NATURE | NEWS

Papers on ‘stress-induced’ stem cells are retracted

High-profile reports claiming an easy way to create pluripotent cells were flawed, *Nature* announces.

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Haruko Obokata, here at a 9 April news conference in Osaka, Japan, was found guilty of misconduct but stands by her claim of having produced stem cells by a novel procedure.

Nature today retracted two controversial papers on stem cells that it published in January[1,2]. The retractions — agreed to by all of the co-authors — come at the end of a whirlwind five months during which various errors were spotted in the papers, attempts to replicate the experiments failed, the lead author was found guilty of misconduct, and the centre where she is employed was threatened with dismantlement. The retraction notice[3] includes a handful of problems with the papers that had not been previously considered by institutional investigation teams.

Questions remain over what exactly was the basis for claims that embryonic-like stem cells could be created by exposing bodily cells to stress — a technology the authors called stimulus-triggered acquisition of pluripotency, or STAP. But the controversy promises to have lasting impact on science in Japan, global stem-cell research, and the scientific community more broadly — including changes in editorial policy at *Nature*. An Editorial posted today with the retractions notes the need for improvements in publishing procedures: “The episode has further highlighted flaws in *Nature*’s procedures and in the procedures of institutions that publish with us.” (*Nature*’s news and comment team is editorially independent of its research editorial team.)

The first of the two papers[1] described a method of using acid exposure or physical pressure to convert spleen cells from newborn mice into pluripotent cells — cells that can become any cell in the body. The second paper[2] further impressed stem-cell scientists with data showing that the STAP process created cells that could differentiate into placenta cells, something that other pluripotent stem cells, such as embryonic stem cells and induced pluripotent stem cells, do not normally do.

But within weeks, duplicated and manipulated images were discovered, focusing attention on the source of data provided by Haruko Obokata, a biochemist at the RIKEN Center for Developmental Biology in Kobe and first author on both papers. Scientists also reported difficulties in replicating the experiments.

A RIKEN investigation team looking into the papers announced on 1 April that Obokata had been found guilty of two counts of scientific misconduct. RIKEN rejected an appeal, and advised her to retract the papers in May. Co-author Teruhiko Wakayama of the University

of Yamanishi had been arguing for retraction since March.

Obokata and Charles Vacanti, an anaesthesiologist at the Brigham and Women's Hospital in Boston, Massachusetts, and the senior corresponding author on the first article, both stood by its claims, but later changed their positions after new errors emerged. Obokata gave her consent to the retraction of both papers on 4 June.

The retraction notice published today lists five new errors. The first four note that captions do not describe what is in the corresponding images or figures, without reflecting on how this relates to the experimental data. The fifth, relating to the first paper[1], notes that purported STAP cells are of a different genetic background from those supposedly used in the experiments — something it calls "inexplicable discrepancies".

The notice concludes: "These multiple errors impair the credibility of the study as a whole and we are unable to say without doubt whether the STAP-SC [stem cell] phenomenon is real."

Austin Smith, a stem-cell biologist at the University of Cambridge, UK, also retracted a News & Views article published alongside the two STAP papers.

Obokata and Vacanti still maintain that the phenomenon is real. In a statement posted on his website, Vacanti says that he agreed to the retraction "although there has been no information that cast doubt on the existence of the [STAP] phenomenon itself".

For many observers, the retraction confirmed doubts they had from the beginning. Alan Trounson, former director of the California Institute for Regenerative Medicine in San Francisco, says that there are plenty of acidic sites in the body, where scientists don't find pluripotent cells. "It doesn't make sense that the cells would respond this way, otherwise we'd have a lot of problems." Pluripotent cells would, for example, be a potential cancer risk.

Other researchers are not ready to completely shut the book on stress induction. Qi Zhou, a cloning researcher at the Institute of Zoology in Beijing, says that external stimulation, either chemical or physical, might be able to change the status of cells, but that the type of full pluripotency seen in embryonic stem cells is unlikely to be possible with such a simple acid method or other single factor. "I hope that can be achieved someday," he says.

Davor Solter, a developmental biologist at the Institute of Medical Biology in Singapore, says: "It is conceivable that such mistreatment of cells might result in reprogramming, though I doubt that such reprogrammed cells could be easily detected." The STAP papers certainly did not convince him. "Cells as described in these papers behaved in a way (if the description was correct and not made up) that is difficult to understand and impossible to independently verify."

Obokata is being given a chance to prove her sceptics wrong. With the disciplinary action to be taken by RIKEN still undecided, Obokata has been invited to assist in ongoing efforts to replicate the experiments being carried out by two senior CDB researchers — Shinichi Aizawa and Hitoshi Niwa, the latter a co-author on the STAP papers.

Today, Obokata, who has been hospitalized, showed up for work for the first time in months, according to the Japanese media. But with suspicions swirling about the source of the cells used in the original experiment, her credibility is low, and her activity in the laboratory will be monitored by video recorder.

Preliminary results of the replication effort are expected in late July or August.

Although the scandal has tainted the reputations of co-authors, scientists around the world have urged RIKEN to avoid shutting down the entire CDB, a drastic option that was mentioned in a report published by an independent committee last month.

The impact of the events extends beyond Kobe, and beyond Japan. It is another blow for stem-cell research, says Solter. The STAP episode "certainly increased the reputation of [pluripotency] as a field where bad results tend to be uncritically published and, for sake of publicity, normal scientific processes are suspended", says Solter.

The episode has also led *Nature* to rethink its review policy. The Editorial accompanying the retractions defends the journal, saying that "the editors and referees could not have detected the fatal faults in this work". Still, it is putting "quality assurance and laboratory professionalism ever higher on our agendas, to ensure that the money entrusted by governments is not squandered, and that citizens'

trust in science is not betrayed". The Editorial cites a planned increase in the number of articles to be scanned for manipulated images as one measure meant to detect misconduct.

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References

1. Obokata, H. *et al. Nature* **505**, 641–647 (2014).
2. Obokata, H. *et al. Nature* **505**, 676–680 (2014).
3. Obokata, H. *et al. Nature* **511**, 112 (2014).