Southwestern
>>
>>
>> Medical Center
>>
>>
>>
>> The future of medicine, today.
>
>
> --
> Kang Shen
> Dept. Biology
> Stanford University
>
>

From:	Kang Shen
To:	Lin Mei; Youxing Jiang; Xiao-Fan Wang, Ph.D.; xdfu@ucsd.edu; Guan, Kun-Liang; mhan@colorado.edu; Xi.He@childrens.harvard.edu; lim@mskcc.org; xin.lu@ludwig.ox.ac.uk; wshou@iu.edu; ltong@columbia.edu
Subject:	Re: final report
Date:	Monday, December 9, 2019 8:41:43 PM

Looks great. Thanks Xiao-Fan.
Kang
On 12/9/19 8:40 PM, Lin Mei wrote:
> Second. Thank you, Xiao-Fan for your leadership.
>
> -----Original Message-----
> From: Youxing Jiang [mailto:Youxing.Jiang@UTSouthwestern.edu]
> Sent: 2019年12月9日 22:06
> To: Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>; xdfu@ucsd.edu; Guan;
> Kun-Liang <kuguan@ucsd.edu>; mhan@colorado.edu;
> Xi.He@childrens.harvard.edu; lim@mskcc.org; xin.lu@ludwig.ox.ac.uk; Lin
> Mei <lxm387@case.edu>; kangshen@stanford.edu; wshou@iu.edu;
> ltong@columbia.edu
> Subject: RE: final report
>
> Looks good to me. Quite impressive report and thank Xiao-Fan for all the
> effort.
>
> Youxing
>
> -----Original Message-----
> From: Xiao-Fan Wang, Ph.D. [mailto:xiao fan.wang@duke.edu]
> Sent: Monday, December 09, 2019 8:11 PM
> To: xdfu@ucsd.edu; Guan; Kun-Liang; mhan@colorado.edu;
> Xi.He@childrens.harvard.edu; Youxing Jiang; lim@mskcc.org;
> xin.lu@ludwig.ox.ac.uk; Lin Mei; kangshen@stanford.edu; wshou@iu.edu;
> ltong@columbia.edu
> Subject: final report
>
> EXTERNAL MAIL
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> Dear Committee members:
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> after the final editing by all members. I would like to receive any
> comments/edits by Thursday noon, and if no comments from any of you, I
> would assume approval of the report. Please go through the main body for
> the whole school and then pay attention to those evaluations for
> individual PIs for whom you are responsible as Primary and Secondary
> Reviewer.
>
> We are almost there, and thank you again for the hard work that will help
> SHTech in its next phase of development!
>
> Best regards, XF
>

>
> _____
>
> UT Southwestern
>
>
> Medical Center
>
>
>
> The future of medicine, today.

--
Kang Shen
Dept. Biology
Stanford University

From:	Xiao-Fan Wang, Ph.D.
To:	xdfu@ucsd.edu; Guan; Kun-Liang; mhan@colorado.edu; Xi.He@childrens.harvard.edu; Youxing.Jiang@UTSouthwestern.edu; lim@mskcc.org; xin.lu@ludwig.ox.ac.uk; Lin Mei; kangshen@stanford.edu; wshou@iu.edu; ltong@columbia.edu
Subject:	final report
Date:	Monday, December 9, 2019 6:15:58 PM
Attachments:	Final Report.SLS.docx

Dear Committee members:

Attached please find the final report that will be submitted to SHTech after the final editing by all members. I would like to receive any comments/edits by Thursday noon, and if no comments from any of you, I would assume approval of the report. Please go through the main body for the whole school and then pay attention to those evaluations for individual PIs for whom you are responsible as Primary and Secondary Reviewer.

We are almost there, and thank you again for the hard work that will help SHTech in its next phase of development!

Best regards, XF

From: Xiao-Fan Wang, Ph.D.
To: Fu, Xiang-Dong
Subject: Re: SLST report
Date: Saturday, November 30, 2019 6:18:19 PM

Thank you very much for the great input and I have incorporated all the changes into the draft. I am now waiting for [redacted] the last four reports before I can circulate the draft to all members for final edits and approval.

Best regards, XF

> On Nov 30, 2019, at 8:12 PM, Fu, Xiang-Dong <xdfu@health.ucsd.edu> wrote:
>
> <Final Report.SLS.docx>

From: Fu, Xiang-Dong
To: Xiao-Fan Wang, Ph.D.
Subject: SLST report
Date: Saturday, November 30, 2019 5:12:05 PM
Attachments: Final Report.SLS.docx

Hi Xiaofan,

You have written an outstanding report, which has comprehensively all critical areas. I have nothing major to add. In the attached fie, I have made some minor additions for your considerations. You may go through the tracked changes to take or leave as you fit.

Best,

Fu

Xiang-Dong Fu,
Distinguished Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

From:	Xiao-Fan Wang, Ph.D.
To:	Xin Lu
Cc:	Li Ming; wshou@iu.edu; xdfu@ucsd.edu; Xi.He@childrens.harvard.edu; mhan@colorado.edu; kangshen@stanford.edu; ltong@columbia.edu; Mei Lin; Youxing.Jiang@UTSouthwestern.edu; Kun-Liang Guan;
Subject:	Re: SLST report and happy thanksgiving
Date:	Wednesday, November 27, 2019 2:02:07 PM

Thank you very much! Please send me any comments from Secondary Reviewers for the four PIs. XF

> On Nov 27, 2019, at 4:05 PM, Xin Lu <xin.lu@ludwig.ox.ac.uk> wrote:
>
> [redacted].docx>

From: lim@mskcc.org
To: xiao.fan.wang@duke.edu
Cc: Guan, Kun-Liang; xdfu@ucsd.edu; mhan@colorado.edu; Xi.He@childrens.harvard.edu; Youxing.Jiang@utsouthwestern.edu; xin.lu@ludwig.ox.ac.uk; lxm387@case.edu; kangshen@stanford.edu; wshou@iu.edu; ltong@columbia.edu
Subject: Re: Re: SHTech review reports
Date: Monday, November 25, 2019 3:10:30 PM

