

OBSTETRICS & GYNECOLOGY



NOTICE: This document contains correspondence generated during peer review and subsequent revisions but before transmittal to production for composition and copyediting:

- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*
- Email correspondence between the editorial office and the authors*

**The corresponding author has opted to make this information publicly available.*

Personal or nonessential information may be redacted at the editor's discretion.

Questions about these materials may be directed to the *Obstetrics & Gynecology* editorial office:

obgyn@greenjournal.org.

Date: Mar 21, 2019
To: "Bruce I Rose" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-153

RE: Manuscript Number ONG-19-153

Genetically modified babies: A "first" application of CRISPR

Dear Dr. Rose:

Your manuscript has been reviewed by the Editorial Board and by special expert referees. Although it is judged not acceptable for publication in *Obstetrics & Gynecology* in its present form, we would be willing to give further consideration to a revised version.

If you wish to consider revising your manuscript, you will first need to study carefully the enclosed reports submitted by the referees and editors. Each point raised requires a response, by either revising your manuscript or making a clear and convincing argument as to why no revision is needed. To facilitate our review, we prefer that the cover letter include the comments made by the reviewers and the editor followed by your response. The revised manuscript should indicate the position of all changes made. We suggest that you use the "track changes" feature in your word processing software to do so (rather than strikethrough or underline formatting).

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by April 11, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: Brown reports and editorial of the first genetically modified live birth. The study addresses a timely and important topic. Comments for the author:

1. Inclusion of a diagram of CRISPR/Cas systems would be informative.
2. Lines 117-118 describing Dr. He should probably be removed.
3. Separation of the description of Dr. He from the technical discussion of CRISPR/Cas should be more clearly delineated.
4. If the section on IVF is included it would be helpful to develop this a bit further.
5. Some discussion of the repercussions for Dr. He or where this experiment currently stands would be useful.
6. Further discussion describing the restrictions countries have placed on genetically altered embryos would also be helpful.

Reviewer #2: This manuscript describes the technology of and context around the recent twins born after genetic modification at the embryonic stage with CRISPR. Also described is the author's opinion of the appropriateness of the procedure.

Generally, the manuscript describes the context of the event and explains the mechanism of the techniques along with possible complications in a clear and straightforward manner—truly, excellent. It is easy for the reader to understand and question the suitability of performing the procedures in humans. Having said this, the tone of the manuscript in places (particularly the Precis) is overbearing and makes the reader feel a bias rather than the true scientific objection than this reviewer suspects the authors intend.

These major and minor suggestions for consideration are listed in line-number order rather than order of importance:

1. Line 29—Please delete "was premature and inappropriate." This is the authors' opinion and the publication may not have given him the authority to adjudicate for it. Suggestion for replacement: "is described."
2. Lines 38-39—"The creation of the first baby..." Creation has religious overtones that may provoke issues that the authors do not intend to provoke. Please delete "The creation of"

3. Line 40 -Please replace "make this experiment premature and inappropriate" with "are described in context."—Reasons as described above. (see line 29)
4. Line 49—Suggest deleting "Although the experiment...Dr. He did. Nonetheless" and start the paragraph with "It seems that..." The previous sentences add nothing and add an unnecessary tone of pedantry.
5. Lines 54-55—Isn't the FDA prohibited from reviewing products which change embryos for a "heritable genetic modification?" For example, they can review products used for pre-implantation genetic diagnosis.
6. Line 64—Please delete "..and how it was used by Dr. He to create....baby." Same reason as above—lines 38-39.
7. Line 67—This reviewer is not a geneticist. However, I believe the genome is in 23 chromosome PAIRS rather than 23 chromosomes. If one says chromosomes, then it should at least be 24 (22 autosomes, X, and Y).
8. Line 77—The sentence might be more clear as "Viruses that attack bacteria (bacteriophages) are very numerous."
9. Line 85—Please replace "Regular" with "Regularly"
10. Lines 84-115—This description is excellent. These suggestions may help to make it a little more clear to the uninitiated reader:
11. Line 86—A sentence added at this point stating that CRISPR is a DNA sequence and Cas 9 is the associated enzyme would help the reader understand what follows.
12. Lines 89-93—At some point, it would help the reader to clarify when you transition from CRISPR's role in bacteria and the engineered functioning in human cells.
13. Lines 104-105—It would help to point out that the repair needs to be done by the cell and not by CRISPR
14. Lines 117-118—Please delete "Dr. HE is part...technologies." This sentence does not add information and may be interpreted negatively.
15. Lines 118-120—Suggest moving the sentence, "After training in the United States..../young.htmnl)" to line 130 after "...Stanford University."
16. Lines 158-159— "Optimally, ...existing technology." This sentence is not exactly true. Future genetic editing in the correct context might be less expensive and less harmful than today's technology. Who knows? Airplanes are now safer than cars and often less expensive.
17. Line 180—Please delete "Dr. He may ...Approach." He also may not have used this approach.
18. Line 195—Please delete " How did this .. occur?" Again, this adds an unnecessary tone to what the readers are best to conclude for themselves from the sentences which follow.
19. Lines 219-227—Please delete the paragraph. This is not relevant to CRISPR. It is only related by being in the realm of "gene therapy."
20. Line 232—Please replace "Creating a child utilizing.." with "A process resulting in a child born after..." Same reason as above—lines 38-39.
21. Line 237—Please replace "create." Same reason as above—lines 38-39.
22. Lines 238-241—Suggest deleting "IVF had ...tools." Many animal experiments and failures may not have been reported. This is especially true in IVF performed in horses.
23. Lines 241-242 -Suggest deleting " Furthermore, ...different issues." IVF has always been more than a single process: ovulation induction, culture of gametes in vitro, processing sperm, culture media, embryo culture, embryo transfer, et al.
24. Lines 251—Surely Dr. He was not the first scientist "involved." Suggest "was the first to report."

