

Suspicions have been raised about research by six professors at the University of Tokyo. | SATOKO KAWASAKI

Todai biomedical research fraud probe seen pointing to wider misconduct

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The so-called STAP scandal of 2014 unleashed the power of anonymous online whistleblowers, who exposed falsified data in what had been hailed as groundbreaking stem cell research by the Riken institute and brought down its star scientist, Haruko Obokata.

While the scandal — which resulted in the retraction of two Nature journal papers on stimulus-triggered acquisition of pluripotency, the firing of Obokata, the suicide of her mentor and the structural overhaul of Riken — is still fresh in people's minds, new allegations of research misconduct are rattling the medical establishment.

This time, suspicions have been raised over research at the University of Tokyo, Japan's venerable academic and research institution known as Todai.

On Sept. 20, the university announced it would launch a full-fledged investigation into six professors at its medical school and the Institute of Molecular and Cellular Biosciences, saying a preliminary probe found that allegations of misconduct warranted further scrutiny.

The investigation, to be undertaken by a panel including outside experts, will conclude within 150 days.

The probe is unprecedented in that it simultaneously covers six top professors in biomedical fields. It was triggered by two sets of documents mailed by an anonymous source to the university — on Aug. 14 and Aug. 29. — that pointed to alleged data fabrication in 22 papers co-authored and supervised by the professors.

The university has refused to name the six researchers, saying in a press release that “the launch of the investigation does not confirm acts of misconduct by the accused.”

But the documents are available on the website run by an anonymous blogger called Sekai Hendo Tenbo that has for years tracked research fraud, including Obokata’s.

The documents, signed by “Ordinary_researchers,” take aim at 22 papers related to various illnesses, including diabetes, hypertension and heart disease. The papers were published between 2003 and this year in such major journals as Cell, Nature, Science and the New England Journal of Medicine.

Experts say the accusations highlight long-running problems around research ethics in Japan. They also say the case reveals how easy it is now for anyone with knowledge of image-editing computer software to detect data irregularities in published research.

The authors of the documents say they picked papers with results that other researchers said were hard to reproduce; that are tied to drug development and therefore pose a big impact on patients and society; and that have received substantial public funding.

What’s more, the use of “vector data” graphics in the papers has made it possible to reproduce original data used to back up their conclusions, the whistleblowers wrote.

They said they checked the authenticity of data by using common image-editing software, including Illustrator.

In the past, many researchers submitted papers using charts made from pixel data, which, when magnified, became blurry and hard to see.

In contrast, in recent years, many journals started requiring submissions of charts made from vector data, which show the exact positions of data points in an x-y axis graph. By using such software, however, anyone can retrieve the original data used for the graphs.

For example, Ordinary_researchers allege the use of false data in six papers produced by one of the professors at Todai.

One chart compares the survival curves of mice with and without adiponectin receptors — hormones that regulate fat and sugar levels in the body. When the vector data were examined, they showed that nearly

two-thirds of mice in one group had died after days ending with zero — such as 700 days, 710 days and 720 days.

“It’s unnatural for mice to die exactly every 10 days,” the whistleblowers wrote, hinting that the data had been tampered to suit the theory envisioned by the researchers.

Such data became available only through an analysis of vector graphics.

Five of the six professors, including the one who led the study on survival curves of mice, did not respond to email requests for comment by The Japan Times. The sixth professor declined comment, saying the matter was being handled by the university’s public relations department.

The department refused to comment on details of the allegations.

Iekuni Ichikawa, a professor at Shinshu University who specializes in research ethics, says the scandal “was bound to happen,” noting such research irregularities are not unique to the nation’s top-ranking university.

Ichikawa, who trained and practiced in the U.S. for more than 20 years before recently starting an e-learning ethics program for young researchers in Japan, says ethics standards in this country, especially in biomedical fields, lag those in the West “by about 25 years.”

