

# COLLATERAL DAMAGE

*How a case of misconduct brought a leading Japanese biology institute to its knees.*

BY DAVID CYRANOSKI

**H**ironobu Fujiwara was already troubled as he made his way to work on 5 August 2014. As a laboratory head at the RIKEN Center for Developmental Biology (CDB) in Kobe, Japan, Fujiwara had been enduring criticism ever since a case of misconduct had been exposed at the centre earlier that year. A media furore had escalated week by week, as newspapers, social media and television programmes all demanded an explanation for how scientists at a prestigious institute could have conducted shoddy work. Although he was not involved in the suspect studies, Fujiwara and many other employees at the centre felt under attack.

And then, when he arrived that day, he heard terrible news. Yoshiki Sasai — a founding member of the CDB who had been implicated in the misconduct case — had hanged himself in an adjoining building that morning. “I was just in shock,” Fujiwara says. “I didn’t know what to think, or whether to believe it was true.”

Revelations of scientific misconduct always cause collateral damage: they taint colleagues and co-authors of the person responsible, and can close down labs. But the case at the CDB triggered unusually strong and far-reaching aftershocks.

The case involved two high-profile papers in *Nature*<sup>1,2</sup> that described a surprisingly simple method to make pluripotent stem cells — cells with the prized ability to develop into any of the body’s cell types. After the misconduct came to light, a crucial report blamed not just the individuals involved, but also the entire centre — and recommended that it be dismantled. Since then, the CDB’s funding has been slashed, half of its labs have been closed, merged or assigned to other organizations, and its leadership has been replaced. The upheaval reaches far beyond the centre. A government science administrative reform has been put on hold and the scientific community across Japan is now bracing for the impact of anti-misconduct policies introduced in the wake of the affair.

To many scientists and journalists in Japan, this was an appropriate response. They thought that the stem-cell results had been sensationalized, and that it was fitting to take drastic action when those results were shown to be false.

But other scientists in Japan and many abroad call it an overreaction and say that events over the past year reveal how responses to a crisis can create their own problems. The way that scientists and the media reacted exposed long-standing jealousies in Japan towards the 15 well-funded RIKEN centres and institutes, which had already made

the CDB a target for critics. The frenetic media and social-media response created a storm that bureaucrats and science-policy administrators were desperate to quell. And reporting by *Nature* calls into question whether the CDB was given enough of a chance to defend itself: a committee behind the key report on the future of the CDB did not interview most of those involved to find the causes of the misconduct. Teruo Kishi, who led the committee, defends the process. “You seem to think that by talking to people involved we would find something out,” he says. “But we wouldn’t have learned anything from asking them.”

Some scientists worry that the ferocity of the response will hamper research for current or former CDB scientists and even dampen Japan’s ability to support innovative science in the long run. “It was only two papers, but from the beginning to the end the media kept blowing it up larger and larger,” says former cancer geneticist Yuko Ito, now a science-policy expert at the Japan Science and Technology Agency in Tokyo. “In the end, a lot of scientists became victims.”

## SCIENTIST’S PARADISE

RIKEN was founded in 1917 as the Institute of Physical and Chemical Research in Tokyo, and it expanded heavily into biological sciences with a series of institutes that opened from the late 1990s onwards. The centres became known in Japan as a scientist’s paradise, because researchers there had no undergraduate teaching responsibilities and enjoyed generous salaries and research funds that meant that they did not depend on grants. Even before the stem-cell crisis, “the relationship between RIKEN and universities was not really good”, says Hiroshi Hamada, a developmental biologist formerly at Osaka University, who took over as CDB director this year.

Even among RIKEN centres, the CDB stood out. Launched in 2000, when Japan was trying to rejuvenate its research infrastructure, the institute abandoned the crusty hierarchical structure that encumbered university laboratories. Scientists and staff address each other with the common *san* rather than the *sensei* typically used for superiors. In a 2002 interview with *Nature*, Sasai vowed to “give young researchers a degree of independence” that was previously unknown in Japan (see *Nature* 415, 952–953; 2002) — and soon young principal investigators, some still in their 20s, were mapping out their research programmes. A handful of established researchers, known as group directors and including Sasai and founding director Masatoshi Takeichi, oversaw operations.

The approach quickly paid off, and high-profile results emerged. Lab leader Mitunori Saitou won acclaim for engineering germ cells in a dish (see *Nature* 500, 392–394; 2013); Sasai built a reputation for his skill growing eye and brain structures in culture (see *Nature* 488, 444–446; 2012). In a country where research

has often struggled to make an international impact, the CDB developed a global reputation for exceptional work in developmental biology. The institute was proud to state that of 163 papers that its researchers published in 2013, one-third were in leading international journals including *Nature*, *Science* and *Cell*.