Reviewer #3: I commend Dr Rose for this review which is a welcome, well written addition to the literature that details currently available reports of the events. It objectively and concisely presents the known facts from the reports provided and appropriately points out the cautions that were overlooked. It suggests the need for increased collaboration, communication about concerns that were noted, preliminary studies in animals as well as institutional, national and international oversight. It highlights multiple circumstances that led to this event and identifies points where admonitions, extra caution, interventions by colleagues/mentors, or restrictions might have occurred to avoid such an event. I suspect it

will help in developing oversight, regulatory and professional interventional strategies for the future. It appears to this reviewer to be a fair assessment, based on my personal review of the available reports.

A few suggested edits for clarity:

1. Line 29...for live birth was absent standard scientific oversight and thus inappropriate.
2. 36: change accomplished to performed
3. 39 The level of available research, apparent absence of external scientific oversight, and the risk intrinsic to genetically modifying an embryo make this experiment inappropriate.
4. 77 ...attack bacteria, or bacteriophages, are
5. 155 ...testing (preimplantation genetic testing- mongenic [PGT-M] and preimplantation genetic testing- structural rearrangements [PGT-SR] formerly referred to a preimplantation genetic diagnosis [PGD]), can be used to avoid...
6. 157: Change sentence starting PGD to - PGT-M or PGT-SR screens embryos created....so that only non-affected embryos are transferred back..
7. 266: ...suggest the need for more caution, collaboration, communication and oversight before undertaking additional attempts...
8. 272: year of publication missing

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter, as well as subsequent author queries. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:
 1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.
 2. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.
2. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Any author agreement forms previously submitted will be superseded by the eCTA. During the resubmission process, you are welcome to remove these PDFs from EM. However, if you prefer, we can remove them for you after submission.

3. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric and gynecology data definitions at <https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize>. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.
4. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Current Commentary articles should not exceed 12 typed, double-spaced pages (3,000 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.
5. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

- * All financial support of the study must be acknowledged.
- * Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
- * All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.

* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

6. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Current Commentary articles, 250 words. Please provide a word count.

7. Only standard abbreviations and acronyms are allowed. A selected list is available online at <http://edmgr.ovid.com/ong/accounts/abbreviations.pdf>. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

8. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

9. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at <http://links.lww.com/LWW-ES/A48>. The cost for publishing an article as open access can be found at <http://edmgr.ovid.com/acd/accounts/ifauth.htm>.

Please note that if your article is accepted, you will receive an email from the editorial office asking you to choose a publication route (traditional or open access). Please keep an eye out for that future email and be sure to respond to it promptly.

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If you submit a revision, we will assume that it has been developed in consultation with your co-authors and that each author has given approval to the final form of the revision.

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Sincerely,

The Editors of Obstetrics & Gynecology

2017 IMPACT FACTOR: 4.982

2017 IMPACT FACTOR RANKING: 5th out of 82 ob/gyn journals

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: <https://www.editorialmanager.com/ong/login.asp?a=r>) Please contact the publication office if you have any questions.

| RE: Manuscript Number ONG-19-153 with responses

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Figure 1
2. Lines 117-118 describing Dr. He should probably be removed.
done
3. Separation of the description of Dr. He from the technical discussion of CRISPR/Cas should be more clearly delineated.
There was a line space missing obscuring the heading; space added
4. If the section on IVF is included it would be helpful to develop this a bit further.
This section was deleted to conform to space limitation
5. Some discussion of the repercussions for Dr. He or where this experiment currently stands would be useful.
Impacts have not been clearly reported even by non-academic sources. As noted in the manuscript, it is rumored that other babies are gestating. It is

reported that Dr. He was fired from his university position. This was added to line 199

6. Further discussion describing the restrictions countries have placed on genetically altered embryos would also be helpful.

