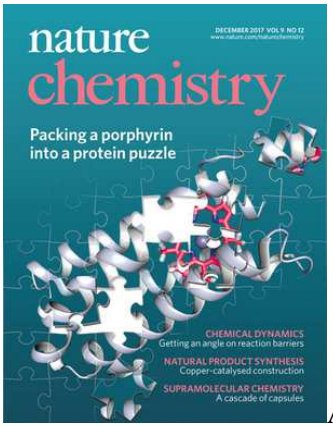
Retraction Watch

Tracking retractions as a window into the scientific process

”Definitely embarrassing:” Nobel Laureate retracts non-reproducible paper in Nature journal

with 17 comments



A Nobel Laureate has retracted a 2016 paper in *Nature Chemistry* that explored the origins of life on earth, after discovering the main conclusions were not correct.

Some researchers who study the origins of life on Earth have hypothesized that RNA evolved before DNA or proteins. If true, RNA would have needed a way to replicate without enzymes. The *Nature Chemistry* paper found that a certain type of peptide — which may have existed in our early history — made it possible for RNA to copy itself.

Jack W. Szostak—a professor of chemistry and chemical biology at Harvard University in Cambridge, Mass., who shared the 2009 Nobel Prize in Physiology or Medicine with Elizabeth Blackburn and Carol Greider for their pioneering research on aging—told us he was “incredibly excited” when he “thought we had at least a partial solution to this problem,” which researchers have been working on for over 50 years.

But in subsequent experiments, Tivoli Olsen — a member of Szostak’s lab — could not reproduce the 2016 findings. When she reviewed the experiments from the *Nature Chemistry* paper, she found that the team had misinterpreted the initial data: The peptide in question did not appear to provide an environment that fostered RNA replication.

The errors were “definitely embarrassing,” Szostak told us:

> In retrospect, we were totally blinded by our belief [in our findings]…we were not as careful or rigorous as we should have been (and as Tivoli was) in interpreting these experiments.

Szostak added:

> The only saving grace is that we are the ones who discovered and corrected our own errors, and figured out what was going on.

Given the issues, the authors requested that the *Nature Chemistry* paper, "Oligoarginine Peptides Slow Strand Annealing and Assist Nonenzymatic RNA Replication," be retracted. This retraction marks the second in six months for *Nature Chemistry* after having none for eight years. The paper has been cited nine times, according to Clarivate Analytics' Web of Science.

A previous replication issue

In 2009, Szostak also retracted a 2008 paper in *Proceedings of the National Academy of Sciences* after an outside researcher could not replicate the results. The retraction notice credited Katherine Berry, then a doctoral student at the University of California, Berkeley, for bringing the issues to their attention. (Full disclosure: RW's Victoria Stern and Berry were roommates freshman year of college).

Berry, who's now an assistant professor of biochemistry at Mount Holyoke in South Hadley, Mass., told us that she was interested in the *PNAS* research because it identified a potential inhibitor of the hepatitis C virus, and she wanted to explore how that inhibitor worked. Berry explained that the authors "were excited to collaborate and sent me peptides."

But in follow-up experiments, Berry was unable to reproduce the findings. Berry presented her data to Szostak. Szostak, she said, "was really supportive and thankful of my efforts" and "took an active role" to correct the literature." She explained that Szostak "immediately asked a postdoc in his lab to follow-up" on the *PNAS* work, and he "moved quickly to retract the publication" when the postdoc's replication attempt also failed.

The paper, "Selection of cyclic peptide aptamers to HCV IRES RNA using mRNA display," has been cited seven times (including once by the retraction notice).

The notice

The notice in *Nature Chemistry* provides a detailed account of what happened:

> We the authors are retracting this Article because our efforts to repeat and follow up on the results have been unsuccessful. Specifically, we have been unable to reproduce observations suggesting that arginine-rich peptides allow the non-enzymatic copying of an RNA template in the presence of its complementary strand (Fig. 4e). We originally dismissed variability in these experiments as resulting from variability in the snap cooling of samples following thermal denaturation. However, we now understand that the data reported in the published article are the result of false positives that arose from an incorrectly designed experiment in which random errors, including transfer and concentration errors, affected the ratio of the concentrations of the RNA template and its complementary strand. This resulted in false positives that were misinterpreted as template copying in the presence of a complementary strand, where in reality these reactions did not contain enough complementary strands to completely inhibit the reaction.
>
> Subsequent experiments suggested that arginine-rich peptides may not slow the reannealing of complementary strands (Fig. 3), and that what we had previously interpreted as a decrease in annealing rate was actually an artefact due to slow coalescence or strand exchange between droplets of RNA–peptide coacervate, as well as droplet coalescence and settling that led to decreased fluorescence intensity. Similarly, the changing circular dichroism spectra shown in Figure 2c, which were originally interpreted to be the result of a change in the global helical structure of RNA upon peptide binding, may also be an artefact due to, for example, loss of