The centre seemed to score another big coup in January 2014, when some of its scientists published the two papers on pluripotent stem cells. Developing the technology, called stimulus-triggered acquisition of pluripotency, or STAP, was the project of biochemist Haruko Obokata, who had started the work at Harvard University in Cambridge, Massachusetts, and brought it to the CDB. She had worked with three highly respected scientists at the centre: mouse-cloning pioneer Teruhiko Wakayama, stem-cell biologist Hitoshi Niwa and Sasai.

When the technique was published, it caused excitement in Japan. Pluripotency had become almost a household word since Shinya Yamanaka at Kyoto University had won a Nobel prize in 2012 for his work on a related technique to make induced pluripotent stem (iPS) cells. And the media made much of Obokata, a young, quirky woman who wore a *kappogi* — a type of traditional apron that she had received from her grandmother — instead of a lab coat, and whose laboratory walls were painted pink and yellow. She was everything that the traditional Japanese scientist was not.

Within weeks of the papers' publication, however, the work began to unravel. Science blogs pointed to manipulated figures and other scientists could not repeat the results (see [go.nature.com/h9tr5w](http://go.nature.com/h9tr5w)). A committee at RIKEN investigated and found signs of

misconduct. RIKEN officials held marathon four-to-five-hour press conferences, formally accused Obokata of misconduct on 1 April, and recommended that the papers be retracted, which they later were. The committee's report said that Sasai and Wakayama had not been involved in the misconduct, but shared "grave responsibility" for not catching the problematic data. Niwa was cleared of wrongdoing.

At this point, the typical university fraud case in Japan — and there have been several high-

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profile examples over the past 15 years — winds down. The researcher implicated in the misconduct usually resigns and the tainted papers are retracted. Witness, for example, the resignation of University of Tokyo molecular biologist Shigeaki Kato and the retraction of dozens of his papers between 2012 and 2014. In that case, the damage was limited to members of Kato's group.

But with STAP, the media was hungry for more. News teams camped in the lobby of the

CDB and filled the corridors of the science ministry, looking for twists to the story. They trailed Obokata, Sasai and many other CDB researchers and administrators. (Japan's national broadcaster, NHK, apologized after Obokata was injured in one scrape with reporters.)

News articles, tweets and blogs started spreading the blame to the CDB and RIKEN as a whole. Critics said that the misconduct investigation had been hastily prepared, and had failed to get to the bottom of the problem. They also focused on a patent that RIKEN and the scientists involved in the work had filed on the STAP technique — standard practice in academia, but taken as evidence that the centre and its researchers were driven by economic incentives. Noriko Osumi, a developmental biologist at Tohoku University and one of the most vocal critics of RIKEN during the STAP crisis, faulted the organization for "inviting excessive attention from the media", which she blamed on "the influence of commercialization and industrialization of research in the life sciences". The desire for money and media attention was seen by others as a reason that senior scientists at the CDB had thrown their weight behind the STAP project and let their guard down, allowing poor science to take place.

Young CDB investigators who had nothing to do with Obokata's work were worried that their reputations were being tarnished. "At first the line was blurred, then we saw that there was no line at all," says Yu-Chiu Wang, who had arrived at the CDB in October 2013 from Princeton University in New Jersey. "We were all seen as part of the same criminal complex." CDB scientists, technical staff and secretaries were being slandered online, says Takeshi Imai, a neurobiologist at CDB. "Myself, my lab members and colleagues were also there," he says. Even researchers at other RIKEN centres felt under attack.

### QUIETING THE STORM

The media hullabaloo was a headache for the science ministry, which was making plans to give certain research organizations unprecedented autonomy. RIKEN was to be the first. The ministry "wanted to finalize the misconduct matter quickly", says Maki Kawai, a former RIKEN executive director. It thought an aggressive action "would seem a more reasonable response to the taxpayers' voice, which is the media".

On 9 April 2014, shortly after Obokata was charged with misconduct, RIKEN established an independent 'reform committee' chaired by Kishi, a lean 75-year-old materials scientist with a long list of top administrative positions. On 12 June, the Kishi committee released eight recommendations, including the promotion of research integrity, new fraud-prevention measures and a more thorough investigation of the STAP papers. But among these, one recommendation leapt out: to "dismantle" the CDB. "The Kishi report threw me out of my chair,"



Teruo Kishi (second left) of the RIKEN reform committee, at a 2014 press conference on the CDB's future.

says Ichiro Hiratani, a developmental biologist who had joined the CDB the previous year.