It's a great summary. Nice seeing you all. Happy Thanksgiving! Ming

Sent from my iPhone

> On Nov 25, 2019, at 6:07 PM, Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu> wrote:
>
> Thanks for reminding me to remove the last part as I was using the template to add our names!
>
> Sent from my iPhone
>
> On Nov 25, 2019, at 5:53 PM, Guan, Kun-Liang <kuguan@health.ucsd.edu> wrote:
>
> > Hi Xiao-Fan,
> >
> > I have nothing to add to the review summary that is nicely prepared. Did you purposely include the last page (review committee for the Shanghai Institute of Advanced Immunochemical Studies)?
> > It was very nice of seeing all of you in Shanghai.
> > Happy Thanksgiving!
> >
> > Regards,
> > Kun-Liang
> >
> > ---
> >
> > **From:** "Xiao-Fan Wang, Ph.D." <xiao.fan.wang@duke.edu>
> > **Date:** Monday, November 25, 2019 at 12:07 PM
> > **To:** "xdfu@ucsd.edu" <xdfu@ucsd.edu>, "Guan; Kun-Liang" <kuguan@ucsd.edu>, "mhan@colorado.edu" <mhan@colorado.edu>, "Xi.He@childrens.harvard.edu" <Xi.He@childrens.harvard.edu>, "Youxing.Jiang@UTSouthwestern.edu" <Youxing.Jiang@UTSouthwestern.edu>, "lim@mskcc.org" <lim@mskcc.org>, "xin.lu@ludwig.ox.ac.uk" <xin.lu@ludwig.ox.ac.uk>, Lin Mei <lxm387@case.edu>, "kangshen@stanford.edu" <kangshen@stanford.edu>, "wshou@iu.edu" <wshou@iu.edu>, "ltong@columbia.edu" <ltong@columbia.edu>

Subject: Re: SHTech review reports

Dear Committee members:

While I wait for the remaining reports on individual PIs to be sent to me, I am circulating the parts of the draft of report assembled so far to you so that you can make comments/edits for me and Min for our drafts on research and education. This way we can finish the draft before the final report is completed with all components assembled and sent for final modifications and approval.

Please use track to mark where you make changes, and you can also write to me to indicate a specific item/issue that needs to be included.

Thank you all for the hard work and have a nice Thanksgiving, except Xin.

Best regards, XF

==========

From:	Xiao-Fan Wang, Ph.D.
To:	Guan, Kun-Liang
Cc:	xdfu@ucsd.edu; mhan@colorado.edu; Xi.He@childrens.harvard.edu; Youxing.Jiang@UTSouthwestern.edu; lim@mskcc.org; xin.lu@ludwig.ox.ac.uk; Lin Mei; kangshen@stanford.edu; wshou@iu.edu; ltong@columbia.edu
Subject:	Re: SHTech review reports
Date:	Monday, November 25, 2019 3:07:29 PM

Thanks for reminding me to remove the last part as I was using the template to add our names!

Sent from my iPhone

On Nov 25, 2019, at 5:53 PM, Guan, Kun-Liang <kuguan@health.ucsd.edu> wrote:

> Hi Xiao-Fan,
>
> I have nothing to add to the review summary that is nicely prepared. Did you purposely include the last page (review committee for the Shanghai Institute of Advanced Immunochemical Studies)?
> It was very nice of seeing all of you in Shanghai.
> Happy Thanksgiving!
>
> Regards,
> Kun-Liang
>
> ---
>
> **From:** "Xiao-Fan Wang, Ph.D." <xiao.fan.wang@duke.edu>
> **Date:** Monday, November 25, 2019 at 12:07 PM
> **To:** "xdfu@ucsd.edu" <xdfu@ucsd.edu>, "Guan; Kun-Liang" <kuguan@ucsd.edu>, "mhan@colorado.edu" <mhan@colorado.edu>, "Xi.He@childrens.harvard.edu" <Xi.He@childrens.harvard.edu>, "Youxing.Jiang@UTSouthwestern.edu" <Youxing.Jiang@UTSouthwestern.edu>, "lim@mskcc.org" <lim@mskcc.org>, "xin.lu@ludwig.ox.ac.uk" <xin.lu@ludwig.ox.ac.uk>, Lin Mei <lxm387@case.edu>, "kangshen@stanford.edu" <kangshen@stanford.edu>, "wshou@iu.edu" <wshou@iu.edu>, "ltong@columbia.edu" <ltong@columbia.edu>
> **Subject:** Re: SHTech review reports
>
> Dear Committee members:
>
> While I wait for the remaining reports on individual PIs to be sent to me, I am circulating the parts of the draft of report assembled so far to you so that you can make comments/edits for me and Min for our drafts on research and education. This way we can finish the draft before the final report is completed with all components assembled and sent for final modifications and approval.
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> Please use track to mark where you make changes, and you can also write to me to indicate a specific item/issue that needs to be included.

Thank you all for the hard work and have a nice Thanksgiving, except Xin.

Best regards, XF

From:	Xiao-Fan Wang, Ph.D.
To:	xdfu@ucsd.edu; Guan; Kun-Liang; mhan@colorado.edu; Xi.He@childrens.harvard.edu; Youxing.Jiang@UTSouthwestern.edu; lim@mskcc.org; xin.lu@ludwig.ox.ac.uk; Lin Mei; kangshen@stanford.edu; wshou@iu.edu; ltong@columbia.edu
Subject:	Re: SHTech review reports
Date:	Monday, November 25, 2019 12:07:16 PM
Attachments:	Final Report.SLS.docx

Dear Committee members:

While I wait for the remaining reports on individual PIs to be sent to me, I am circulating the parts of the draft of report assembled so far to you so that you can make comments/edits for me and Min for our drafts on research and education. This way we can finish the draft before the final report is completed with all components assembled and sent for final modifications and approval.

Please use track to mark where you make changes, and you can also write to me to indicate a specific item/issue that needs to be included.

Thank you all for the hard work and have a nice Thanksgiving, except Xin.

Best regards, XF

From:	Xiao-Fan Wang, Ph.D.
To:	Min Han
Cc:	wshou@iu.edu; Xiangdong Fu; xin.lu@ludwig.ox.ac.uk
Subject:	Re: Comments on education
Date:	Monday, November 25, 2019 11:50:14 AM

Thank you so much for such a great job! I have inserted the text into the final report with some minor edits, and will circulate to all members of the committee for comments/edits, in addition to the parts that I wrote for research and faculty development in my next message.

