

Manuscript Number (if applicable):

NCOMMS-20-30761B

Journal Name (if applicable):

Nature Communications

Manuscript Title:

AKT3-mediated IWS1 phosphorylation promotes the proliferation of EGFR-mutant lung adenocarcinomas through cell cycle-regulated U2AF2 RNA splicing

Author Name:

Philip N Tsichlis

Retraction Statement Text (to be added by editor)

The authors are retracting this Article as an independent researcher brought to their attention the fact that his bioinformatic analyses of multiple data sets could not confirm the alternative splicing of the U2AF2 exon 2. On further investigation, the authors observed that the proposed splicing mechanism could not give rise to a functional U2AF2 protein. In addition, the authors identified errors in the electropherogram in Figure 1g, raising questions on its integrity. In light of this information, the authors have no confidence in the key findings of the paper, and therefore, wish to retract it.

I agree with the retraction and the wording above.*I do not agree with this retraction (please give reasons for dissent)*

Print Name: Philip N. Tsichlis

Signature: _____ Date: 1/31/2022

Nature Research reserve complete independence and specifically, the right to proceed to a retraction without consent of one or all of the authors.

From: Tsichlis, Philip
Sent: Monday, February 7, 2022 7:16 PM
To: 'Stephanie Koo' <stephanie.koo.1@springernature.com>
Cc: Garfinkel, SusanJ. (OSU) <garfinkel.18@osu.edu>
Subject: RE: comment on your Nature Communications manuscript

Dear Stephanie

Thank you for your answer to my earlier Email. The fact is that the two statements are not different, except the statement I wrote is more specific, which I believe should be what we want. The truth is that I would like to retract this paper because what it says is wrong and I am very embarrassed by it. At the same time, I would like to describe the events that led to the retraction, as clearly as it can be. First, I want to be transparent by pointing out that indeed the process was initiated with the Email I received from an independent investigator. However, the description of the events, as they happened after this Email, should also be truthful and clear, with no ambiguities, so that anybody who reads it understands what happened. This is important to me and all the other people who had the misfortune to be involved in this work. Please, find in the attachment the statement you wrote with my comments, the statement I had written, and a new statement I wrote now, which is even more specific than my earlier statement. Unless you think that what I suggest is factually incorrect, I am not sure why it cannot be used.

Thank you and I do apologize for my persistence on this.
Philip

From: Stephanie Koo <stephanie.koo.1@springernature.com>
Sent: Friday, February 4, 2022 1:09 PM
To: Tsichlis, Philip <Philip.Tsichlis@osumc.edu>
Cc: Garfinkel, SusanJ. (OSU) <garfinkel.18@osu.edu>
Subject: RE: comment on your Nature Communications manuscript

External Email: CAUTION

Dear Dr Tsichlis,

Many thanks for sending us the files. I have discussed the edited statement with my editorial colleagues and we felt that the initial retraction text is more appropriate. Could you please reach out to the co-authors of the paper for their signatures with this form? Thank you.

Best wishes,
Stephanie

Stephanie Koo, PhD
Senior Editor
Nature Communications

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Twitter: @naturecomms

From: Tsichlis, Philip <Philip.Tsichlis@osumc.edu>
Sent: 31 January 2022 17:14
To: Stephanie Koo <stephanie.koo.1@springernature.com>; Garfinkel, SusanJ. (OSU) <garfinkel.18@osu.edu>
Subject: RE: comment on your Nature Communications manuscript

[External - Use Caution]

Dear Stephanie,
Thank you. I filled the form with the edited statement and I am sending you two copies, one with and one without my signature. I sent the unsigned copy, in case you plan to send this statement for signature to the co-authors of the paper.
Thank you,
Philip

From: Stephanie Koo <stephanie.koo.1@springernature.com>
Sent: Monday, January 31, 2022 9:45 AM
To: Garfinkel, SusanJ. (OSU) <garfinkel.18@osu.edu>; Tsichlis, Philip <Philip.Tsichlis@osumc.edu>
Subject: RE: comment on your Nature Communications manuscript

External Email: CAUTION

Dear Philip and Susan,

Many thanks for suggesting the edits. I am wondering if you can input these changes in the form we sent you and please sign on it so I can discuss them with my other editorial colleagues.

Best wishes,
Stephanie

Stephanie Koo, PhD
Senior Editor
Nature Communications

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Twitter: @naturecomms

From: Garfinkel, Susan J. <garfinkel.18@osu.edu>
Sent: 27 January 2022 13:31
To: Tsichlis, Philip <Philip.Tsichlis@osumc.edu>; Stephanie Koo <stephanie.koo.1@springernature.com>
Subject: RE: comment on your Nature Communications manuscript

[External - Use Caution]

Thank you both for sharing your correspondence with our office. I have one small suggestion to Dr. Tsichlis' proposed statement for the last sentence, with the reasoning being that "errors" has a specific meaning that we may not want to convey.

In light of ~~these errors~~ **this information**, the authors have no confidence in the key findings of the paper, and therefore, wish to retract the Article.

Thanks,
Susan

From: Tsichlis, Philip <Philip.Tsichlis@osumc.edu>
Sent: Wednesday, January 26, 2022 7:34 PM
To: 'Stephanie Koo' <stephanie.koo.1@springernature.com>
Cc: Garfinkel, Susan J. <garfinkel.18@osu.edu>
Subject: RE: comment on your Nature Communications manuscript

Dear Stephanie

Thank you for your Email. This time I should apologize for my late response. What you wrote for the retraction is fine with me, but I would like to make it a little more specific. I am sending you in the attachment my edits of the statement you wrote. If you agree, we can proceed with the next steps.