The Kishi committee's main task was to suggest measures to prevent misconduct, but half of its report analysed what had happened in the STAP misconduct episode, and why. The centre should be dismantled, the report said, because "the CDB, as an organization, had structural flaws, that induced or could not deter fraud". One of the main problems was an ossification of leadership: since its founding, the centre had had basically the same group directors. These, the report said, had come unconsciously to rely on each other in a cosy relationship that prevented critical scrutiny of each other's decisions.

Takeichi says that he and the CDB had been aware that a change was overdue well before the crisis. Over the preceding three years, the centre had searched for a foreign director to breathe new life into the CDB and increase its global status, but found it difficult to recruit a scientist of suitable calibre. However, Takeichi's leadership had not been in question before the STAP crisis. In 2011, RIKEN's advisory committee opposed his retirement.

The Kishi report said that poor governance at the CDB had led to mistakes. It accused the centre of circumventing normal procedures to help hire Obokata, and "surmises" a reason: "the CDB was strongly motivated by a desire to acquire a groundbreaking result" that would outdo Yamanaka's discovery of iPS cells. The report "surmises" that Sasai "naturally was involved in STAP in anticipation of the huge budget" that it would bring to the CDB. The report also said that Obokata's decision to wear a *kappogi* was part of a "showy PR strategy" orchestrated by Sasai.

In response to the report, RIKEN quickly convened a committee to start working out how to implement the recommendations. "Given how harshly the media was treating RIKEN, it had no choice but just accept it," a science-ministry official who does not want to be named told *Nature*. But Takeichi and Sasai contested many of the assertions in the report. Takeichi said that the hiring process for Obokata was normal; he and Sasai denied that there was a desire to outdo the iPS discovery, and other researchers at the CDB say that there was no pressure to do so. Part of Sasai's job as CDB deputy director was to organize and seek funding — a job at which he was very successful — but in an e-mail to *Nature*'s news team in June 2014, he denied that he had become involved in STAP because it would attract money to the institute. Sasai, Takeichi and RIKEN's public-relations office have all denied being involved in Obokata's choice of clothes.

In the interview with *Nature* in February, Kishi stood by his committee's report and acknowledged that it went beyond fact. "There was a lot of speculation, guesses, in the report," he said. "But they were guesses made with confidence," on the basis of what he had seen in long, televised press conferences.

Kishi said that in preparing its report, the committee did not talk to Obokata, Sasai or anyone at the CDB aside from Takeichi — a fact that other members of the committee confirmed. Kishi says that RIKEN would not let the committee meet with Sasai. But, Kishi said, "his televised conference made me feel that I didn't need to hear any more than what he said. I felt he said enough, he cannot be changed."

## "GETTING ALMOST NO SUPPORT FROM SCIENTISTS WAS SHOCKING AND DEPRESSING."

Then Kishi passed a surprisingly harsh judgement on Sasai. "Even if we had asked him, he would not have told us the truth," he said. This differs from the opinion of those who knew Sasai well, who say he was an honest, broad-minded person, devoted to scientific research.

Committee member Masaki Nakamura, a research-integrity specialist and historian of science at Osaka University, also defended the report. He says that speculation was used in it the same way that a prosecutor will fill in the motivations of a defendant in a court of law. Four other members of the Kishi committee did not respond to requests for comment, or refused to comment. Nicholas Steneck, an expert in research integrity at the University of Michigan in Ann Arbor, says that in a misconduct case, he personally "would not be comfortable speculating about anything that was not based on some facts and direct information". He says, however, that such speculation is surprisingly common among scientists. "History and reporting on current events should follow basically the same methods as science," he says.

When the Kishi report came out, many foreign scientists found its conclusions excessive and arbitrary, and more than 150 letters of support were sent to the CDB. But in Japan, it was mostly received uncritically. Scientific organizations such as the Science Council of Japan threw their weight behind the judgement. The most dispiriting thing for many CDB researchers was the indifference or criticism from their scientific colleagues — some of it a reflection of the resentment of the CDB and RIKEN that had built up over the years. "Newspaper and

media, fine, they are trying to sell newspapers," says Hiratani. "But getting almost no support from scientists was shocking and depressing."

The fallout was especially hard on Sasai. Until June he had been "somehow getting by", says Keiko Muguruma, a stem-cell biologist at the CDB and a frequent collaborator with Sasai — they had just submitted a paper for publication. "In science, he felt he could recover from the harm to his reputation. But for things that he had no control, like the dismantling and budget decrease, which would affect all the young researchers, he felt guilt and responsibility," says Muguruma. According to the lawyer working with Sasai's family, the Kishi report and media attacks were factors in explaining Sasai's suicide. Kishi and Nakamura respond that it is difficult to know why Sasai took his own life.

