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Theo Baker
Staff Writer, The Stanford Daily
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Dear Mr. Baker:

I represent Stanford President Marc Tessier-Lavigne, from whom I received the letter you sent him on February 7, 2023 regarding a paper entitled "APP binds DR6 to trigger axon pruning and neuron death via distinct caspases," published in the journal Nature in 2009 (the "Paper"). Your letter's allegations regarding Dr. Anatoly Nikolaev, the experiments described in the Paper, and the Paper's scientific findings are incorrect, and any dissemination of these allegations has been and will continue to be extremely reckless.

In particular, your letter includes the following falsehoods, among others:

- Dr. Tessier-Lavigne is not aware of any internal investigation of the Paper. Given that there was no investigation of the Paper, Dr. Tessier-Lavigne categorically disputes any allegation by unnamed scientists that he "covered up" any findings regarding such investigation or was opposed to allowing such (non-existent) findings to become public.
- No one involved in the experiments described in the Paper forged gels or falsified assays.
- The experiments reported in the Paper were not fabricated.
- Dr. Nikolaev was still employed at Genentech when Dr. Tessier-Lavigne left the company in March 2011. To the best of Dr. Tessier-Lavigne's knowledge, Dr. Nikolaev left Genentech on his own accord.

In addition to these inaccuracies, your letter's assertions regarding the underlying science in the Paper are equally indefensible and evince a fundamental misunderstanding of the Paper's scientific work and findings. Contrary to your assertions, Dr. Tessier-Lavigne's later papers did not repudiate the Paper's primary findings and a correction or retraction of those findings would have been unwarranted and inappropriate. Rather, the follow-on studies arose from the normal progression of science.

Contrary to your assertions, the Paper's central tenets – which reported involvement of DR6, APP and Caspase-6 in developmental axon degeneration, also known as pruning – have been validated *in vitro* and *in vivo*. The Paper also proposed an initial model for how DR6 and APP interact biochemically, and raised the question of whether this mechanism also regulates axon degeneration in the adult nervous system.

Later studies by Dr. Tessier-Lavigne, including (Simon et al. J. Neurosci. 32:17540 (2012)) and (Olsen et al. J. Neurosci. 34:6438 (2014)), fully validated the involvement of these three factors

in pruning and deepened the understanding of their molecular mechanisms. For example, the Simon paper discovered that Caspase-6 is activated by Caspase-3, and that activation can only be blocked by full genetic knock-out, not the partial inhibition provided by pharmacological agents, explaining prior results. As well, the Olsen paper, which you conspicuously omit from your letter, reported experiments using knock-out mice that validated involvement of DR6 and APP in pruning *in vitro* and *in vivo*. Further analysis with knockout mice revealed that a number of reagents used in the Paper, including some widely used by other investigators[1], had off-target effects, and led them to propose a revised model for how DR6 and APP interact at a molecular level. As explained in the Olsen paper, "This analysis unexpectedly revealed that several pharmacological reagents . . . used in prior analysis had off-target effects that affected the conclusions. Nonetheless, genetic analysis supports the model that DR6 and APP contribute to sensory axon degeneration following trophic deprivation in vitro."

For these reasons, among others, no correction was warranted – the Paper's original results were accurately reported. This was the normal progression of science that caused Dr. Tessier-Lavigne's group to revise their initial model as reported in the Paper. In this regard, the use of knockout mice, which is arduous and can take many years, is a common technique to test theories based on initial *in vitro* experiments (see, for example, https://journals.physiology.org/doi/full/10.1152/physrev.1998.78.4.1131 (p.1132), which explains that: "Several other benefits can come from mutant mouse studies. Assumptions about the in vivo targets of particular drugs can be tested rigorously using genetically altered mice.")

Further studies then validated the revised model for DR6/APP interactions (Xu et al. Genes Dev. 29:785 (2015)) and extended involvement of this mechanism from development to the healthy adult brain (Kallop et al. J. Neurosci. 34: 6425 (2014); Marik et al. J. Neurosci. 33:14998 (2013); Marik et al. Proc. Natl. Acad. Sci. 113:7912 (2016)). And while the mechanism has not yet been implicated in Alzheimer's disease (Kallop et al. J. Neurosci. 34: 6425 (2014)) – a speculative possibility – it has in fact been implicated in a different neurodegenerative disease, ALS (Mishra et al. Nature Comm. 11:5579 (2020)).

In sum, your errors are many, fundamental, and egregious. With that in mind, we have some questions: do you plan to identify any of the anonymous "people" and "scientists" referenced in your letter; did your sources have first-hand information concerning any of the alleged activities surrounding the Paper, including the existence and purported findings of any internal investigation; have you seen a report of an "internal investigation;" have you seen a report on the supposed findings regarding the Paper from the RRC; and have you and the scientists you cite

1. See for example *Wei et al. (2012) (Fig. 2C) (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3339962/) as well as Guo et al. (2012)(https://www.jbc.org/article/S0021-9258(20)53205-5/fulltext) (referenced in the Olsen paper).*

studied Dr. Tessier-Lavigne's follow-on articles, including the Olsen article, and articles by other researchers who have built on his work, including the Mishra article?

Given that the falsehoods in your letter concern activities at Genentech and the conduct of Genentech personnel, we felt compelled to notify Genentech of your allegations. To follow up on that notification, I am sending a copy of this letter to Genentech's General Counsel.

Finally, we expect that going forward you and your editors at the Stanford Daily will adhere to principles of professional ethical journalism, including reporting that is accurate, fair, and thorough.

Sincerely,

Stephen C. Neal

cc: (Via Email)

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