Yoshiki Sasai

(1962–2014)

Stem-cell biologist who decoded signals in embryos.

How does a fertilized egg — a single cell — produce the myriad specialized cells that assemble into three-dimensional tissues and functioning organs? This fundamental secret has captivated generations of embryologists. Using creative culture conditions and unmatched insight into the action of biological signals that govern tissue development, Yoshiki Sasai found ways to mimic these mysterious processes in the laboratory. He leaves a legacy of remarkable discoveries that expand the frontiers of stem-cell research and tissue regeneration.

Yoshiki struck me as a happy scientist. He spoke softly and with a unique smile as he described Japanese traditions or revealed his astonishing findings. My first experience of his pride and passion came during a long walk on Japan's Rokko Mountain in 2008. We looked over the splendour of Kobe and the reclaimed island where his institute, the RIKEN Center for Developmental Biology, lay. The sight brought that smile to his face. As he taught me the art of ninja walking, recounted the local thousand-year-old methods used to make sake, and dissected the etiquette of Japanese bathing, he explained some of his incredible scientific discoveries.

Sasai was a master at deciphering the code by which cells learn their place in a developing embryo. He tested this code on cultures of embryonic stem (ES) cells derived from early-stage embryos, and instructed these unspecialized cells into becoming specific types of neuron. He made nerve cells found in different parts of the forebrain by varying concentrations of morphogens, molecules that guide the patterning of tissues. Sasai's laboratory developed the first methods to make inhibitory interneurons, which hold promise for brain repair. He also discovered a simple set of cues to make the brain's hypothalamic neurons and pituitary cells, important for several bodily functions.

Sasai instructed both mouse and human ES cells to become cortical neurons, the type that expanded markedly during the evolution of the human brain. Remarkably, his ES-cell-derived cortical cells assembled into floating, three-dimensional organoids similar to the embryonic organ from which the brain's cerebral cortex arises. By carefully adding growth factors, he coaxed the organoids into forming the front or the back of the cortex. These advances provide powerful tools for understanding healthy and aberrant human brain development. The methods that he developed may one day be used to make replacement cells to treat currently uncurable diseases.

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Sasai amazed the stem-cell community with time-lapse videos showing human and mouse ES cells turning into optic vesicles, the precursors of eyes. He demonstrated that these go on to form an optic cup and all the major cell types in the retina. Sasai's laboratory inferred the basic principles of how eyes form from self-directed cell assembly, gaining insights into a process that is difficult to monitor and manipulate in developing animals. When I visited his laboratory in February, Sasai shared recent work indicating how these optic cups acquired polarity, in which individual cells take on different properties according to their position in a larger structure. This trait is crucial for neural connectivity and vision.

Sasai's work deriving cortical, visual and pituitary tissues demonstrated that complex, highly organized structures could be made from isolated human ES cells. The work broke new ground in understanding tissue and organ formation, modelling disease and advancing regenerative medicine. He thought that it could be pushed even further, thinking of ways to generate multiple brain structures *in vitro* that could become interconnected.

Sasai obtained his MD in 1986 and his PhD in 1993 from Kyoto University, where he trained as a molecular biologist in the laboratory of neuroscientist Shigetada Nakanishi. He then went to the University of California, Los Angeles, and worked with embryologist Edward De Robertis to discover chordin, one of the key early inducers in the formation of the nervous system. In 1996, Sasai moved back to Kyoto University, where he began his extraordinary work mimicking embryonic development in a dish. He moved to RIKEN in 2000.

Given the pride that Yoshiki felt for the work he was doing in his home country, his enjoyment of and devotion to good science, his family, and life in general, I was shocked to learn that on 5 August my admired colleague and dear friend had taken his own life. Clearly, his mental state took a very heavy blow from the onslaught of media attention and the months of allegations surrounding two *Nature* papers published in January from the laboratory of Haruko Obokata, on the generation of stimulus-triggered acquisition of pluripotency (STAP). Laboratories around the world were unable to reproduce the findings, and after serious problems were found with the studies, the papers were retracted in July. Although the work was not a direct product of his laboratory, Sasai was a co-author of the papers. In June, he wrote to me expressing his deep concerns about the worsening STAP situation in Japan.

Yoshiki's career was full of insights that prompted the unique smile that we will greatly miss. I hope that his realized and unrealized ideas inspire the next generations of scientists to follow his solid legacy of research. It is a true tragedy that the scientific community is left without this forward thinker. ■

Arturo Alvarez-Buylla *is professor of neurological surgery at the University of California, San Francisco, USA. He collaborated with Yoshiki Sasai between 2008 and 2014.*
e-mail: abuylla@stemcell.ucsf.edu