Stem-cell scientists mourn loss of brain engineer

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Scientists around the world are struggling to get to grips with the loss of one of the brightest stars in stem-cell science. Yoshiki Sasai of the RIKEN Center for Developmental Biology (CDB) in Kobe brought excitement and rigour to the field but died today, 5 August, aged 52. The reasons for Sasai's apparent suicide are still not clear but a scandal swirling about two stem-cell papers published in *Nature* in January had wreaked havoc on his career.

"Dr Sasai was a rigorous and innovative scientist and his loss will be deeply felt," says Janet Rossant at the Hospital for Sick Children in Toronto, Canada, a former head of the International Society for Stem Cell Research. "His most important contributions to the stem-cell field came from his background in developmental biology."

Sasai's research spanned developmental biology, stem cells, organogenesis and tissue engineering. His success was built on his painstaking efforts to understand exactly which factors needed to be added or removed to cell cultures to guide embryonic stem cells as they differentiated to mature cell types, especially neuronal cells.

"He sees things that others don't see," Eddy De Robertis told *Nature* in a 2012 interview. De Robertis, a developmental biologist at the University of California, Los Angeles, who supervised Sasai's postdoctoral work in the mid 1990s, recalled Sasai once retyping a manuscript lost in a computer from

memory with word-for-word perfection. “I’d never seen anything like that,” he said.

Lab-grown cortex

One of Sasai’s innovations was the discovery in 2007 of a pharmacological compound that kept embryonic stem cells from dying when separated from each other. Previously, embryonic stem cells had to be manually cut with a cumbersome method and transferred as partial colonies, which resulted in experimental variation. “His paper solved that overnight,” says Luc Leyns of the Vrije Universiteit in Brussels.

But Sasai's show-stoppers came shortly after that. Based on his success in differentiating neurons, Sasai started mimicking embryonic development with such fidelity that his cells would organize themselves into three-dimensional structures, including a goblet-shaped clump of retinal tissue known as an optic cup and intricate layers of tissue that resembled a cerebral cortex.

Both these discoveries opened the field of *in vitro* brain organogenesis. “Finally, we have easy access to the developing brain without having to micro dissect embryos,” says Leyns. Leyns says he uses Sasai’s papers “to show master’s students how a modern scientific discovery is made and progressively built-up to a climax”.

Sasai’s work was inspirational, says Pete Coffey of University College London, where Sasai presented the optical cup research last November. “The clarity of his presentation, the excitement and post lecture discussions with fellows and students are still discussed today. He had a major impact on my group,” says Coffey. Sasai’s research will probably contribute to treatments for various disorders, such as macular degeneration. “His findings galvanized the ophthalmology community in truly developing a cell therapy for blinding disorders,” says Coffey.

Rare misstep

Sasai planned to improve on each of his three-dimensional brain structures, for example creating a pituitary gland with a blood supply. He had an even grander vision of figuring out how all of the different brain parts link up to create the complex networked structure we have.

But back in December 2012, he had started helping Haruko Obokata, then a visiting researcher at the CDB, to prepare a manuscript that reported a method of creating embryonic-like stem cells merely by subjecting mature cells to stress. The method, known as stimulus-triggered acquisition of pluripotency, or STAP, resulted in two papers that were published in *Nature* in January 2014 and included Sasai as a co-author. Both papers were subsequently shown to be full of problems, and on 2 July, *Nature* retracted them.

On 1 April , a committee judged that Obokata had committed scientific misconduct by including in one of the papers a manipulated figure and an image that she had already used in her dissertation to

illustrate a different phenomenon. Sasai was cleared of any direct involvement, but he was found to have “heavy responsibility” for failure in oversight of the project. He was still awaiting the judgment of a RIKEN disciplinary committee.

Peers say that Sasai should have more carefully ensured the reproducibility of such extraordinary claims and that he was guilty of overhyping the research when it was first announced. But those who know Sasai think it was a rare misstep. Leyns who got to know Sasai during pizza lab seminars at the University of California, Los Angeles, says that Sasai was always the one to insist on independent confirmation. “He may have dropped the ball on a story which was not his core research field [STAP] but, knowing him, I have not the slightest doubt about his scientific integrity.”

In Japan, the media rained criticism on Sasai, including unsubstantiated accusations, some of which made it into a harsh independent investigative report. Among other things, the report suggested that CDB management, including Sasai who was deputy director, had made Obokata wear an apron given to her by her grandmother to a press conference in an attempt to sensationalize the STAP cell results. The report also “surmised” that Sasai was driven by the desire for large grants in pursuing STAP research.

Loving father

In his last e-mail to *Nature*'s news team (which is editorially independent of its research editorial team), on 26 June, Sasai admitted that he failed to subject the data to sufficient scrutiny, but he vehemently denied that he was thinking of funding opportunities or that he had a hand in deciding what Obokata wore to the laboratory.

In June, when we asked for substantiation of various allegations brought against Sasai and the CDB, neither materials scientist Teruo Kishi of the University of Tokyo, the head of the committee, nor other committee members offered any. *Nature*'s news team was told: “Our committee has fulfilled our mission and has now been dissolved.” Committee members also noted the desire “to avoid any unnecessary confusion and/or misunderstanding” when refusing to provide evidence for their claims.

In an apparently unprecedented move, the independent committee recommended that the CDB be disbanded. For Sasai, who was a major driver in the establishment of the CDB in 2000, “those sorts of threats would have weighed heavily”, says Robin Lovell Badge, a stem-cell and developmental biologist at the Medical Research Council in London. “They were very unfair.”

The reason for Sasai’s apparent suicide is still not clear. He was found hanging in the stairwell of a research building adjacent to the CDB. Three farewell notes were in a bag there, one addressed to the CDB management, one to Sasai’s laboratory members and one to Obokata.

“This is a great loss to science and regenerative medicine in particular. A tremendous loss for his family,” says Coffey. Leyns remembers Sasai as ”a loving father who left the lab in the early evening to go home to share good moments with his young kids at bath and bed time and then came back to the

lab to work late." "My thoughts go first to his very kind wife and children," says Leyns.

Back in 2012, De Robertis noted that he was proud of Sasai, "an absolute leading light" whose research had a "long trajectory of achievement". That trajectory has now been cut tragically short.