Thank you,
Philip

From: Stephanie Koo <stephanie.koo.1@springernature.com>
Sent: Tuesday, January 18, 2022 8:25 AM
To: Tsichlis, Philip <Philip.Tsichlis@osumc.edu>
Cc: Garfinkel, SusanJ. (OSU) <garfinkel.18@osu.edu>
Subject: RE: comment on your Nature Communications manuscript

External Email: CAUTION

Dear Philip,

Many apologies for the extreme delay as it has been a very busy period for us. Please refer to the attached pdf and let us know if you approve the retraction text. You can send back the signed copy to me and we will then proceed with the necessary for the paper to be retracted.

Best wishes,
Stephanie

Stephanie Koo, PhD
Senior Editor
Nature Communications

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From: Tsichlis, Philip <Philip.Tsichlis@osumc.edu>
Sent: 11 January 2022 17:40
To: Stephanie Koo <stephanie.koo.1@springernature.com>
Cc: Garfinkel, SusanJ. (OSU) <garfinkel.18@osu.edu>
Subject: RE: comment on your Nature Communications manuscript

[External - Use Caution]

Dear Stephanie,

I am writing to see what is the status of the retraction of the Laliotis paper we published in Nature Communications. Please, note that the Laliotis paper in Communications Biology was retracted about a month ago.

Thank you,

Philip

From: Stephanie Koo <stephanie.koo.1@springernature.com>
Sent: Wednesday, December 8, 2021 6:26 AM
To: Tsichlis, Philip <Philip.Tsichlis@osumc.edu>
Cc: Garfinkel, SusanJ. (OSU) <garfinkel.18@osu.edu>
Subject: RE: comment on your Nature Communications manuscript

CAUTION: External Email

Dear Philip,

Many thanks for your email. I had already notified my Chief Editor regarding the retraction of this paper and it is pending approval. Please bear with us for taking some time to as this is a very busy period for us. I will get back to you as soon I can. Thank you for being patient with us.

Best wishes,
Stephanie

Stephanie Koo, PhD
Senior Editor
Nature Communications

Nature Research
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www.nature.com/naturecommunications
Twitter: @naturecomms

From: Tsichlis, Philip <Philip.Tsichlis@osumc.edu>
Sent: 06 December 2021 23:56
To: Stephanie Koo <stephanie.koo.1@springernature.com>
Cc: Susan, Garfinkel (OSU) <garfinkel.18@osu.edu>
Subject: RE: comment on your Nature Communications manuscript

[External - Use Caution]

Dear Stephanie

I am contacting you regarding the retraction of the Nature Communications paper by Laliotis et al. I know that Communications Biology is progressing with the retraction, but I have not heard from you

yet. I was wondering if there is anything else you may need.
Thank you,
Philip

From: Stephanie Koo <stephanie.koo.1@springernature.com>
Sent: Tuesday, November 23, 2021 3:02 PM
To: Tsichlis, Philip <Philip.Tsichlis@osumc.edu>
Subject: RE: comment on your Nature Communications manuscript

CAUTION: External Email

Dear Dr Tsichlis,

As you mentioned earlier that you are retracting two papers. I am wondering if it is the paper that you have recently published in Communications Biology and if you have already contacted their Editorial Office regarding your request for paper retraction? I am asking this as we may liaise with our sister journal on the retraction process.

Best wishes,
Stephanie

Stephanie Koo, PhD
Senior Editor
Nature Communications

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www.nature.com/naturecommunications
Twitter: @naturecomms

From: Tsichlis, Philip <Philip.Tsichlis@osumc.edu>
Sent: 22 November 2021 13:55
To: Stephanie Koo <stephanie.koo.1@springernature.com>
Subject: RE: comment on your Nature Communications manuscript

[External - Use Caution]

Thank you Stephanie

This has been a nightmare and I blame myself for not having detected it earlier. However, we cannot

go back. I hope that we will retract this paper as soon as possible. In my letter of retraction I can mention that we were alerted to the problem by Dr Maucuer and that once alerted, we identified the problem and we retracted it. Hopefully, any additional publicity will be avoided, because it does not really serve a purpose.

Thank you for your understanding.

Philip

From: Stephanie Koo <stephanie.koo.1@springernature.com>

Sent: Monday, November 22, 2021 6:33 AM

To: Tsichlis, Philip <Philip.Tsichlis@osumc.edu>

Subject: RE: comment on your Nature Communications manuscript

CAUTION: External Email

Dear Dr Tsichlis,

Many thanks for your emails. I am sorry to hear about the unfortunate incident involved in your published paper. Please bear with us while I discuss these matters with my colleagues and my Chief Editor. I will respond to you as soon as I can.

Best wishes,
Stephanie

Stephanie Koo, PhD
Senior Editor
Nature Communications

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www.nature.com/naturecommunications
Twitter: @naturecomms

From: Tsichlis, Philip <Philip.Tsichlis@osumc.edu>

Sent: 21 November 2021 22:05

To: Stephanie Koo <stephanie.koo.1@springernature.com>

Subject: FW: comment on your Nature Communications manuscript

[External - Use Caution]

Dear Stephanie,

This is my initial response to Dr Maucuer, prior to uncovering the evidence of data manipulation, which I sent to you. At this point I do not think that there is a “matter arising”, because we investigated the problem once the suggestion was made, we identified the evidence of manipulation, which we missed earlier unfortunately, and the papers have been retracted. However, I understand that this is your call.