In August, the CDB began making changes in line with the Kishi report. RIKEN announced a plan to introduce new fraud-prevention measures and strengthen governance.

Months later, in November, Takeichi stepped down and an interim director was put in place. The CDB saw 9 of its 40 laboratories shifted to other RIKEN centres, and another 11 were merged or closed. The centre also changed its Japanese name to "centre for research into the formation of multicellular systems", although it kept its original English name. In December, after announcing that she had failed to repeat her experiments, Obokata resigned.

The changes are still going on. On 1 April this year, Hamada took over as director and a 40% cut to the centre's budget kicked in. Researchers have been scrambling to supplement their finances with grants.

### ASSESSING IMPACT

In interviews in the past two months, Kishi and Nakamura expressed tempered views of the CDB. Nakamura says that Takeichi's leadership had been "extremely good in comparison to other universities and research institutes". Although "we wrote about problems in their research ethics and education", Nakamura says, the CDB "was relatively speaking really quite advanced".

The word dismantle (*kaitai*) was a strategic choice meant to please an angry press rather than to put an end to the CDB, say both Kishi and Nakamura. It was "an appeal to society, trying to show the idea that RIKEN was taking this problem seriously", Nakamura says. Both say that they wanted to see the centre rebooted under new leadership and with a new name. Kishi says he wanted a "reborn CDB" — and in his view, the restructuring has met that aim. "Nothing's really changed," says Kishi.

But that is not how it looks to those on the ground. Hamada and other CDB researchers worry about whether they will be able to attract new principal investigators and postdoctoral researchers to the now-tarnished centre. It has lost two of its most prominent researchers in Sasai and Niwa, who is moving to Kumamoto



Yoshiaki Sasai (right), co-author of the controversial stem-cell papers, bows after speaking at a press conference in April 2014.

University this year. Fujiwara has stayed at the CDB, but says that his research has suffered. When he was supported by secure funding from the centre, he had planned a five-year project to map proteins in the extracellular matrix of hair follicles. Now that he must secure year-to-year grants, that project looks harder to realize.

The impact of the STAP episode has also been felt further afield. Since August, policies for preventing and dealing with science misconduct have been released by the science ministry, the health ministry and other bodies. As part of this, data-management rules are being tightened to ensure that data are checked more often and are made available for verification. Such rules are frustrating scientists, and there are widespread concerns that research is becoming overly bureaucratic. “We had a pretty good system, but now we have to check this and that,” says Kawai. “I don’t want to grab time from scientists.”

The new science-ministry guidelines make an institution responsible for fraud, and say that its funding can be cut if fraud-prevention measures are deemed inadequate. Imai says that this could be counterproductive, because it could push institutes and scientists to cover up suspected misconduct.

STAP could have a more subtle but pervasive impact on science, says Ito. Historically, young researchers in Japan have been able to take an

experiment in a different direction from their supervisor’s, and to follow their hunches down often productive paths. But the fear of fraud is likely to lead to stricter internal auditing, including the checking of lab notebooks, so “now they’ll be afraid to. That will affect their ability to be innovative and they will be less motivated,” says Ito. “That will be the biggest impact going forward.” It is ironic, she says, that the experience of the CDB, which was born out of the desire to encourage young scientists, could end up stifling them.

Steneck says that it is useful to assess whether the STAP case was handled in the best way. He says that RIKEN responded well when the issue came to light: “They faced up to the problem quickly and brought in other opinions.” But he questions the make-up of the Kishi committee, which was dominated by scientists. He thinks that a misconduct investigation should be led by experts in studying behaviour in scientific and research institutions. “Having a committee of non-experts gather their own evidence does not work.”

Paul Taylor, director of the Office for Research Ethics and Integrity at the University of Melbourne in Australia, says that a Japanese investigatory organization akin to the US Office of Research Integrity might have helped. “It provides an independent source of expertise in

conducting investigations, and perhaps ensures that trust in research is maintained,” he says. He adds that Japan’s tightened requirements on data management and research-integrity training might help to prevent scientific misconduct in the future — but there are limits. “If someone is able to justify to themselves why it is OK to fabricate an image, or steal someone’s work, then they will do that even in the presence of the best research-integrity environment.”

Hamada is optimistic that the CDB can move on. He hopes to negotiate with the science ministry to restore researchers’ budgets within three years, and plans to continue the CDB’s mission of gambling on promising young scientists. “I have to reorganize, refresh,” he says. “My job is to forget about what happened.”

That will not be easy for Fujiwara. He was just starting to get good data — but is worried that he will have trouble getting funding for the mouse experiments that he needs to even publish his work so far. “It was going to be an important year for us,” he says. Now, he just hopes that his science can survive. ■

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