“Everyone knows that biomedical research is hard to reproduce,” he said. “That’s because, as opposed to experiments of chemicals, for example, biomedical experiments are conducted using animals, whose conditions vary significantly from subject to subject, depending on what they have eaten, whether the tests were conducted in the morning or during the day, and so on.”

Because of this, biomedical researchers have been somewhat exempt from the pressure to present reproducible results, creating room for some to engage in misconduct, he said.

For example, some researchers pick only “positive data,” or results that back up the researchers’ hypothesis, and ignore the data that don’t, he said.

Ichikawa cited the theoretical example of a study where a researcher conceives and tests a hypothesis that eating daikon leads to colon cancer.

The researcher tests not only daikon but also cucumbers and eggplant. It then turns out the test subjects that ate eggplant were shown to be more likely to get colon cancer.

Ichikawa said researchers can then tweak the hypothesis and write a paper saying the experiment confirmed the hypothesis that eggplant causes colon cancer.

“Such acts, known as HARK (hypothesizing after the results are known), are a no-no, because the results were only a product of chance and not proven,” Ichikawa said. “But researchers often submit the papers without doing the further statistical analysis needed.”

Shigeaki Yamazaki, a professor at the faculty of human informatics at Aichi Shukutoku University who has studied research integrity, says the University of Tokyo case reinforces his conviction that research misconduct is pervasive in Japan, and that it is only “the tip of the iceberg.”

He cites a 2013 survey on research misconduct by the Molecular Biology Society of Japan, a group of life and medical scientists. Of the 1,022 member researchers who responded to the survey, 10 percent said they had witnessed or experienced research misconduct first-hand in their labs, while another 38 percent said they had heard rumors of misconduct involving their labs or other labs close to them.

Yamazaki, who says he has been consulted by whistleblowers for advice, said the enormous pressure researchers face to get their research published in premier journals, thereby to win competitive research grants, was contributing to the problem.

But the culture that stymies or ostracizes those who fight against misconduct is a bigger problem, he said.

“Ideally, those whistleblowers should have peers they can confide in nearby, whether at their university or the academic societies they belong to. If they can build a network of support, they can find the energy to bring changes to labs” and eradicate misconduct, he said.

Ichikawa, meanwhile, said changing lab culture is difficult, as seen in the University of Tokyo case.

It is also not the first time the university has investigated misconduct allegations; in December 2014, a panel at the university concluded that a team of researchers led by Shigeaki Kato at its Institute of Molecular and Cellular Biosciences had conspired to use false graphics in 33 research papers.

While Kato left the university in March 2012, soon after the allegations first surfaced, he has earned the dishonor of ranking No. 7 in the world for the number of papers retracted, at 39, according to the latest tally by Retraction Watch, a website that tracks retractions of scientific papers.

Presiding at the top of the global ranking is another Japanese, Yoshitaka Fujii, who holds the record of retractions by a single author, at a whopping 183. The anesthesiologist at Toho University was forced to quit the university in February 2012.

Ichikawa said that Japanese scientists have a long way to go to catch up with the West on ethical standards, particularly concerning how to prepare and present statistics.

Until then, misdeeds from the past, especially concerning research more than 10 years old, will continue to surface, he predicted.

Biomedical researchers in Japan also need to correct their often too-cozy relations with drugmakers, Ichikawa pointed out, saying such relations cause ethical and conflict-of-interests issues.

Doctors' ties with Big Pharma have been a long-standing issue worldwide, but in the U.S. efforts to eradicate the seeds of corruption are growing, he said, adding that more universities today ban drugmakers on campus.

"In Japan, there are about 60,000 sales representatives for drugmakers," he said, noting that doctors still get financial assistance from drugmakers in many forms, such as expensive honoraria for speeches and luncheon seminars sponsored by them at academic conferences.

"Medical researchers in Japan are not alert enough. They are being 'doped' by drugmakers."

<http://www.japantimes.co.jp/news/2016/10/12/national/science-health/todai-biomedical-research-fraud-probe-seen-pointing-wider-misconduct/>