Thank you,
Philip

From: alexandre.maucuer@inserm.fr <alexandre.maucuer@inserm.fr>

Sent: Monday, November 15, 2021 7:17 AM

To: Tsihchlis, Philip <Philip.Tsihchlis@osumc.edu>

Cc: glalot1@jhmi.edu; Serhii Pankivskyi <s.pankivskyi@gmail.com>

Subject: RE: comment on your Nature Communications manuscript

CAUTION: External Email

Dear Dr Tsihchlis,

Thank you very much for your quick response. Indeed, we would be grateful if you could share the comments of your bioinformaticians when they will have compared your and our analyzes. While waiting to submit, we hope you will get new material for a more detailed response to our comment.

Very sincerely,

Alexandre Maucuer

Le 2021-11-14 01:13, Tsihchlis, Philip a écrit :

Dear Dr Maucuer

Thank you for your Email. I understand that your bioinformatics analysis of both our RNASeq data and other publicly available datasets did not detect the alternative RNA splicing of the U2AF2 exon2. To answer your comment, I will have to discuss this issue with our bioinformaticians. However, in addition to the bioinformatics analysis, Dr Lalot detected the alternative splicing of exon 2 in numerous wet lab experiments, which cannot be ignored. At this point, I need to do two things. First, as I said, I will have to discuss with our bioinformaticians the nature of their analysis and how it relates to your analysis. In addition, I will have to repeat the experiment on the U2AF2 exon 2 splicing myself and I will have another person in the lab to repeat it as well. I believe that the repeat of the experiment is the most important and the most definitive way to answer your comment. Since I will have to repeat everything from scratch, this will take approximately two weeks. Once I repeat it, I will send you all the experimental details, so that you can repeat it as well. I hope that you

can wait until all this is done before you submit your paper.

Thank you,
Philip Tsichlis

From: alexandre.maucuer@inserm.fr <alexandre.maucuer@inserm.fr>

Sent: Saturday, November 13, 2021 12:09 PM

To: glalot1@jhmi.edu; Tsichlis, Philip <Philip.Tsichlis@osumc.edu>

Cc: Serhii Pankivskyi <s.pankivskyi@gmail.com>

Subject: comment on your Nature Communications manuscript

CAUTION: External Email

Dear Drs Lalotis and Tsichlis,

We read with interest your recent publication in Nature Communications entitled "AKT3-mediated IWS1 phosphorylation promotes the proliferation of EGFR-mutant lung adenocarcinomas through cell cycle-regulated U2AF2 RNA splicing."

We were very interested by your results but still surprised that U2AF2 would experience alternative splicing leading to the expression of an isoform lacking its RS domain. We tried to detect this isoform by analysing a variety of RNAseq data but could not detect the skipping of U2AF2 exon 2. We believe that our results should lead to some revision of the model you propose concerning the action of IWS1 on splicing and cell proliferation. In order to provide this new information to the research community we propose to publish our results as a "matters arising" manuscript in Nature communications and we are asked to first ask you for an informal reply. You will find our manuscript attached.

Looking forward to hearing from you.

Very sincerely

Alexandre Maucuer

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The “Nature Communications” suggested statement

The authors are retracting this Article as an independent researcher brought to their attention data irregularities in the reporting of U2AF2 exon 2 alternative splicing. On further investigation, the authors cannot confirm that the proposed splicing mechanism will give rise to a functional U2AF2 protein. The authors cannot confirm the integrity of the electropherogram in Figure 1g. In light of these errors, the authors have no confidence in the key findings of the paper, and therefore, wish to retract the Article.

The Edited statement

The authors are retracting this Article as an independent researcher brought to their attention the fact that his bioinformatic analyses of multiple data sets could not confirm the alternative splicing of the U2AF2 exon 2. On further investigation, the authors observed that the proposed splicing mechanism could not give rise to a functional U2AF2 protein. In addition, the authors identified errors in the electropherogram in Figure 1g, raising questions on its integrity. In light of these errors, the authors have no confidence in the key findings of the paper, and therefore, wish to retract it.

The Edited statement # 2

The authors are retracting this Article as an independent researcher brought to their attention the fact that his bioinformatic analyses of multiple data sets could not confirm the alternative splicing of the U2AF2 exon 2. On further investigation, the authors observed that the proposed splicing mechanism could not give rise to a functional U2AF2 protein. In addition, the authors confirmed that the electropherogram in Figure 1g, was generated by artificial splicing of two separate electropherograms. In light of this information, the authors have no confidence in the key findings of the paper, and therefore, wish to retract it.

From: Brooke La Flamme <brooke.laflamme@us.nature.com>
Sent: Wednesday, November 24, 2021 7:28 AM
To: Garfinkel, Susan J. <garfinkel.18@osu.edu>
Cc: Tsichlis, Philip <Philip.Tsichlis@osumc.edu>; Pek Jun Wei (Bai Junwei) <junwei@tll.org.sg>; Eve Rogers <eve.rogers.1@nature.com>; Carruthers, Bridget <carruthers.39@osu.edu>
Subject: Re: Retraction

CAUTION: External Email

Hi Susan,

Thanks so much for letting me know. I will reach out today to see if I can get a response. Do you want to be copied into the email?

Thanks,
Brooke

Brooke LaFlamme, PhD
Chief Editor
Communications Biology

On Nov 24, 2021, at 7:23 AM, Garfinkel, Susan J. <garfinkel.18@osu.edu> wrote:

[External - Use Caution]

One more thing: we were told his last day at JHU is today.