This could be another paper in itself and is part of an ongoing process. We added a reference to one such paper in line 195 (ref 24).

Reviewer #2: This manuscript describes the technology of and context around the recent twins born after genetic modification at the embryonic stage with CRISPR. Also described is the author's opinion of the appropriateness of the procedure.

Generally, the manuscript describes the context of the event and explains the mechanism of the techniques along with possible complications in a clear and straightforward manner—truly, excellent. It is easy for the reader to understand and question the suitability of performing the procedures in humans. Having said this, the tone of the manuscript in places (particularly the Precis) is overbearing and makes the reader feel a bias rather than the true scientific objection than this reviewer suspects the authors intend.

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1. Line 29—Please delete "was premature and inappropriate." This is the authors' opinion and the publication may not have given him the authority to adjudicate for it. Suggestion for replacement: "is described."

deleted

2. Lines 38-39—"The creation of the first baby..." Creation has religious overtones that may provoke issues that the authors do not intend to provoke. Please delete "The creation of"

done

3. Line 40 -Please replace "make this experiment premature and inappropriate" with "are described in context."—Reasons as described above. (see line 29)
done

4. Line 49—Suggest deleting "Although the experiment...Dr. He did. Nonetheless" and start the paragraph with "It seems that..." The previous sentences add nothing and add an unnecessary tone of pedantry.

The first sentence is a justification for my using so many non-academic sources.
This part has been modified to reflect the intention of this comment.

5. Lines 54-55—Isn't the FDA prohibited from reviewing products which change

embryos for a "heritable genetic modification?" For example, they can review products used for pre-implantation genetic diagnosis.

Yes, this is reference (2)

6. Line 64—Please delete "..and how it was used by Dr. He to create....baby." Same reason as above—lines 38-39.

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made more precise

8. Line 77—The sentence might be more clear as "Viruses that attack bacteria (bacteriophages) are very numerous."

done

9. Line 85—Please replace "Regular" with "Regularly"

done

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Modifications made to reflect this

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Line 90 modified

13. Lines 104-105—It would help to point out that the repair needs to be done by the cell and not by CRISPR

Emphasized; see lines 105 and 107

14. Lines 117-118—Please delete "Dr. HE is part...technologies." This sentence does not add information and may be interpreted negatively.

done

15. Lines 118-120—Suggest moving the sentence, "After training in the United States..../young.htmnl)" to line 130 after "...Stanford University."

rearranged

16. Lines 158-159— "Optimally, ...existing technology." This sentence is not exactly true. Future genetic editing in the correct context might be less

expensive and less harmful than today's technology. Who knows? Airplanes are now safer than cars and often less expensive.

Modified to reflect this

17. Line 180—Please delete "Dr. He may ...Approach." He also may not have used this approach.

deleted

18. Line 195—Please delete " How did this .. occur?" Again, this adds an unnecessary tone to what the readers are best to conclude for themselves from the sentences which follow.

deleted

19. Lines 219-227—Please delete the paragraph. This is not relevant to CRISPR. It is only related by being in the realm of "gene therapy."

done

20. Line 232—Please replace "Creating a child utilizing.." with "A process resulting in a child born after..." Same reason as above—lines 38-39.

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changed

2. 36: change accomplished to performed

done

3. 39 The level of available research, apparent absence of external scientific oversight, and the risk intrinsic to genetically modifying an embryo make this experiment inappropriate.

deleted

4. 77 ...attack bacteria, or bacteriophages, are

done

5. 155 ...testing (preimplantation genetic testing- mongenic [PGT-M] and preimplantation genetic testing- structural rearrangements [PGT-SR] formerly referred to a preimplantation genetic diagnosis [PGD]), can be used to avoid...

PGD changed to PDT (types -M, -SR were unnecessary for meaning)

6. 157: Change sentence starting PGD to - PGT-M or PGT-SR screens embryos created.....so that only non-affected embryos are transferred back..

done

7. 266: ...suggest the need for more caution, collaboration, communication and oversight before undertaking additional attempts...

incorporated

8. 272: year of publication missing:

Year is 2017, but book format requires different placement of date

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online.

Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter, as well as subsequent author queries. If you opt out of including your response, only the revision letter will be posted.

Please reply to this letter with one of two responses:

1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.

OPT-IN chosen

2. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.

2. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

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Shortened with many small deletions and the deletion of a large section to meet this limitation

5. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

* All financial support of the study must be acknowledged.

* Any and all manuscript preparation assistance, including but not limited to topic

development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.

* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.

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In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Current Commentary articles, 250 words. Please provide a word count.