> signal or light scattering. Although the binding of arginine-rich peptides to RNA does form condensed-phase droplets, and although most of the RNA does reside within the condensed phase, follow-up experiments to confirm that non-enzymatic RNA polymerization occurs within these coacervate droplets have been inconclusive (Fig. 5d).
>
> The experiments showing that vesicles are stable in the presence of arginine-rich peptides (Supplementary Figure 26, by N. Kamat), and the failure of acidic peptides to condense RNA (Supplementary Figure 8, by K. Adamala) have been reproduced. However, since the main conclusions of our paper are incorrect, all of the authors are now retracting the Article. The authors would like to thank Dr Tivoli Olsen for her extensive efforts to unravel the errors in our Article and we apologize to the scientific community for any confusion arising from our publication.

Moving forward

Olsen, the researcher in Szostak's lab who discovered the issue with the 2016 paper in *Nature Chemistry*, told us:

> As a scientist the job is to troubleshoot. You can't help nor can you ignore where that takes you. I fulfilled my obligation to insure that no one after me would waste their time on this.

Szostak told us that he plans to continue working to unravel "the problem of chemically replicating RNA:"

> Although we are disappointed that that approach does not work, we are going back to the drawing board and looking into other ways of overcoming this roadblock.

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Written by Victoria Stern

December 5th, 2017 at 11:00 am

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Comments

rfg December 5, 2017 at 12:58 pm

This is how it is supposed to work. Tip of the cap to all involved including the very senior and very junior scientists for doing the right thing.

Olsen nails it:
"As a scientist the job is to troubleshoot. You can't help nor can you ignore where that takes you. I fulfilled my obligation to insure that no one after me would waste their time on this."

Fake or erroneous data in the basic science wastes precious effort -people pursue false leads- grants to honest scientists are not awarded.

Fake or erroneous data in clinical science and people may die – resources to real countermeasures are side-lined for bogus ones.

Honest scientists recognize this and correct their honest mistakes as soon as possible. Dishonest scientists stonewall, attack the whistleblower and do all they can to avoid accountability for their dishonest data. Of course these are merely personal observations that are anecdotal and biased. My strong feeling (not data driven) is that they are generalizable.

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Narad December 5, 2017 at 2:47 pm

> This is how it should work before you publish it.

OK, but bear in mind that Olsen wasn't an author on the retracted paper.

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Bob bobberton December 5, 2017 at 6:57 pm

This is how science is supposed to be done. Anyone who thinks that there is a prodigious lab out there

that has NOT accidentally published incorrect science has no idea what it is to work in a prodigious lab. What sets this lab apart is that not only were they willing to retract their mistakes but they uncovered those mistakes themselves. They self corrected. This should be a model for science. Instead, people will jeer and pretend that science is perfect and these sorts of mistakes are not common. That's exactly wrong. These sorts of mistakes are all TOO common. The willingness to correct them is what is uncommon. Bravo.

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So it is December 5, 2017 at 9:44 pm

Correction, revision, and retraction of findings are a key mechanisms in the progress of science. No stigma should be associated with the messy pursuit of truth sought in good faith. Of course, it should surprise no thinking person to find that science doesn't really proceed in the breezy manner that it's portrayed by university press offices and science journalists. Good on Tivoli and Jack for upholding the high standards we expect for the field.

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Maurice Devaraj December 6, 2017 at 10:49 pm

So what exactly happened during the peer review process? Definitely mine is a case of sour grapes, but my papers never got past the editor, while this one seems to have gone all the way through peer review and publication.

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M. K. Parida December 8, 2017 at 12:50 am

Is it possible to know the subjects, physics,chemistry, biology, medicine, or engineering where there are more plagiarism compared to others?

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Dave Fernig December 8, 2017 at 4:04 pm

This is science.

What is not science includes:

1. Defending the indefensible
2. Mega corrections
3. Reaching for a lawyer
4. etc.

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- *Leonard Hayflick* December 11, 2017 at 4:40 pm

  "Jack W. Szostak—a professor of chemistry and chemical biology at Harvard University in Cambridge, Mass., who shared the 2009 Nobel Prize in Physiology or Medicine with Elizabeth Blackburn and Carol Greider for their pioneering research on aging—"

  Blackburn and Greider were NOT awarded the Nobel prize for their pioneering research on aging. The award never uses the word aging. The award was for discovering the method for protecting chromosome ends. Both denied in print (references upon request) that their work had anything to do with aging.

  My phenomenological discoveries (of their molecular explanation for my findings) were made 47 years earlier. I discovered the limited replicative capacity of normal human cells that was interpreted by me to suggest that this was telling us something about aging. This has not been admitted by Blackburn who has reversed her views after learning of my wok.

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