From: Garfinkel, Susan J.
Sent: Wednesday, November 24, 2021 7:21 AM
To: 'Brooke La Flamme' <brooke.laflamme@us.nature.com>; Tsichlis, Philip <Philip.Tsichlis@osumc.edu>
Cc: Pek Jun Wei (Bai Junwei) <junwei@tll.org.sg>; Eve Rogers <eve.rogers.1@nature.com>; Carruthers, Bridget <carruthers.39@osu.edu>
Subject: RE: Retraction

Hello Brooke,

The current email we have for the 1st author, who is at Johns Hopkins, is glaliot1@jhmi.edu. However, we have been told he has resigned from his position and will be going back to Greece. We tried to contact him to get a forwarding email, but he has not responded to us.

Thanks,
Susan

From: Brooke La Flamme <brooke.laflamme@us.nature.com>
Sent: Tuesday, November 23, 2021 11:32 AM
To: Tsichlis, Philip <Philip.Tsichlis@osumc.edu>
Cc: Pek Jun Wei (Bai Junwei) <junwei@tll.org.sg>; Eve Rogers <eve.rogers.1@nature.com>; Garfinkel, Susan J. <garfinkel.18@osu.edu>; Carruthers, Bridget <carruthers.39@osu.edu>
Subject: RE: Retraction

Dear Philip,

Thanks so much for contacting your co-authors. I can confirm that we are withdrawing the paper currently under review.

Susan and Bridget – Are you able to contact the first author, or do you have an email address that I could contact him at?

Best,
Brooke

--

Brooke LaFlamme, PhD

(she/her/hers)

Chief Editor, *Communications Biology*

From: Tsichlis, Philip <Philip.Tsichlis@osumc.edu>
Sent: Tuesday, November 23, 2021 10:10 AM
To: Brooke La Flamme <brooke.laflamme@us.nature.com>
Cc: Pek Jun Wei (Bai Junwei) <junwei@tll.org.sg>; Eve Rogers <eve.rogers.1@nature.com>; Garfinkel, Susan J. <garfinkel.18@osu.edu>; 'Carruthers, Bridget' <carruthers.39@osu.edu>
Subject: RE: Retraction

[External - Use Caution]

Thank you Brooke,

The note sounds OK to me. In my earlier Email to Dr Pek I indicated that we have another paper under review on a related topic, also in "Communications Biology", and I would like to withdraw it from the review process. I have copied in this Email the OSU ORI officers, Susan Garfinkel and Bridget Caruthers, to obtain permission to contact the coauthors of this and another manuscript we are retracting from "Nature Communications". Also, I am not in contact with the first author, who was the one who did essentially all the work in these papers. I assume that if we need to contact him, he will have to be contacted through official channels and not by me.

Thank you,
Philip

From: Brooke La Flamme <brooke.laflamme@us.nature.com>
Sent: Tuesday, November 23, 2021 9:29 AM
To: Tsichlis, Philip <Philip.Tsichlis@osumc.edu>
Cc: Pek Jun Wei (Bai Junwei) <junwei@tll.org.sg>; Eve Rogers <eve.rogers.1@nature.com>
Subject: RE: Retraction

CAUTION: External Email

Dear Dr. Tsichlis,

Thank you for alerting us to this data integrity issue and for requesting to retract the paper. Before I can proceed, I will need a statement from each author as to whether or not they agree with the retraction. This can be done in the form of forwarded emails.

I've drafted some preliminary text for the retraction note. Can you please check it and let me know if you would like to make any changes?

The authors are retracting this Article as irregularities were found in the data that indicate the splicing of the U2AF2 exon 2 does not occur as reported in the Article. The irregularities call into question the conclusions and undermine our full confidence in the integrity of the study. The authors therefore wish to retract the Article.

[Pending agreements] All the authors agree with the retraction.

Many thanks,
Brooke

--

Brooke LaFlamme, PhD
(she/her/hers)
Chief Editor, *Communications Biology*

From: Pek Jun Wei (Bai Junwei) <junwei@tll.org.sg>
Sent: Friday, November 19, 2021 10:24 PM
To: Eve Rogers <eve.rogers.1@nature.com>; Brooke La Flamme
<brooke.laflamme@us.nature.com>
Cc: Pek Jun Wei (Bai Junwei) <junwei@tll.org.sg>
Subject: Fw: Retraction

[External - Use Caution]

Dear Eve and Brooke,

I received an email from Prof. Tschlis below requesting to retract a paper he recently published in Communications Biology. As you were the internal editors for this manuscript, I am forwarding to you to seek advice.

Note that he has requested to withdraw a manuscript currently under review in Communications Biology too. Appreciate your follow-up actions.

Thank you.

Kind regards,

Jun Wei

From: Tschlis, Philip <Philip.Tschlis@osumc.edu>
Sent: Saturday, November 20, 2021 11:12 AM
To: Pek Jun Wei (Bai Junwei) <junwei@tll.org.sg>
Cc: Garfinkel, Susan J. <garfinkel.18@osu.edu>; Carruthers, Bridget
<carruthers.39@osu.edu>
Subject: Retraction

Dear Jun Wei

It is very difficult for me to write this letter. However, I am obliged to report that we have confirmed several irregularities in the data on the alternative RNA splicing of U2AF2, which is a central point in the proposed mechanism of RNA transport we reported in in our recent paper in "Communications Biology" (Phosphor-IWS1-dependent U2AF2 splicing regulates trafficking of CAR-E-positive intronless gene mRNAs and sensitivity to viral infection).