Word count is 53 words

7. Only standard abbreviations and acronyms are allowed. A selected list is available online at <http://edmgr.ovid.com/ong/accounts/abbreviations.pdf>. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

8. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

9. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at <http://links.lww.com/LWW-ES/A48>. The cost for publishing an article as open access can be found at <http://edmgr.ovid.com/acd/accounts/ifauth.htm>.

Please note that if your article is accepted, you will receive an email from the editorial office asking you to choose a publication route (traditional or open access). Please keep an eye out for that future email and be sure to respond to it

promptly.

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2017 IMPACT FACTOR: 4.982

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In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: <https://www.editorialmanager.com/ong/login.asp?a=r>) Please contact the publication office if you have any questions.

Daniel Mosier

From: Bruce Rose [REDACTED]
Sent: Wednesday, April 10, 2019 11:16 PM
To: Daniel Mosier
Subject: Re: Manuscript Revisions: ONG-19-153R1

April 10, 2019

Dear Mr. Mosier,

I would like to respond to your questions in a different order as it will help me discuss these issues more effectively.

3. CRISPR and CRISPR-Cas9 are used interchangeably. It is not uncommon to see both terms used in the same paragraph in writings by experts in this field. This has been sufficiently confusing to people (journalists?) that The Broad Institute/Feng Zhang (who demonstrated the applicability of CRISPR to genetic engineering in eukaryotes) has published the following statement on nomenclature: “In the field of genetic engineering the term “CRISPR” or “CRISPR-Cas9” is used loosely to refer to various CRISPR-Cas9 and -CPF1 (and other) systems that can be programmed.”

Although CRISPR stands for “clustered regularly interspaced small palindromic repeats”, this is more of an historical comment than an explanation of the CRISPR used in eukaryotic genetic engineering. For example, the pieces of DNA from phages (the spacers- or interspaced DNA) have been replaced by RNA directed at the target DNA sequence and other small RNA molecules. These have evolved recently into a single guide RNA molecule: sgRNA. CRISPR is a ribonucleoprotein complex based on discoveries in bacteria systems.

Cas9 stands for CRISPR associated system/genes/proteins 9. These are classified into 3 types of CRISPR-Cas systems, each with several subtypes. This is also a non-specific term as it has been modified to do many different things (activate or suppress expression of genes, replace a single nucleotide, etc.). Zheng believes, that because of increased simplicity of use and differences that are a better solution to problems with Cas9, Cas-CPF1 may become a better choice than Cas9 for genetic engineering.

The CRISPR system contains many molecules with distinct functions, e.g., nucleases, helicases, RNases. The terms CRISPR and CRISPR-Cas encompass all the components of the tools that are still evolving from the original discovery in bacteria.

Thus the difference between “CRISPR” and “CRISPR-Cas9” is a matter of emphasis and I don’t think that the paper is improved by using only one term. (If we did have to move to one term, CRISPR-Cas9 has a more inclusive emphasis and would be the better choice.)

After re-reading the paper, I would replace CRISPR by CRISPR-Cas9 in the third line of the introduction page.

4. I am away from home and do not have a copy of the paper with line numbers (or a word processor that can add them). After carefully reading the two pages starting with the introduction which should encompass line 40, I do not see anything that is incorrect (or that was edited on these pages).

1. After re-reading the paper, I would replace CRISPR by CRISPR-Cas9 in the third line of the introduction page. All editing changes (except the title) are fine.
2. Samuel Brown is my employer and partner. The idea of writing this paper grew out of a conversation we had just after the babies were born. I had originally planned to write a short paper for a local medical journal (with both our names on it). But as the project evolved, it was more time consuming and interesting than I expected and I forgot about our original plan to write this jointly. Samuel Brown reviewed the final product.

If it would be helpful (e.g., to provide confirmation of authorship), Sam's personal email address is
[REDACTED]

I appreciate the quality of your editing. It has produced a better product. Thank you.

Bruce Rose

On Tue, Apr 9, 2019 at 2:40 PM Daniel Mosier <dmosier@greenjournal.org> wrote:

Dear Dr. Rose,

Thank you for submitting your revised manuscript. It has been reviewed by the editor, and there are a few issues that must be addressed before we can consider your manuscript further:

1. Please note the minor edits and deletions throughout. Please let us know if you disagree with any of these changes.
2. Please explain why Samuel Brown was added as an author during the revisions stage, but was not listed as an author in the original submission.
3. LINE 2: Is the correct name just "CRISPR" or "CRISPR-Cas9"? Please make this consistent throughout the paper.
4. LINE 40: Is this edit correct?

When revising, use the attached version of the manuscript. Leave the track changes on, and do not use the "Accept all Changes"

Please let me know if you have any questions. Your prompt response to these queries will be appreciated; please respond no later than COB on **Thursday, April 11th**.

Sincerely,

-Daniel Mosier

Daniel Mosier

Editorial Assistant

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