Best regards, XF

> On Nov 25, 2019, at 1:24 PM, Min Han <mhan@colorado.edu> wrote:
>
> Dear Weinian, Xiangdong, Xin and Xiao-fan:
> Under Xiao-fan's request, I finished drafting a document briefly commending on all three aspects of education. I don't know if **Xiangdong** and **Xin** have already worked on postdoctoral education since you are listed as primary and secondary, respectively, on postdoc training. if you did, we can either just use yours or combine both.
> **Weinian** was listed as secondary for graduate education, so please give your addition/modification suggestions. I was actually not in the discussion group with graduate students. My writing was partly based on notes provided by Ming Li, so your verification might be important. I also cleared some confusion issues (such as where are all the current 838 graduate students) with Zhenge.
> There was no one assigned to undergraduate education, and much of my writing was based on my reading the documents they provided and further communication with Leo Zhenge and Haifan. I would hope some of you or all of you would read and give me your comments. **Xin** was in the undergraduate discussion group so you may verify some specific comments related to our conversation with the students there.
> **It would be great if all of you can make modification suggestions on this write-up**. It is kind difficult document to write because we had very limited exposure to the education system which they have put a lot effort to establish. In addition, because we essentially had no discussion between us on education, some of the suggestions may reflect more on my personal view. Please make any addition/deletion and suggestions.
> Comparing to what we wrote on education in Tsinghua last year, this one is much briefer.
>
> Thanks and best wishes, Min
>
> Min Han, Ph.D.
> Distinguished Professor
> University of Colorado at Boulder
> Boulder, Colorado 90309-0347
> mhan@colorado.edu
> https://www.colorado.edu/lab/han/
>
> <Education_SHTech_SLST_MH.docx>

From: Min Han
To: wshou@iu.edu; Xiangdong Fu; xin.lu@ludwig.ox.ac.uk; Xiao-Fan Wang, Ph.D.
Subject: Comments on education
Date: Monday, November 25, 2019 10:27:51 AM
Attachments: Education_SHTech_SLST_MH.docx

Dear Weinian, Xiangdong, Xin and Xiao-fan:
Under Xiao-fan's request, I finished drafting a document briefly commending on all three aspects of education. I don't know if **Xiangdong** and **Xin** have already worked on postdoctoral education since you are listed as primary and secondary, respectively, on postdoc training. if you did, we can either just use yours or combine both.
Weinian was listed as secondary for graduate education, so please give your addition/modification suggestions. I was actually not in the discussion group with graduate students. My writing was partly based on notes provided by Ming Li, so your verification might be important. I also cleared some confusion issues (such as where are all the current 838 graduate students) with Zhenge.
There was no one assigned to undergraduate education, and much of my writing was based on my reading the documents they provided and further communication with Leo Zhenge and Haifan. I would hope some of you or all of you would read and give me your comments. **Xin** was in the undergraduate discussion group so you may verify some specific comments related to our conversation with the students there.
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Comparing to what we wrote on education in Tsinghua last year, this one is much briefer.

Thanks and best wishes, Min

Min Han, Ph.D.
Distinguished Professor
University of Colorado at Boulder
Boulder, Colorado 90309-0347
mhan@colorado.edu
https://www.colorado.edu/lab/han/

From: Xiao-Fan Wang Ph.D.
To: Xin Lu
Cc: xdfu@ucsd.edu; lim@mskcc.org; wshou@iu.edu
Subject: Re: SHTech review reports
Date: Friday, November 22, 2019 10:27:14 AM

Thanks! XF

> On Nov 22, 2019, at 1:20 PM, Xin Lu <xin.lu@ludwig.ox.ac.uk> wrote:
>
> Dear Xiaofang
> I will modify if. I sent it is for score adjusting.
> Xin
>
> Professor Xin Lu, FMedSci, FRCPath, FRSB, PhD
> Director, Ludwig Institute for Cancer Research
> Nuffield Department of Clinical Medicine, University of Oxford
> Old Road Campus Research Building
> Oxford, OX3 7DQ
>
> > On 22 Nov 2019, at 17:48, Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu> wrote:
> >
> > Xin:
> >
> > Some members of our committee wondered if you can update your reports based on the format requirement and also elaborate more on some specific points as a Primary Reviewer before the secondary reviewers can edit. I have attached your write up as separate files that you can modify with items of separate entries.
> >
> > Thanks! XF
> >
> > > On Nov 21, 2019, at 10:58 AM, Xin Lu <xin.lu@ludwig.ox.ac.uk> wrote:
> > >
> > > Dear XiaoFang and all
> > > It was great to see you and I have a specific question to ask [redacted]. Please see a copy of the write up I have for all people I am asinged as primary reviewer.
> > > Warm regards
> > > Xin
> > >
> > > ---
> > >
> > > **From:** Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
> > > **Sent:** 21 November 2019 14:44
> > > **To:** xdfu@ucsd.edu <xdfu@ucsd.edu>; Guan; Kun-Liang <kuguan@ucsd.edu>; mhan@colorado.edu <mhan@colorado.edu>; Xi.He@childrens.harvard.edu <Xi.He@childrens.harvard.edu>; Youxing.Jiang@UTSouthwestern.edu <Youxing.Jiang@UTSouthwestern.edu>; lim@mskcc.org <lim@mskcc.org>; Xin Lu <xin.lu@ludwig.ox.ac.uk>; Lin Mei <lxm387@case.edu>; kangshen@stanford.edu <kangshen@stanford.edu>; wshou@iu.edu <wshou@iu.edu>; ltong@columbia.edu <ltong@columbia.edu>
> > > **Cc:** Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
> > > **Subject:** SHTech review reports
> > >
> > > Dear Committee members:
> > >
> > > Thank you all for the hard work with the evaluation of 41 PIs and the School of Life Sciences as a whole during our onsite visit. In the next week, I hope you can all send

me the report for individual PIs based on the assignments, with Primary Reviewer responsible for finalizing the report after the Secondary Reviewer has gone through the draft (some of you have already sent me the reports, thank you very much!). I have also asked some of you to draft the portion of the report on education and core facilities, and I will put together the assessments and recommendations for the general area of research. When I assemble the final draft of the report with all components, I will circulate to you for final editing before we submit to the leadership of SHTech.