The reason we went back to investigate this issue was an Email from Dr Alexandre Maucuer in INSERM, who indicated that he could not find evidence for the alternative splicing of the U2AF2 exon 2 in several bioinformatics analyses he performed. In the process of addressing his comment, we (me and other people in the lab) realized that the alternative RNA splicing of U2AF2 could not give a functional U2AF2 protein and therefore it could not be a physiological mechanism of U2AF2 regulation. In addition, we carefully scrutinized figure 1g of the earlier paper we had published in "Nature Communications" and we discovered evidence of data manipulation (see attachment). I was planning to repeat the U2AF2 alternative splicing experiment myself, but given this evidence, I decided that it will not be necessary to do that. The problem is that the

alternative splicing of the U2AF2 exon 2 is repeated over and over again, and it is a central piece of the model we proposed in the “Communications Biology” paper. How these experiments were done to reproduce an event which cannot happen, is unknown. Based on this, we need to retract the paper effective immediately. I should point out here that some of the experiments, including the viral infection experiments were done in the laboratory of Dr Yount [REDACTED] and there is no reason to doubt that they were done correctly. However, they were done using cells which were provided by a post-doc in my lab and the exact nature of these cells is uncertain. It is also possible that IWS1 phosphorylation renders the cells more resistant to viral infection. However, even if this happens, it will have to be by a mechanism that is different than the mechanism we proposed. Please, note that I have informed the Office of Research Compliance at my Institution about the pending retraction and you may reach out to the Research Integrity Officers, if necessary, Susan Garfinkel at Garfinkel.18@osu.edu or Bridget Carruthers at Carruthers.39@osu.edu. I sincerely apologize for the time and effort you spent reviewing this paper. I am really embarrassed by this, which is definitely a new experience for me. I have contacted most of the coauthors of the paper regarding this problem and the pending retraction, but there are some more, I need to contact. Please, let me know if there is a specific format for a retraction letter and I will write it and send it to you. In addition to this paper, we have another paper on a related topic, which is currently under review in “Communications Biology”. The paper is titled “Overexpression of the SETD2 WW domain inhibits the phosphor-IWS1/SETD2 interaction and the oncogenic AKT/IWS1 RNA splicing program” and the first author is Dr George Laliotis. Given the problem with the previous papers, we would like to withdraw this paper from the review process effective immediately. We will consider resubmitting it, if the results in this paper are independently confirmed and the mechanism is determined.

My sincere apologies

Philip

Philip N. Tschlis MD
Professor and Chair, Cancer Biology and Genetics
The Ohio State University, Wexner Medical Center
Co-Leader, Cancer Biology Program
OSU Comprehensive Cancer Center
982 Biomedical Research Tower,
460 W. 12th Ave. Columbus, OH 43210

TEL : 614-293-6326

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From: Tsichlis, Philip

Sent: Tuesday, November 23, 2021 11:10 AM

To: glaliot1@jhmi.edu; [REDACTED] Chavdoula, Evangelia <Evangelia.Chavdoula@osumc.edu>; [REDACTED] La Ferlita, Alessandro <Alessandro.LaFerlita@osumc.edu>; Anastas, Vollter <Vollter.Anastas@osumc.edu>; 'Christos Tsatsanis' <tsatsani@uoc.gr>; Beane, Joal <Joal.Beane@osumc.edu>; Sehgal, Lalit <Lalit.Sehgal@osumc.edu>; Coppola, Vincenzo <Vincenzo.Coppola@osumc.edu>; Yount, Jacob <Jacob.Yount@osumc.edu>; 'arturo.orlacchio@hotmail.it' <arturo.orlacchio@hotmail.it>

Cc: 'brooke.laflamme@us.nature.com' <brooke.laflamme@us.nature.com>; 'Garfinkel, Susan J.' <garfinkel.18@osu.edu>; Carruthers, Bridget <carruthers.39@osu.edu>

Subject: FW: Retraction

Dear all,

It is unfortunate, but we have discovered issues with the data in our paper in “Communications Biology” and we have to retract it. I am sending to you the Email from the journal with the retraction statement they suggested. Please, give your agreement for the retraction directly to the journal (Brooke La Flamme-copied in this Email), and cc me. Also, please, let me know if you have any questions.

Thank you and I apologize for this,
Philip

From: Brooke La Flamme <brooke.laflamme@us.nature.com>

Sent: Tuesday, November 23, 2021 9:29 AM

To: Tsichlis, Philip <Philip.Tsichlis@osumc.edu>

Cc: Pek Jun Wei (Bai Junwei) <junwei@tll.org.sg>; Eve Rogers <eve.rogers.1@nature.com>

Subject: RE: Retraction

CAUTION: External Email

Dear Dr. Tsichlis,

Thank you for alerting us to this data integrity issue and for requesting to retract the paper. Before I can proceed, I will need a statement from each author as to whether or not they agree with the retraction. This can be done in the form of forwarded emails.

I've drafted some preliminary text for the retraction note. Can you please check it and let me know if you would like to make any changes?

The authors are retracting this Article as irregularities were found in the data that indicate the splicing of the U2AF2 exon 2 does not occur as reported in the Article. The irregularities call into question the conclusions and undermine our full confidence in the integrity of the study. The authors therefore wish to retract the Article.

[Pending agreements] All the authors agree with the retraction.

Many thanks,
Brooke

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Brooke LaFlamme, PhD

(she/her/hers)

Chief Editor, *Communications Biology*

From: Pek Jun Wei (Bai Junwei) <junwei@tll.org.sg>

Sent: Friday, November 19, 2021 10:24 PM

To: Eve Rogers <eve.rogers.1@nature.com>; Brooke La Flamme <brooke.laflamme@us.nature.com>

Cc: Pek Jun Wei (Bai Junwei) <junwei@tll.org.sg>

Subject: Fw: Retraction

[External - Use Caution]

Dear Eve and Brooke,

I received an email from Prof. Tschlis below requesting to retract a paper he recently published in Communications Biology. As you were the internal editors for this manuscript, I am forwarding to you to seek advice.

