Exhibit J

Retraction Watch

Tracking retractions as a window into the scientific process

Popular paper by famous longevity researcher gets mega-correction

with 4 comments

Leonard Guarente

A highly cited paper by a well-known scientist at the Massachusetts Institute of Technology who studies longevity could have aged better: The ten-year-old paper has earned its second correction.

It's one of multiple papers by lead author Leonard Guarente that have been questioned on PubPeer. Guarente has already retracted one, and plans to address another.

Guarente's work focuses on sirtuins, enzymes that some hypothesize can prolong life if activated through resveratrol, calorie restriction, or someday drugs (here's a review paper). In the 2005 *PLOS Biology* paper, Guarente and his colleagues found that the mammalian form of Sirt1 affects the body's production of insulin in response to diet. Nearly 10 years later, PubPeer commenters began raising questions about some of the images. Guarente told us he worked with MIT and the journal to investigate and find the original data. Though the resulting correction is long, the conclusions are unaffected, and Guarente noted that other studies have verified the paper's findings.

The paper has been cited 321 times, according to Thomson Scientific's Web of Knowledge. The correction for "Sirt1 Regulates Insulin Secretion by Repressing UCP2 in Pancreatic β Cells" addresses issues with several figures: undisclosed gel splices, legend errors, and incorrect controls:

> The authors would like to clarify that the controls previously depicted in Figs 4E and 7A were for different experiments and were included in error.
>
> The correct control for Fig 4E was located and used to prepare a corrected figure.
>
> The correct control for the original Fig 7A could not be located; this panel has therefore been removed after a careful assessment and investigation determined that the result for which original Fig 7A was cited is supported elsewhere in this article, and that removal of this panel does not affect the conclusions of the paper.

> We have also taken this opportunity to provide new versions of several figures (Figs 4, 5, 6, 7) in which gel/blot splices and a non-linear level adjustment were made but were not previously indicated or declared, or to replace incorrectly spliced gels/blots with the un-spliced originals. We also take the opportunity to correct two errors in the legend to Fig 6, first to remove a redundant and incorrect sentence, and second to address incorrect description of *p* values.
>
> The text in the Results section titled "UCP2 Levels Increase in Food-Deprived Mice" has been edited to accommodate the removal of the original Fig 7A and the relabeling of Fig 7B, 7C and 7D as Fig 7A, 7B and 7C, respectively. The corrected text and Figs 4, 5, 6 and 7 are provided here.

Read the entire notice to see the new figures and text.

At the time of publication, the journal published a synopsis of the paper, which explained that the researchers

> disrupted the *Sirt1* gene of mice, and found that these mice produced very little insulin, regardless of whether they were well fed or starved. These results suggested that Sirt1 is necessary for glucose to induce insulin production.

The journal learned of concerns about the paper on PubPeer in January 2015, and contacted Guarente, who alerted MIT. The journal, Guarente and the university worked together to investigate the concerns, Guarente explained to us on the phone:

> So it was a tremendous effort to get to the figures, but we did so in almost every case…The investigation required finding files that are 10 years old.

First author Laura Bordone, who was a postdoc at MIT at the time of the research, had saved the files. She's now a scientist at the Genomics Institute of the Novartis Research Foundation.

"What we found all told is there were a few errors, "Guarente told us. Those errors "did not change any conclusions of the paper."

He elaborated in an email:

> In the one case we could not find the original, we removed an unnecessary panel, as explained in the Correction. Note that splicing of gel lanes was not prohibited by the rules of the journal at the time. The few figure errors were found in the investigation, did not affect the interpretation of any experiment, and were corrected. So, yes, I think the Correction was the fair course. Note, that the findings in the paper have been shown to be correct by independent studies by others.

A spokesperson for *PLOS* told us that they also consulted "with a scientific expert who is familiar with this area for oversight of the data." And, echoing Guarente, he said:

> This collective investigation deemed that the conclusions remained unchanged.

Here's the first correction that the paper earned, in 2006:

> In the first paragraph of the Materials and Methods subsection "Retroviral infection of INS1 and MIN6 cells," "pSUPERretro SiRNA-T1 (5′-GCTGCATCCAAGGGCCATG-3′)" should be "pSUPERretro SiRNA-T1 (5′-gatgaagttgacctcctca-3′)".