Best regards, XF
<Report for SLST 2019-XL.docx>

[redacted]

From: Xin Lu
To: Xiao-Fan Wang, Ph.D.
Cc: xdfu@ucsd.edu; lim@mskcc.org; wshou@iu.edu
Subject: Re: SHTech review reports
Date: Friday, November 22, 2019 10:20:35 AM

Dear Xiaofang
I will modify if. I sent it is for score adjusting.
Xin

Professor Xin Lu, FMedSci, FRCPath, FRSB, PhD
Director, Ludwig Institute for Cancer Research
Nuffield Department of Clinical Medicine, University of Oxford
Old Road Campus Research Building
Oxford, OX3 7DQ

> On 22 Nov 2019, at 17:48, Xiao-Fan Wang, Ph.D. <xiao fan.wang@duke.edu> wrote:
>
> Xin:
>
> Some members of our committee wondered if you can update your reports based on the format requirement and also elaborate more on some specific points as a Primary Reviewer before the secondary reviewers can edit. I have attached your write up as separate files that you can modify with items of separate entries.
>
> Thanks! XF
>
> > On Nov 21, 2019, at 10:58 AM, Xin Lu <xin.lu@ludwig.ox.ac.uk> wrote:
> >
> > Dear XiaoFang and all
> > It was great to see you and I have a specific question to ask. [redacted]
> > Please see a copy of the write up I have for all people I am asinged as primary reviewer.
> > Warm regards
> > Xin
> >
> > ---
> >
> > **From:** Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
> > **Sent:** 21 November 2019 14:44
> > **To:** xdfu@ucsd.edu <xdfu@ucsd.edu>; Guan; Kun-Liang <kuguan@ucsd.edu>; mhan@colorado.edu <mhan@colorado.edu>; Xi.He@childrens.harvard.edu <Xi.He@childrens.harvard.edu>; Youxing.Jiang@UTSouthwestern.edu <Youxing.Jiang@UTSouthwestern.edu>; lim@mskcc.org <lim@mskcc.org>; Xin Lu <xin.lu@ludwig.ox.ac.uk>; Lin Mei <lxm387@case.edu>; kangshen@stanford.edu <kangshen@stanford.edu>; wshou@iu.edu <wshou@iu.edu>; ltong@columbia.edu <ltong@columbia.edu>
> > **Cc:** Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
> > **Subject:** SHTech review reports
> >
> > Dear Committee members:
> >
> > Thank you all for the hard work with the evaluation of 41 PIs and the School of Life Sciences as a whole during our onsite visit. In the next week, I hope you can all send me the report for individual PIs based on the assignments, with Primary Reviewer responsible for finalizing the report after the Secondary Reviewer has gone through the draft (some of you have already sent me the reports, thank you very much!). I have also asked some of you to draft the portion

of the report on education and core facilities, and I will put together the assessments and recommendations for the general area of research. When I assemble the final draft of the report with all components, I will circulate to you for final editing before we submit to the leadership of SHTech.

Best regards, XF
<Report for SLST 2019-XL.docx>

From: Xiao-Fan Wang_Ph.D.
To: Xin Lu
Cc: xdfu@ucsd.edu; Guan_Kun-Liang; mhan@colorado.edu; Xi.He@childrens.harvard.edu; Youxing.Jiang@UTSouthwestern.edu; lim@mskcc.org; Lin Mei; kangshen@stanford.edu; wshou@iu.edu; ltong@columbia.edu
Subject: Re: SHTech review reports
Date: Friday, November 22, 2019 5:06:04 AM

Thanks! If anybody has further suggestions in this case, please let me know. Best regards, XF

> On Nov 21, 2019, at 10:58 AM, Xin Lu <xin.lu@ludwig.ox.ac.uk> wrote:
>
> Dear XiaoFang and all
> It was great to see you and I have a specific question to ask [redacted] Please see a copy of the write up I have for all people I am asinged as primary reviewer.
> Warm regards
> Xin
>
> ---
>
> **From:** Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
> **Sent:** 21 November 2019 14:44
> **To:** xdfu@ucsd.edu <xdfu@ucsd.edu>; Guan; Kun-Liang <kuguan@ucsd.edu>; mhan@colorado.edu <mhan@colorado.edu>; Xi.He@childrens.harvard.edu <Xi.He@childrens.harvard.edu>; Youxing.Jiang@UTSouthwestern.edu <Youxing.Jiang@UTSouthwestern.edu>; lim@mskcc.org <lim@mskcc.org>; Xin Lu <xin.lu@ludwig.ox.ac.uk>; Lin Mei <lxm387@case.edu>; kangshen@stanford.edu <kangshen@stanford.edu>; wshou@iu.edu <wshou@iu.edu>; ltong@columbia.edu <ltong@columbia.edu>
> **Cc:** Xiao-Fan Wang, Ph.D. <xiao.fan.wang@duke.edu>
> **Subject:** SHTech review reports
>
> Dear Committee members:
>
> Thank you all for the hard work with the evaluation of 41 PIs and the School of Life Sciences as a whole during our onsite visit. In the next week, I hope you can all send me the report for individual PIs based on the assignments, with Primary Reviewer respons ble for finalizing the report after the Secondary Reviewer has gone through the draft (some of you have already sent me the reports, thank you very much!). I have also asked some of you to draft the portion of the report on education and core facilities, and I will put together the assessments and recommendations for the general area of research. When I assemble the final draft of the report with all components, I will circulate to you for final editing before we submit to the leadership of SHTech.
>
> Best regards, XF
> <Report for SLST 2019-XL.docx>

From: Fu, Xiang-Dong
To: Xiao-Fan Wang, Ph.D.
Subject: Fwd: Firm support
Date: Thursday, November 21, 2019 6:20:58 AM
Attachments: [redacted]
General commonts on Core Facilities.doc

Hi Xiaofan,

The following letter has been sent to Xuetao.

Here I attach 4 files, 3 on PI's reviews [redacted] and 1 on the core facilities. Except for [redacted] the other two reviews have been proven by [redacted]

Xiang-Dong Fu,
Distinguished Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Email: xdfu@health.ucsd.edu

Begin forwarded message:

From: "Fu, Xiang-Dong" <xdfu@health.ucsd.edu>
Subject: Firm support
Date: November 21, 2019 at 6:02:27 AM PST
To: Xuetao Cao <caoxt@immunol.org>

Dear Xuetao,

I would like to write this letter to express my firm support to you at this challenging moment. I completely trust that you have the ability and wisdom to address the problem and bring it to full resolution. This unfortunate thing happened to me a few year ago, which led to the withdraw of a beautiful cover story from Cell, and more recently to my close friend Kunliang Guan. It also happened to a long list of outstanding scientists, including David Baltimore, Bob Weinberg, Francs Collins, etc. If you treat the problem thoroughly and objectively, as indicated by your well crafted response letter, the scientific community will be understanding and fully supportive.