Note that he has requested to withdraw a manuscript currently under review in Communications Biology too. Appreciate your follow-up actions.

Thank you.

Kind regards,

Jun Wei

From: Tschlis, Philip <Philip.Tschlis@osumc.edu>

Sent: Saturday, November 20, 2021 11:12 AM

To: Pek Jun Wei (Bai Junwei) <junwei@tll.org.sg>

Cc: Garfinkel, Susan J. <garfinkel.18@osu.edu>; Carruthers, Bridget <carruthers.39@osu.edu>

Subject: Retraction

Dear Jun Wei

It is very difficult for me to write this letter. However, I am obliged to report that we have confirmed several irregularities in the data on the alternative RNA splicing of U2AF2, which is a central point in the proposed mechanism of RNA transport we reported in our recent paper in "Communications Biology" (Phosphor-IWS1-dependent U2AF2 splicing regulates trafficking of CAR-E-positive intronless

gene mRNAs and sensitivity to viral infection).

The reason we went back to investigate this issue was an Email from Dr Alexandre Maucuer in INSERM, who indicated that he could not find evidence for the alternative splicing of the U2AF2 exon 2 in several bioinformatics analyses he performed. In the process of addressing his comment, we (me and other people in the lab) realized that the alternative RNA splicing of U2AF2 could not give a functional U2AF2 protein and therefore it could not be a physiological mechanism of U2AF2 regulation. In addition, we carefully scrutinized figure 1g of the earlier paper we had published in “Nature Communications” and we discovered evidence of data manipulation (see attachment). I was planning to repeat the U2AF2 alternative splicing experiment myself, but given this evidence, I decided that it will not be necessary to do that. The problem is that the alternative splicing of the U2AF2 exon 2 is repeated over and over again, and it is a central piece of the model we proposed in the “Communications Biology” paper. How these experiments were done to reproduce an event which cannot happen, is unknown. Based on this, we need to retract the paper effective immediately.

I should point out here that some of the experiments, including the viral infection experiments were done in the laboratory of Dr Yount [REDACTED] and there is no reason to doubt that they were done correctly. However, they were done using cells which were provided by a post-doc in my lab and the exact nature of these cells is uncertain. It is also possible that IWS1 phosphorylation renders the cells more resistant to viral infection. However, even if this happens, it will have to be by a mechanism that is different than the mechanism we proposed. Please, note that I have informed the Office of Research Compliance at my Institution about the pending retraction and you may reach out to the Research Integrity Officers, if necessary, Susan Garfinkel at Garfinkel.18@osu.edu or Bridget Carruthers at Carruthers.39@osu.edu. I sincerely apologize for the time and effort you spent reviewing this paper. I am really embarrassed by this, which is definitely a new experience for me. I have contacted most of the coauthors of the paper regarding this problem and the pending retraction, but there are some more, I need to contact. Please, let me know if there is a specific format for a retraction letter and I will write it and send it to you.

In addition to this paper, we have another paper on a related topic, which is currently under review in “Communications Biology”. The paper is titled “Overexpression of the SETD2 WW domain inhibits the phosphor-IWS1/SETD2 interaction and the oncogenic AKT/IWS1 RNA splicing program” and the first author is Dr George Laliotis. Given the problem with the previous papers, we would like to withdraw this paper from the review process effective immediately. We will consider resubmitting it, if the results in this paper are independently confirmed and the mechanism is determined.

My sincere apologies

Philip

Philip N. Tsichlis MD

Professor and Chair, Cancer Biology and Genetics

The Ohio State University, Wexner Medical Center

Co-Leader, Cancer Biology Program

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Artificially-generated U2AF2 Exon 1-3 splice junction