Other papers by Guarente have been questioned on PubPeer. Over the phone, he told us:

> It seems we're being targeted for some reason…It's ridiculous that these anon comments have any sway…The only real problems that have happened are with the [Donmez] papers, and we're fixing them.

That's Gizem Donmez, an alum of Guarente's MIT lab, who has two retractions and left her post as a Tufts professor in 2014. Guarente is an author on one of those retractions — a *Cell* paper on Sirt1.

There are issues with another Donmez paper, "SIRT1 protects against alpha-synuclein aggregation by activating molecular chaperones," published in the *Journal of Neuroscience*, which Guarente told us they're now working to fix. He couldn't confirm if there would be a correction or retraction, but said via email,

> Likely something will be forthcoming.

The other comments are much ado about nothing, Guarente said.

There are PubPeer comments on two papers for which his lab provided mice, but didn't complete most of the work: "SIRT2 ablation has no effect on tubulin acetylation in brain, cholesterol biosynthesis or the progression of Huntington's disease phenotypes in vivo" (see comments), and "Hepatic overexpression of SIRT1 in mice attenuates endoplasmic reticulum stress and insulin resistance in the liver" (see comments). For "Acute oxidative stress can reverse insulin resistance by inactivation of cytoplasmic JNK" (see comments), he just provided some advice on the experiments, which were completed at Novartis.

The SIRT2 paper was published in *PLOS One*. A spokesperson told us that the journal,

> is aware of the queries raised regarding Figure 5 in the article by Bobrowska *et al*. and the journal is following up on this matter.

Some of the comments focus on a *Development* paper, "SirT1 is required in the male germ cell for differentiation and fecundity in mice." In this case, Guarente told us that the commenters disagree with each other:

> The criticism is bogus because it was claiming that we juxtaposed something in the figure that shouldn't have been together naturally, but they should have been.

Other comments focus on a *Cell* paper, "Mammalian SIRT1 represses forkhead transcription factors," whose first author is Maria Carla Motta, also at MIT and a co-author on the newly corrected paper. Of those comments, Guarente said:

> The comments on [the] Motta [paper] are very speculative and then peers themselves don't agree.

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Written by Shannon Palus

March 8th, 2016 at 2:00 pm

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Comments

- *Paul Brookes* March 9, 2016 at 8:37 am

  I find it a troubling that there's a "fix" in the works for the *J. Neurosci.* paper. To me, that term means a correction rather than a retraction. Here's the PubPeer entry for the paper… https://pubpeer.com/publications/22219275, and here's a somewhat outdated story (Jan 2014) on the long road to try and get the journal to do something about it… http://www.psblab.org/?p=167

  Guarente's admission that this paper needs to be fixed, would appear to conflict with (former editor in chief) John Maunsell's previous assertion that SfN was satisfied with the institutional investigation that found no problems (detailed in the link above). There is an SfN ethics panel investigating the paper, but repeated attempts to find out what's happening (including calling out EiC Marina Picciotto on Twitter – https://twitter.com/PSBROOKES/status/679870425225023488) have so far yielded nothing.

  ———————

  I also take issue here with Guarente's statement *"It seems we're being targeted for some reason…It's ridiculous that these anon comments have any sway…"*

  Firstly, there's no "targeting" in the personal sense of the word. If scientists publish problem data, they can expect it to be targeted. I find it incredulous that he would write this off as being "for some reason", as if the reason is not clear.

  Secondly, in this statement he perpetuates the fallacy that the identity of the messenger is important. As has been proven time and again, if the criticisms are valid (and in this case they are) then the identity of the person making them is irrelevant.

  Third, it's worth noting that many of the comments are not actually anonymous. Rather, they're coming from named individuals, one of whom is me. As a result, the first author of the paper threatened to sue me, and you can't sue an anonymous person!

  The narrative set up by this statement, suggesting that some random anonymous person (whose opinions should not count anyway) is personally "targeting" the authors, is not consistent with the reality.

  Reply Link Quote

- *C Beall* March 17, 2016 at 1:03 pm

  Shannon-

You say “someday drugs”, but Dr. Guarente formed a supplement company (Elysium) that has been selling a product based on the same general research. Surprisingly to me he has a stellar group of scientists (inc. 6 Nobel Laureates) implicitly endorsing it.

http://www.elysiumhealth.com/

I have looked on Medline but not found any clinical data about the product.

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