You are a true leader in China as well as in the world. I have been a great admire

of your scientific achievements and your ability to lead. Every time when I was attending your lecture, I found that you are truly a visionary pioneer in immunology and biologic sciences in general. I have not contacted you since you became the president of Nankai, as I figure that you must be super busy. I heard that you normally go to the lab after a long day of consecutive meetings and spend time with your students way into the evening to discuss science and their progress. It is simply incredible. When the dust is finally settled, I would like to come to Nankai to give a seminar and pay you a personal salute.

I completely trust that you will be able to address all of the papers in question in a scientific manner and according to the highest moral standard. In the meantime, you may also institute some critical measures to prevent these things from happening again. As we all know, we become blinded after many rounds of revision for a given paper so that we can no longer catch some obvious mistakes, some of which might be introduced unintentionally. One way to deal with this problem is to have a trustful colleague who is not part of the authorship to go through the manuscript carefully before submission. It is also important to ask all students to organize lab notebooks to document original data and assemble all raw data for a given paper in preparation. It is also important to find a way to easy enormous amounts of pressure among young scientists. I am sure that all of these are in your agenda.

The bottom line is that there is a large scientific community behind you and all of us have complete confidence on you!

Best wishes,

Xiang-Dong

Xiang-Dong Fu,
Distinguished Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937 (office), [redacted] (cell)
Email: xdfu@health.ucsd.edu

From: 李秋凝
To: Youxing Jiang; Fu, Xiang-Dong; Guan, Kun-Liang; Min Han; He, Xi; lim@mskcc.org; Xin Lu; Kang Shen; Shou, Weinian; Liang Tong; Lin Mei; minglinewyork@gmail.com
Cc: Xiao-Fan Wang, Ph.D.; 江舸; 林海帆; 罗振革; 刘冀珑; 周宇
Subject: 答复: SLST International Review - Reception in the evening of Nov. 15
Date: Thursday, November 14, 2019 11:44:58 PM

Dear all Professors,

We had prepared both all the most updated review materials in an e-copy version with a Flash Disk as well as a printing version.
If you prefer the electronic version, please bring your laptop with you tomorrow. If you need a laptop, please just let me know, we will prepare it for you.

Thanks and best wishes,

Qiuning Li
Assistant Dean
School of Life Science and Technology
ShanghaiTech University

Phone +86-21-20685017
Website http://www.shanghaitech.edu.cn/

发件人: 李秋凝
发送时间: 2019年11月15日 15:32
收件人: 'Youxing Jiang'; 'Fu, Xiang-Dong'; 'Guan, Kun-Liang'; 'Min Han'; 'He, Xi'; 'lim@mskcc.org'; 'Xin Lu'; 'Kang Shen'; 'Shou, Weinian'; 'Liang Tong'; 'Lin Mei'; 'minglinewyork@gmail.com'
抄送: 'Xiao-Fan Wang, Ph.D.'; 江舸; 林海帆; 罗振革; 刘冀珑; 周宇
主题: SLST International Review - Reception in the evening of Nov. 15

Dear all Professors,

Welcome you all to visit ShanghaiTech. Attached please find the updated itinerary for our international review.

We will have the Dinner Banquet at 17:30 with the Leadership of ShanghaiTech & SLST.
Please gather at the Lobby of Aloft Hotel at 17:10, Qiuning Li will escort you to the VIP room of No. 2 Canteen of ShanghaiTech.

If it is convenient, would you please bring your boarding pass to me if your ticket was purchased by us or if you want to have your flight ticket been reimbursed by us.

Thanks and best wishes,

Qiuning Li
Assistant Dean
School of Life Science and Technology

ShanghaiTech University

Phone +86-21-20685017
Website http://www.shanghaitech.edu.cn/

From:	李秋凝
To:	Youxing Jiang; Fu, Xiang-Dong; Guan, Kun-Liang; Min Han; He, Xi; lim@mskcc.org; Xin Lu; Kang Shen; Shou, Weinian; Liang Tong; Lin Mei; minglinewyork@gmail.com
Cc:	Xiao-Fan Wang, Ph.D.; 江舸; 林海帆
Subject:	答复: SLST International Review - Progress Report of SLST
Date:	Monday, November 11, 2019 6:21:08 AM
Attachments:	Agenda of SLST International Review - Nov. 16-18 - 41PIs(revised).docx

Dear all Professors,

Attached is the latest agenda for the Five Year Review in SLST, ShanghaiTech.
If you have any further questions, please feel free to contact with me.

Thanks and best wishes,

Qiuning Li
Assistant Dean
School of Life Science and Technology
ShanghaiTech University

Phone +86-21-20685017
Website http://www.shanghaitech.edu.cn/

发件人: 李秋凝
发送时间: 2019年11月9日 17:04
收件人: 'Youxing Jiang'; 'Fu, Xiang-Dong'; 'Guan, Kun-Liang'; 'Min Han'; 'He, Xi'; 'lim@mskcc.org'; 'Xin Lu'; 'Kang Shen'; 'Shou, Weinian'; 'Liang Tong'; 'Lin Mei'; 'minglinewyork@gmail.com'
抄送: 'Xiao-Fan Wang, Ph.D.'; 江舸; 林海帆
主题: SLST International Review - Progress Report of SLST

Dear all Professors,

Would you please find the first version of our Progress Report of SLST as below?
I will also upload it to the Dropbox.

If you have any further questions, please do not hesitate to contact with me.

Thanks and best wishes,

Qiuning Li
Assistant Dean
School of Life Science and Technology
ShanghaiTech University

Phone +86-21-20685017
Website http://www.shanghaitech.edu.cn/

发件人: LIQIUNING [mailto:qiuning.li@icloud.com]

发送时间: 2019年11月9日 16:58
收件人: 李秋凝
主题:

December 9, 2019前可查看附件

From:	李秋凝
To:	Youxing Jiang; Fu, Xiang-Dong; Guan, Kun-Liang; Min Han; He, Xi; lim@mskcc.org; Xin Lu; Kang Shen; Shou, Weinian; Liang Tong; Lin Mei; minglinewyork@gmail.com
Cc:	Xiao-Fan Wang, Ph.D.; 江舸; 林海帆
Subject:	答复: SLST International Review - Progress Report of SLST
Date:	Sunday, November 10, 2019 1:44:38 AM

Dear all Professors,

We have booked the Aloft hotel for your stay in ShanghaiTech and the hotel is located at No. 550 Haike Road in Zhangjiang Hi-Tech Park, Shanghai.
The hotel is on the ShanghaiTech campus.

