

## **Findings of 2023 Genentech Review of 2009 Nature Paper and Related Research**

**April 6, 2023**

Recent news reports in the Stanford Daily (on [February 17](#) and [March 6](#)) and elsewhere have alleged fraud and a cover-up in relation to a 2009 scientific paper published in the journal Nature ([Nature. 2009 Feb 19;457\(7232\):981-9](#)). The 2009 Nature paper generally describes research directed at understanding the involvement of certain proteins, including those known as DR6 and APP, in neuronal death and degeneration with possible implications for Alzheimer's Disease. The paper was co-authored by former Genentech researchers Drs. Anatoly Nikolaev and Marc Tessier-Lavigne, along with two scientists at the Salk Institute. Dr. Nikolaev held the titles of postdoc and then scientist, and Dr. Tessier-Lavigne, the paper's senior author, was an Executive Vice President of the Genentech Research organization.

The news reports included allegations that (i) certain of the results reported in the 2009 Nature paper could not be reproduced by other scientists, (ii) Genentech's Research Review Committee (RRC) conducted "an internal inquiry into the underlying experiments of the paper" and "discovered falsification of data in the research," (iii) Dr. Tessier-Lavigne "kept the finding [of falsification of data] from becoming public," and (iv) the paper also "appears to contain several visible duplications of images."

We have taken these allegations seriously. Genentech is a company founded on principles of scientific excellence and integrity, and we remain as committed to those principles today as we have been throughout our 46-year history. In response to these allegations, the current senior leadership of Genentech's Research and Early Development organization (gRED) asked the Genentech Legal Department to lead a retrospective review of the facts and circumstances surrounding the 2009 Nature paper.

The diligence team has completed its review and the following is a summary of the process they followed and their findings.

### **Our Diligence Process**

Members of the diligence team reviewed historical documents likely to contain relevant information (including laboratory notebooks, meeting minutes, and emails) and interviewed more than 35 current and former Genentech employees who, at the time of the matters in question, were members of the RRC or Research leadership, or scientists

or research associates in Genentech's neuroscience research group or a supporting function. Because of the roles they held, each of the interviewees was able to share with us, to varying extents, recollections about the 2009 Nature paper and the related research that preceded and followed the publication of the paper.

The publication of the 2009 Nature paper and the related research occurred 11-16 years ago. We recognize that there are other documents or evidence that the diligence team was unable to find or that no longer exist. We also recognize that interviewees may not have complete recollections of events occurring so long ago. Nevertheless, there was a high degree of consistency in what the team found (and didn't find) in the materials they reviewed and the interviews they conducted.

### **Genentech's DR6-Related Programs**

The experiments reported in the 2009 Nature paper were part of a DR6 early-stage research program that began in 2008. Genentech continued to invest in this area of research for several years following the publication of the 2009 Nature paper. The early-stage research program evolved into a DR6 drug discovery program in 2009 and that program continued until it was ultimately terminated in 2012.

At Genentech, drug discovery programs receive regular scientific reviews by the RRC. The DR6 program was no exception. The RRC is a group of senior Genentech scientific leaders who meet weekly, in the ordinary course of business, to follow the progress of each of our drug discovery programs and to provide scientific guidance and decision-making related to prioritization and resource allocation for all our drug discovery programs.

### **Factual Findings:**

1. None of the current or former employees who were interviewed reported observing or knowing of any fraud, fabrication, or other intentional wrongdoing in the research leading to and reported in the 2009 Nature paper.
2. We found no evidence that the RRC conducted any investigation of fraud, fabrication, or other misconduct involving the 2009 Nature paper or the research leading to it. The RRC is not, and never has been, an investigative body. Consistent with its actual role, the RRC reviewed and supported further work on the DR6 drug discovery program until the committee terminated it in 2012.
3. We found no record or other evidence that the company's anonymous complaint "hotline," Legal Department, or Healthcare Compliance Office ever received a

complaint or report from anyone raising a concern about the 2009 Nature paper or the research leading to it.

