

CRISPR-Cas9 Discoverers Not Taking Criticism Lying Down



By Julianna LeMieux — June 13, 2017



When people start to use a newly developed scientific technique it is put through the ringer. That is the nature of science. So, it was not unexpected when a paper was published recently regarding the hitherto seemingly infallible CRISPR-Cas9 technique.

The recent publication in *Nature Methods* entitled "Unexpected mutation after CRISPR-Cas9 editing *in vivo*" claimed that using the CRISPR-Cas9 technique may cause unexpected mutations to occur, resulting in a collective 'gasp' from the scientific community.

But the discoverers of CRISPR-Cas9 did not come to play, especially not when the stock value of their companies dipped significantly due to the publication. They are not taking criticism of their technique lightly, and both companies that are based on the technique issued letters that are on the full defensive.

It should be noted that the short report, that includes only one figure in the paper and four in the supplement, is published in the "Correspondence" area of *Nature Methods*. (1)

The manuscript, originating from work done primarily at Stanford University and the University of Iowa, used CRISPR-Cas9 to edit the mutated gene that causes retinitis pigmentosa in mice. When they found mutations in the mice that were not predicted, they claimed that the technique may cause off-target mutations.

The paper states:

"Our study places the onus on researchers to carefully assay their specific gRNA

and Cas9 for off-target mutations. More work may be needed to increase the fidelity of CRISPR–Cas9 with regard to off-target mutation generation before the CRISPR platform can be used without risk, especially in the clinical setting. Future studies employing new CRISPR methods and reagents should consider using WGS to determine the presence of off-target mutations in vivo."

However, scientists from two companies founded on the technique, Editas Medicine (started by CRISPR-Cas9 co-discoverers Feng Zhang, Ph.D and George Church, Ph.D.) and Intellia Therapeutics (started by CRISPR-Cas9's co-discoverer Jennifer Doudna, Ph.D.) are critical of, well, basically everything in the paper.

They point out flaws with the number of animals used (three), to the design of the control experiments, and the inconsistency with other, well done, reports of off target mutations. They charge that the paper wrongly accuses the CRISPR-Cas9 technique of introducing variation that is normally found between animals. Both letters call for either an edit of the paper, or a full on retraction.

Editas and Intellia are not the only ones. Gaetan Burgio, MD, Ph.D., a scientist very familiar with CRISPR-Cas9, published [a lengthy and comprehensive essay](#) [1] on medium.com that spells out his criticism of the manuscript. He ends by commenting,

"I find absolutely astonishing this paper got published in Nature Methods. This is a terrible paper and as a reviewer I would have dismissed it from the first round of review. This is a worrying trend from 'high impact' journals to promote the hype over good science. The publication of this paper is clearly a failure in the peer review process."

Nature Methods has responded by telling the MIT Technology Review that it is "carefully considering all concerns that have been raised with us and are discussing them with the authors."

Notes:

(1) From the [Nature Methods website](#) [2]:

Correspondence is a flexible format providing readers with the opportunity to comment on papers published in a previous issue of the journal, to present resources of broad interest to *Nature Methods* readership (such as databases), or to describe a further methodological development to a method recently published in *Nature Methods* by the same authors. A Correspondence may describe primary research data, but is not intended for full presentation of data. Correspondence should never be more than one printed page and one figure. The total length is typically 250-450 words. As a guideline, Correspondences or their Replies allow up to 6 references, and article titles are omitted from the reference list. Titles for correspondence are supplied by the editors. In cases

where a correspondence is critical of a previous research paper, the authors are normally given the option of publishing a brief reply. Criticism of opinions or other secondary matter does not involve an automatic right of reply. Authors must provide a [competing financial interests](#) [3] statement before publication. Refutations are always peer reviewed. Other types of correspondence may be peer reviewed at the editors' discretion.

(2) Complete letters

The full letter from Intellia Therapeutics can be read [here](#) [4].

The full letter from Editas Medicine can be read [here](#) [5].

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Links

[1] <https://medium.com/@GaetanBurgio/should-we-be-worried-about-crispr-cas9-off-target-effects-57dafaf0bd53>

[2] http://www.nature.com/nmeth/authors/article_types/index.html

[3] http://www.nature.com/authors/editorial_policies/competing.html

[4] <http://www.intelliatx.com/intellias-response-nature-methods-article-crisprcas9/>

[5] http://arep.med.harvard.edu/pdf/Schaefer_Opinion_2Jun2017.pdf