If you have any further questions, please feel free to contact with me.

Thanks and best wishes,

Qiuning Li
Assistant Dean
School of Life Science and Technology
ShanghaiTech University

Phone +86-21-20685017
Website http://www.shanghaitech.edu.cn/

发件人: 李秋凝
发送时间: 2019年11月9日 17:04
收件人: 'Youxing Jiang'; 'Fu, Xiang-Dong'; 'Guan, Kun-Liang'; 'Min Han'; 'He, Xi'; 'lim@mskcc.org'; 'Xin Lu'; 'Kang Shen'; 'Shou, Weinian'; 'Liang Tong'; 'Lin Mei'; 'minglinewyork@gmail.com'
抄送: 'Xiao-Fan Wang, Ph.D.'; 江舸; 林海帆
主题: SLST International Review - Progress Report of SLST

Dear all Professors,

Would you please find the first version of our Progress Report of SLST as below?
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If you have any further questions, please do not hesitate to contact with me.

Thanks and best wishes,

Qiuning Li
Assistant Dean
School of Life Science and Technology
ShanghaiTech University

Phone +86-21-20685017
Website http://www.shanghaitech.edu.cn/

发件人: LIQIUNING [mailto:qiuning.li@icloud.com]
发送时间: 2019年11月9日 16:58
收件人: 李秋凝
主题:

December 9, 2019前可查看附件

From:	李秋凝
To:	Youxing Jiang; Fu, Xiang-Dong; Guan, Kun-Liang; Min Han; He, Xi; lim@mskcc.org; Xin Lu; Kang Shen; Shou, Weinian; Liang Tong; Lin Mei
Cc:	Xiao-Fan Wang, Ph.D.; 江舸; 林海帆
Subject:	答复: SLST International Review - Faculty Members Files
Date:	Thursday, November 7, 2019 5:03:42 PM

Dear Prof. Jiang,

Do apologize that we are still working on the other part of our review materials. I will send them to you all ASAP.

Thanks and best wishes,

Qiuning Li
Assistant Dean
School of Life Science and Technology
ShanghaiTech University

Phone +86-21-20685017
Website http://www.shanghaitech.edu.cn/

发件人: Youxing Jiang [mailto:Youxing.Jiang@UTSouthwestern.edu]
发送时间: 2019年11月8日 4:03
收件人: 李秋凝; Fu, Xiang-Dong; Guan, Kun-Liang; Min Han; He, Xi; lim@mskcc.org; Xin Lu; Kang Shen; Shou, Weinian; Liang Tong; Lin Mei
抄送: Xiao-Fan Wang, Ph.D.; 江舸; 林海帆
主题: RE: SLST International Review - Faculty Members Files

How about information about Core facilities?

From: 李秋凝 [mailto:liqn@shanghaitech.edu.cn]
Sent: Thursday, November 07, 2019 10:23 AM
To: Fu, Xiang-Dong; Guan, Kun-Liang; Min Han; He, Xi; Youxing Jiang; lim@mskcc.org; Xin Lu; Kang Shen; Shou, Weinian; Liang Tong; Lin Mei
Cc: Xiao-Fan Wang, Ph.D.; 江舸; 林海帆
Subject: SLST International Review - Faculty Members Files

EXTERNAL MAIL

Dear All Professors,

Deeply apologize for the delay of our Review Materials.

1 Below, please find the link to download the 8 files of SLST FACULTY MEMBERS from **iCloud**.

2 Another email regarding the Invitation from **Dropbox** will be sent to you soon and you will be able to check the files from Dropbox too.

The files of our Faculty Member Part were organized by the sections based on the review arrangement as attached.

Besides those 7 Sections, we had also collected files from the faculty members who had joined SLST less than 3yr but longer than 1yr but will not give talks during the review.

I hope this can be downloaded both inside and outside of the Mainland.

If you have any further questions, please just let me know.

Thanks and best wishes,

Qiuning Li
Assistant Dean
School of Life Science and Technology
ShanghaiTech University

Phone +86-21-20685017
Website http://www.shanghaitech.edu.cn/

December 7, 2019前可查看附件

From:	李秋凝
To:	Fu, Xiang-Dong; Guan, Kun-Liang; Min Han; He, Xi; Youxing Jiang; lim@mskcc.org; Xin Lu; Kang Shen; Shou, Weinian; Liang Tong; Lin Mei
Cc:	Xiao-Fan Wang, Ph.D.; 江舸; 林海帆
Subject:	SLST International Review - Faculty Members Files
Date:	Thursday, November 7, 2019 8:35:59 AM
Attachments:	Agenda of SLST International Review - Nov. 16-18 - 41PIs(revised).docx

Dear All Professors,

Deeply apologize for the delay of our Review Materials.

1 Below, please find the link to download the 8 files of SLST FACULTY MEMBERS from **iCloud**.

2 Another email regarding the Invitation from **Dropbox** will be sent to you soon and you will be able to check the files from Dropbox too.

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I hope this can be downloaded both inside and outside of the Mainland.

If you have any further questions, please just let me know.

Thanks and best wishes,

Qiuning Li
Assistant Dean
School of Life Science and Technology
ShanghaiTech University

Phone +86-21-20685017
Website http://www.shanghaitech.edu.cn/

December 7, 2019前可查看附件

From:	Xiao-Fan Wang, Ph.D.
To:	Fu, Xiang-Dong; Guan, Kun-Liang; mhan@colorado.edu; Xi.He@childrens.harvard.edu; Youxing.Jiang@UTSouthwestern.edu; lim@mskcc.org; xin.lu@ludwig.ox.ac.uk; Lin Mei; kangshen@stanford.edu; wshou@iu.edu; ltong@columbia.edu
Cc:	Xiao-Fan Wang, Ph.D.
Subject:	Review of SHTech
Date:	Wednesday, October 30, 2019 1:53:27 PM
Attachments:	Review Com.SHTech.doc Shanghai Tech Review.docx Agenda of SLST International Review - Nov. 16-18 - 41PIs(revised).docx sample 1.doc Sample 2.doc Sample 3.doc Sample 4.doc

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Dear Committee:

We should receive soon the information to access the review materials and please try to see if you have any issues regarding those whom you have been assigned as Primary or Secondary reviewer (the assignments are attached). If you find the documents unsatisfying, please let me know ASAP so that I can inform the leaders of SHTech to make remedies.