Confidential

U2AF2 Exon1/Exon 2 Junction

Sequence

CAGCTCAACGAGAATAAACAAGAGCGGGACAAGGAGAACCGGC
GTCGAGTTGCTCTTATTTGTTCTCGCCCTGTTTCCTCTTGGCCG

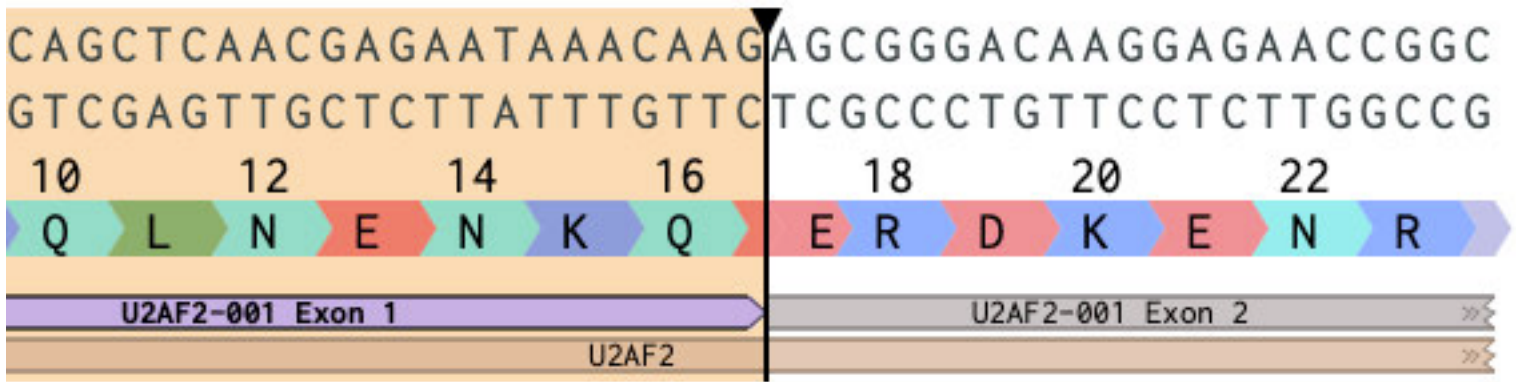
Amino Acids



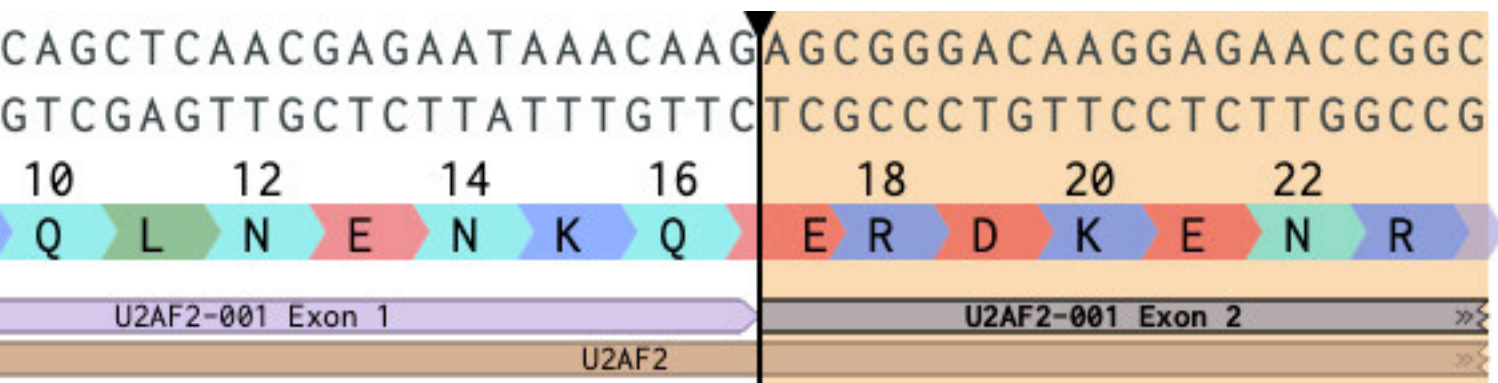
Annotation

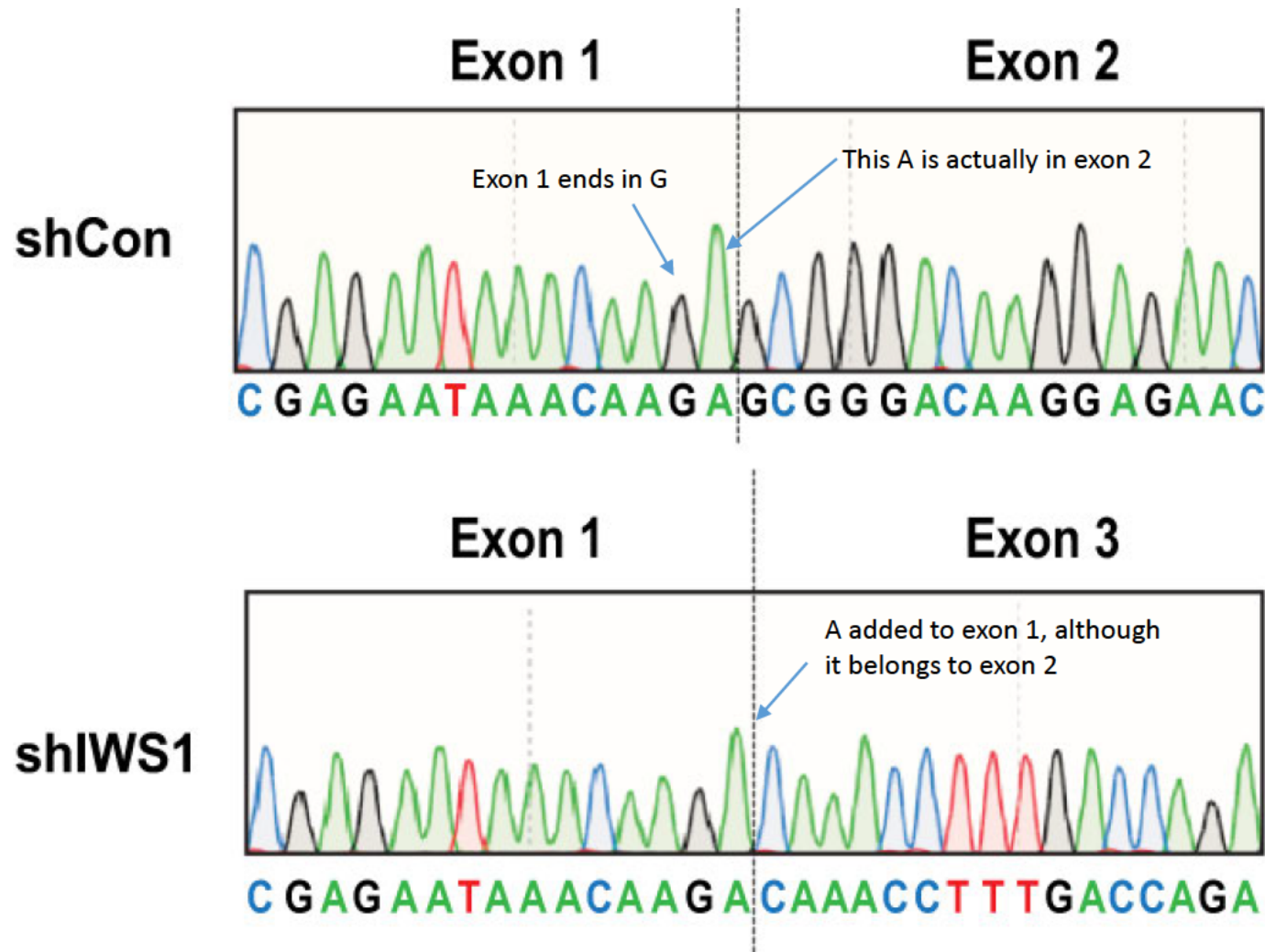


Exon 1 Highlighted

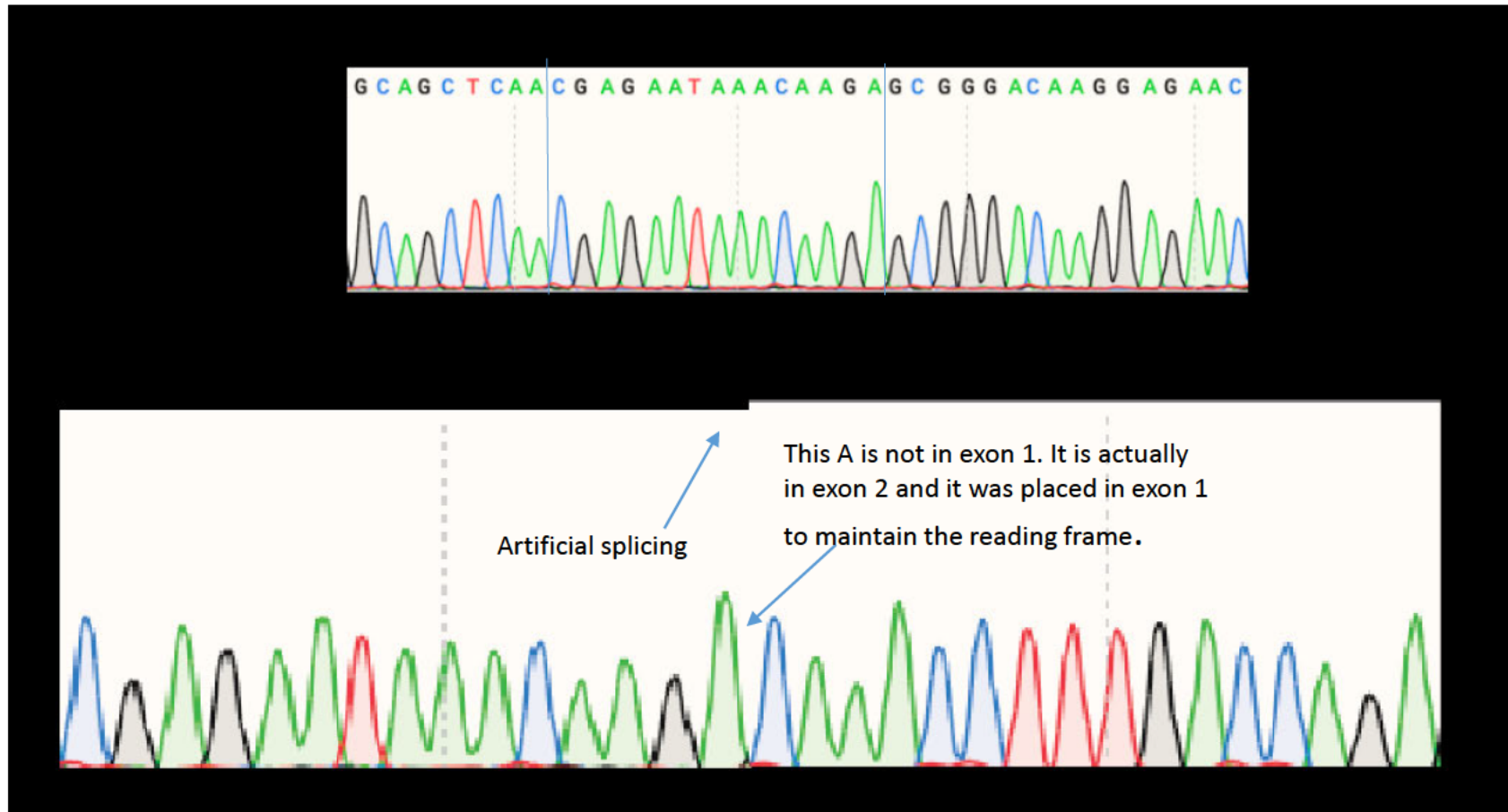


Exon 2 Highlighted





This is figure 1g in the published paper. After scrutinizing it carefully, we observed that the blue line representing the C in the exon 1-3 junction in the lower panel continues as a black line as it touches the green line of the last A in exon 1. Also, the reference lines in the lower panel are 15 bases apart, which is longer than the normal 10 bases (see upper panel). Importantly, the intensity of these lines is also different.



Data deposited by Dr Laliotis in Mendeley. These data leave no doubt that the exon 3 sequence was spliced artificially to the sequence of exon 1. However the third A of the AGA codon is normally in exon 2 and not in exon 1, as shown here. Clearly, it was added here to preserve the open reading frame. The blue lines in the upper panel were added by me to indicate how the left part of the lower panel was generated