4. There was a complaint in mid-2010 alleging scientific misconduct by another postdoc working in Dr. Tessier-Lavigne's laboratory. The complaint related to research reported in a manuscript that had been submitted for publication and was unrelated to the DR6 research and drug discovery programs. The manuscript was co-authored by the postdoc, Dr. Tessier-Lavigne, and others. The complaint led to a formal investigation by the company, resulting in withdrawal of that manuscript and termination of the postdoc's employment in August 2010. The same postdoc also conducted unpublished experiments involving DR6 and N-APP that were not the basis for or subject of the 2009 Nature paper.
5. We were unable to find certain original data and images from the research underlying the 2009 Nature paper, including the images referenced in the Stanford Daily's March 6 article. The research occurred nearly 15 years ago and some data and images were saved on electronic storage media that may no longer exist.
6. In order to assess whether the 2009 Nature paper contains duplicate images, the diligence team consulted an independent, outside expert who specializes in detecting image manipulations in scientific publications. This expert concluded that two sets of figures, Figures 1d and 5e and Supplementary Figures 9c and 17c, include duplicate images. The expert also concluded that a Western blot panel for Caspase 6 in Supplementary Figure 6d appears to include a composite of two images. We have not determined how these anomalies occurred. Following the receipt of these findings, Genentech reported them to Nature.
7. Genentech scientists and research associates had difficulty reproducing certain results reported in the 2009 Nature paper, in particular, the binding interaction between DR6 and N-APP (the N-terminal portion of APP). Prior to publication of the paper, employees other than the authors performed binding experiments that showed inconsistent results – sometimes binding between DR6 and N-APP was detected, and other times, it was not. Some of the employees who performed those experiments attributed the inconsistent results to variability in the purity and quality of the reagents used. Following the publication, for approximately three years, Genentech scientists and research associates made a concerted effort to detect meaningful binding between DR6 and N-APP using several different methodologies, without consistent success.

8. Senior leaders at Genentech including Dr. Tessier-Lavigne knew of the inconsistent binding results, and there was uncertainty and speculation within the Genentech Research organization about why the binding interaction between DR6 and N-APP could not be reliably reproduced or confirmed.
9. After Dr. Tessier-Lavigne left Genentech for his new role at Rockefeller University in March 2011, at least one senior leader in gRED learned that scientists outside of Genentech also were having difficulty reproducing the binding of DR6 and N-APP.
10. Also following Dr. Tessier-Lavigne's departure, one senior leader in gRED urged that the 2009 Nature paper should be retracted or corrected in light of the inconsistent binding results. Other senior leaders recognized at the time that this was an action only Dr. Tessier-Lavigne or another co-author could take with the journal. It was decided that additional experiments should be conducted, in any event, to evaluate definitively whether there is meaningful binding between DR6 and N-APP and whether DR6 remained a viable target for developing a drug to treat Alzheimer's Disease.
11. The DR6 program continued, and in November 2011, the RRC received an update on it as part of the committee's regular review of the company's drug discovery programs. The DR6 team presented their experimental results to date, and the RRC supported the team's ongoing work, including using additional methodologies (for example, cell-based assays) to analyze the binding between DR6 and N-APP, as well as utilizing mouse genetic models to assess the potential role of DR6 and N-APP in Alzheimer's Disease. These *in vivo* animal experiments were considered to be a more rigorous means of determining the role of DR6 and N-APP than previous biochemical experiments. In parallel, researchers in Dr. Tessier-Lavigne's lab at Rockefeller University were doing other genetic and biochemical experiments on DR6 and APP.
12. The genetic experiments performed at Genentech showed that in two different mouse models of Alzheimer's Disease, the neurologic features associated with that disease (for example, deposition of amyloid plaques, synaptic loss, or cognitive behavior defects) were not dependent on DR6. On that basis, the RRC terminated the DR6 drug discovery program in 2012.
13. The results of the genetic experiments – at Genentech and Rockefeller – were reported in a pair of papers submitted to the Journal of Neuroscience in 2013 and published in 2014 ([J Neurosci. 2014 May 7;34\(19\):6425-37](#) and [J Neurosci. 2014 May 7;34\(19\):6438-47](#)). Dr. Tessier-Lavigne, along with researchers from

Genentech and elsewhere, co-authored both papers. Upon the publication of those papers, the scientific community began to discuss how the results and conclusions reported there differed in several respects from those reported in the 2009 Nature paper (see, for example, [Reports Weaken Death Receptor Link to Alzheimer's Disease](#)).

14. Genentech's termination of the DR6 drug discovery program marked the end of many years of challenging and often frustrating research that many hoped would culminate in a treatment for Alzheimer's Disease. Many scientists who worked on the project were disheartened by having devoted substantial time and energy to a program whose underlying biology was ultimately proven wrong. That sentiment gave rise to rumors about why the DR6 program failed.

### **Concluding Remarks**

We undertook our review of the 2009 Nature paper and the related research with a commitment to rigorous diligence. We are grateful to the many current and former Genentech scientists and other employees whose recollections, insights, and candor have helped us better understand events that happened many years ago.