I have attached four examples for the reviews of PIs in different categories in terms of their performances. Please write your reviews as the Primary Reviewer following the exact format as those examples as it would save me a lot of time to assemble the final report. As you all know, we will give a tentative score for each PI by the Primary and Secondary Reviewers at the beginning of our discussion but would modify it following the discussion and eventually recalibrate all the scores when we have the final discussion of all PIs.

Please also see the schedule for the meeting, and let me know if you have any specific questions.

Best regards and have a nice trip to SH! XF

From: 李秋凝
To: Fu, Xiang-Dong
Cc: Xiao-Fan Wang, Ph.D.
Subject: 答复: Internat onal rev ew of SLST ShanghaiTech
Date: Thursday, October 24, 2019 12:01:20 AM

Dear Prof. Fu

Thank you very much for your information. It is our great honor to have your participant to our international review.

Would you please keep your boarding pass for the reimbursement?

And we might be able to pay the reimbursement by cash since the university might not be able to do wire transfer to personal bank account abroad... Hope it is find with you.

I will book the Haike Aloft hotel located on ShanghaiTech campus for you check-in on Nov. 12 and check-out on Nov. 18.
And we will also book a car to pick you up at the airport on Nov. 12 and send you to the airport on Nov. 18.

If you need any further information please just let me know.

Thanks and best wishes

Qiuning Li
Assistant Dean
School of Life Science and Technology
ShanghaiTech University

Phone 86-21-20685017
Website http://www.shanghaitech.edu.cn/

发件人: Fu, Xiang-Dong [mailto:xdfu@ucsd.edu]
发送时间: 2019年10月24日 8:41
收件人: 李秋凝
抄送: Xiao-Fan Wang, Ph.D.
主题: Re: International review of SLST, ShanghaiTech

Dear Qiuning,

My sincere apology. I actually made a mistake in communicating with you. I thought the review was for SUStech in Shengzhen in the time, which I have declined. I have committed to the review session at ShanghaiTech from Nov. 15-18. Thanks, Xiaofan, to remind me.

Attached please find the following 3 files as you have requested:

1. My passport front page.

2. My flight ticket. Please note that I will couple this trip with another meeting at Tsinghua, and thus, I will only need the reimbursement for half of the ticket.
3. My US bank information. If possible, I would like to have the reimbursement transferred to my US bank.
Thanks. Sorry again for my mistake.

Fu

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

On Oct 22, 2019, at 11:23 AM, 李秋凝 <lion@shanghaitech.edu.cn> wrote:

Dear Dr. Fu

Do apologize for the miscommunication. Thank you so much for your information. Do hope you can come to visit ShanghaiTech in the near future!

Best wishes

Qiuning Li
Assistant Dean
School of Life Science and Technology
ShanghaiTech University

Phone 86-21-20685017
Website http://www.shanghaitech.edu.cn/

发件人: Fu Xiang-Dong [mailto:xdfu@ucsd.edu]
发送时间: 2019年10月21日 16:43
收件人: 李秋凝
主题: Re: International review of SLST, ShanghaiTech

Dear Qiuning,

Thanks for your email. As I indicated earlier, I will not be able to attend the review session because of travel conflict. I will participate in future activities.

Best regards,

Fu

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

> On Oct 20, 2019, at 6:21 PM, 李秋凝 <liqn@shanghaitech.edu.cn> wrote:
>
> Dear Prof. Fu
>
> This is Qiuning Li from School of Life Science and Technology, ShanghaiTech University.
> Thank you so very much for your time and effort to join the Review Committee of our 5 year international review committee.
>
> Our review will be on Nov. 16-18, 2019, and we will have a banquet in the evening of Nov. 15.
> We will help you to book a business class flight to Shanghai and we will host your stay in ShanghaiTech in our on-campus Aloft hotel.
>
> It would be really helpful if you can send us:
> 1. the photopage of your passport
> 2. your preferred flight with time
> 3. your debit bank account in China Mainland with the bank branch information, if you have
>
> Thanks and best wishes
>
> Qiuning Li
> Assistant Dean
> School of Life Science and Technology
> ShanghaiTech University
>
> Mobile 86-18621311027 (WeChat)
> Website http://www.shanghaitech.edu.cn/

From: Xiao-Fan Wang, Ph.D.
To: Fu, Xiang-Dong
Cc: 李秋凝
Subject: Re: International review of SLST, ShanghaiTech
Date: Wednesday, October 23, 2019 6:02:14 PM

Thanks for the clarification! XF

> On Oct 23, 2019, at 8:41 PM, Fu, Xiang-Dong <xdfu@ucsd.edu> wrote:
>
> Dear Qiuning,
>
> My sincere apology. I actually made a mistake in communicating with you. I thought the review was for SUStech in Shengzhen in the time, which I have declined. I have committed to the review session at ShanghaiTech from Nov. 15-18. Thanks, Xiaofan, to remind me.
>
> Attached please find the following 3 files as you have requested:
>
> 1. My passport front page.
> <Fu Passport Front page.JPG>
> 2. My flight ticket. Please note that I will couple this trip with another meeting at Tsinghua, and thus, I will only need the reimbursement for half of the ticket.
> 3. My US bank information. If possible, I would like to have the reimbursement transferred to my US bank.
> Thanks. Sorry again for my mistake.
>
> Fu
>
> Xiang-Dong Fu, Professor
> Dept. of Cellular and Molecular Medicine
> University of California, San Diego
> George Palade Laboratories
> 9500 Gilman Drive, Room 217
> La Jolla, CA 92093-0651
>
> Phone: 858-534-4937
> Fax: 858-822-6692
> Email: xdfu@ucsd.edu
>
> > On Oct 22, 2019, at 11:23 AM, 李秋凝 <liqn@shanghaitech.edu.cn> wrote:
> >
> > Dear Dr. Fu,
> >
> > Do apologize for the miscommunication. Thank you so much for your information. Do hope you can come to visit ShanghaiTech in the near future!

Best wishes,

Qiuning Li
Assistant Dean
School of Life Science and Technology
ShanghaiTech University

Phone +86-21-20685017
Website http://www.shanghaitech.edu.cn/

发件人: Fu, Xiang-Dong [mailto:xdfu@ucsd.edu]
发送时间: 2019年10月21日 16:43
收件人: 李秋凝
主题: Re: International review of SLST, ShanghaiTech

Dear Qiuning,

Thanks for your email. As I indicated earlier, I will not be able to attend the review session because of travel conflict. I will participate in future activities.

Best regards,

Fu

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

> On Oct 20, 2019, at 6:21 PM, 李秋凝 <liqn@shanghaitech.edu.cn> wrote:
>
> Dear Prof. Fu,
>
> This is Qiuning Li from School of Life Science and Technology, ShanghaiTech University.
> Thank you so very much for your time and effort to join the Review Committee of our 5 year international review committee.

Our review will be on Nov. 16-18, 2019, and we will have a banquet in the evening of Nov. 15.
We will help you to book a business class flight to Shanghai and we will host your stay in ShanghaiTech in our on-campus Aloft hotel.

It would be really helpful if you can send us:
1, the photopage of your passport
2, your preferred flight with time
3, your debit bank account in China Mainland with the bank branch information, if you have

Thanks and best wishes,

Qiuning Li
Assistant Dean
School of Life Science and Technology
ShanghaiTech University

Mobile +86-18621311027 (WeChat)
Website http://www.shanghaitech.edu.cn/

<Fu trip to China 117-11182019.pdf><Fu-US Bank account.doc>

From:	Fu, Xiang-Dong
To:	李秋凝
Cc:	Xiao-Fan Wang, Ph.D.
Subject:	Re: International review of SLST, ShanghaiTech
Date:	Wednesday, October 23, 2019 5:41:14 PM
Attachments:	ATT00001.htm Fu trip to China 117-11182019.pdf ATT00002.htm Fu-US Bank account.doc ATT00003.htm

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Dear Qiuning,

My sincere apology. I actually made a mistake in communicating with you. I thought the review was for SUStech in Shengzhen in the time, which I have declined. I have committed to the review session at ShanghaiTech from Nov. 15-18. Thanks, Xiaofan, to remind me.

Attached please find the following 3 files as you have requested:

1. My passport front page.

From: Xiao-Fan Wang, Ph.D.
To: Fu, Xiang-Dong
Subject: Fwd: International review of SLST, ShanghaiTech
Date: Wednesday, October 23, 2019 8:08:00 AM
Attachments: 国际评估专家来沪行程一览表.xlsx

I did not remember that you had decided not to attend the review which would be right after our meeting at Zheda that you just confirmed to attend. Please confirm either way as I may need to modify the assignments if you cannot go. Thanks, XF

Begin forwarded message:

From: 李秋凝 <liqn@shanghaitech.edu.cn>
Subject: 转发**: International review of SLST, ShanghaiTech**
Date: October 23, 2019 at 4:59:53 AM EDT
To: "Xiao-Fan Wang, Ph.D." <xiao.fan.wang@duke.edu>

Dear Prof. Wang,

I have received the reply from Prof. Xiangdong Fu as below. I am not quite sure whether you have got the indication, so I just want to give you an update on it. And I think other review committee members' trip arrangements are ready as attached.

If you need any further assistance, please just let me know.

Thanks and best wishes,

Qiuning Li
Assistant Dean
School of Life Science and Technology
ShanghaiTech University

Phone +86-21-20685017
Website http://www.shanghaitech.edu.cn/

发件人: Fu, Xiang-Dong [mailto:xdfu@ucsd.edu]
发送时间: 2019年10月21日 16:43
收件人: 李秋凝
主题: Re: International review of SLST, ShanghaiTech

Dear Qiuning,

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Best regards,

Fu

Xiang-Dong Fu, Professor
Dept. of Cellular and Molecular Medicine
University of California, San Diego
George Palade Laboratories
9500 Gilman Drive, Room 217
La Jolla, CA 92093-0651

Phone: 858-534-4937
Fax: 858-822-6692
Email: xdfu@ucsd.edu

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2, your preferred flight with time
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Thanks and best wishes,

Qiuning Li
Assistant Dean
School of Life Science and Technology
ShanghaiTech University

Mobile +86-18621311027 (WeChat)
Website http://www.shanghaitech.edu.cn/

From:	Xiao-Fan Wang, Ph.D.
To:	Min Han; Chen, Eugene; Fu, Xiang-Dong; Guan, Kun-Liang; Guo-Min.Li@UTSouthwestern.edu; lim@mskcc.org; Shou, Weinian
Subject:	Re: SIBS SAB and SHTech review
Date:	Monday, July 1, 2019 2:04:12 PM

Hi Everyone:

After discussion with Dr. Lin Li, we will have our SAB meeting for the newly named Institute of Nutrition and Health on Nov. 13. Some of us will need to go to Zheda in the afternoon as in the past for its SAB on Nov. 14. Taking this opportunity, I want to invite all of you to join a committee that I am organizing to evaluate 56 PIs in the School of Life Sciences of Shanghai University of Science and Technology, as invited by Pres. Mianheng Jiang and Dean Haifan Lin. The review will last three days, starting in the morning of Nov. 16 (some of us will return to SH from HZ the day before) and completing by the end of Nov. 18. Around a third of those PIs have been in their positions for less than three years, but Haifan still wanted us to evaluate them for their potential and if their program is in the right direction. I will have to invite additional members to cover neuroscience and structural biology.

Please let me know ASAP if you can participate in both or either of the meetings.

Best regards, XF

From:	Xiao-Fan Wang, Ph.D.
To:	dingsw@ucr.edu; Xinnian Dong, Ph.D.; Fu, Xiang-Dong; Guan, Kun-Liang; haobo.jiang@okstate.edu; sluan@berkeley.edu; maj@rib.okayama-u.ac.jp; SongQ@missouri.edu; dbsyuhao@nus.edu.sg; zhao5@illinois.edu; Zhao, Yunde
Cc:	Xiao-Fan Wang, Ph.D.
Subject:	Draft of Final Report
Date:	Friday, January 4, 2019 8:26:21 AM
Attachments:	IPPE.Final report.2018.doc

Hi Everyone:

Thank you all so much for the hard work with the review and completion of reports for individual PIs. Please go through the draft of the final report, particularly those that you are responsible as Primary and Secondary Reviewer, and make edits (with tracking) wherever deemed necessary. Please send back to me by Noon of this Sunday, EST, Jan. 6, so that I can finalize it and send to leaders of SIPPE before they start to work on Monday.

Best regards and Happy 2019! XF