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THE STRESS TEST

Rivalries, intrigue, and fraud in the world of stem-cell research.

By Dana Goodyear

A group of researchers believed that subjecting tissues to trauma could give ordinary cells stem-cell-like properties.

Yoshiki Sasai was known as "the brainmaker." One of Japan's foremost developmental biologists, he made discoveries that illuminated the formation of the embryonic nervous system, and, using stem cells, he grew the optic cup, parts of the cerebral cortex, and the rudiments of a cerebellum. Calm and precise in the lab, Sasai was cultivated and erudite outside it, with a reputation as a gracious host who escorted visiting colleagues to *onsen* spas and prepared sushi for lab parties. "There are not too many people in our field who like to discuss Goethe," Christof Niehrs, a prominent biologist, told me. "His talks were exquisite. He was a perfectionist in whatever he did."

In 2000, during a period of explosive growth in his field, Sasai helped found the Center for Developmental Biology, a branch of the prestigious, government-funded research institute Riken. C.D.B., based in Kobe, was staffed with ambitious scientists who, freed from teaching obligations and equipped with sophisticated laboratories, were expected to make significant discoveries, and publish them illustriously. At this, too, Sasai excelled, announcing his discoveries in major journals such as *Nature* and *Cell,* and keeping the center's laboratories well funded by skillfully marketing their achievements. "He understood how to push the science," Ken Cho, a friend and colleague of Sasai's, told me. "He had that sixth sense."

Several years ago, Sasai began to collaborate on a novel stem-cell technology being developed at C.D.B. The idea was so simple as to be heretical: ordinary cells could be turned into stem cells by subjecting them to profound stress. Few cells could survive the abuse, but those which did emerged transformed, apparently able to make any cell in the body. Sasai named the cells STAP, for stimulus-triggered acquisition of pluripotency.

Sasai and his colleagues announced STAP in January of 2014, in two simultaneous papers in *Nature*, the British journal that first published Watson and Crick's double-helix model of DNA. The findings were exhilarating, suggesting an innate regenerative mechanism in the body. Austin Smith, a stem-cell scientist at the University of Cambridge, wrote a companion piece, touting the cells' "unusually broad developmental potency." Here, theoretically, was a never-ending supply of super-versatile custom stem cells, free of ethical baggage. By 2020, according to the consulting firm Frost & Sullivan, stem-cell therapies will be a forty-billion-dollar global industry. STAP seemed to be a bridge to long-held goals of patient-specific drug development, advanced disease modelling, and, ultimately, the ability to regenerate body parts without the risk of immune-system rejection. Sasai compared STAP to Copernicus's reorganization of the cosmos. A financial windfall, if not a Nobel Prize, might await its discoverers.

The revolutionary behind the work was Haruko Obokata, a thirty-year-old postdoctoral researcher who was the first author on both papers. With the publications, Obokata—a stylish, self-possessed beauty, uncommonly adept at maneuvering in the mostly male world of Japanese science—was hailed as a maverick. "A brilliant new star has emerged in the science world," an editorial in the *Asahi Shimbun* read. "This is a major discovery that could rewrite science textbooks." As an outsider—young, female, and not an established stem-cell biologist—Obokata, the newspapers argued, was unhindered by conventional notions of what cells can and cannot do. Her fresh perspective, coupled with dogged work and natural genius, had conspired to create one of the great scientific breakthroughs of the twenty-first century.

The promises of stem-cell research lie at the core of human desires—to understand our origins and to cheat death—and there is a great deal of money and prestige at stake. It is a ruthlessly competitive field, susceptible to fantasy and correspondingly sensitive to bunglers. Human embryonic stem cells were first cultured in 1998; nearly twenty years later, basic assumptions about cell behavior are still routinely overturned. Andrew McMahon, a top researcher at the Broad Center for Regenerative Medicine and Stem Cell Research, at the University of Southern California, told me, "It's not unusual to see something and not be able to explain it." In reporting results, researchers must often craft a narrative to make sense of mysterious phenomena. What to ignore and what to privilege—that discernment can be the difference between brilliance and quackery, and between fame and obscurity.

Five months after publication, both STAP papers were retracted, under intense scrutiny and growing doubt about their validity. By that point, Riken had cited Obokata for research misconduct and charged her mentors with "heavy responsibility"; one of those mentors had implicated her in a fraud; she had been hospitalized for depression; a co-author had suffered a stress-related stroke; and an outside committee had recommended that Riken dismantle C.D.B.

Sasai may have felt the anguish most profoundly. Distracted in the lab, he seemed frail and diminished, and was being treated by a psychiatrist. Then, in August, 2014, a security guard found him hanged from a handrail in a stairwell at C.D.B., his shoes placed neatly on the steps. In an obituary, Edward De Robertis, who had been Sasai's mentor at the University of California, Los Angeles, wrote, "Yoshiki was a man of rectitude and a scientist of high personal integrity." De Robertis did not refer to STAP: the name was by then unmentionable. Talking to me on the phone, De Robertis said ruefully, "He got trapped."

Thoroughly discredited, Obokata went into hiding for more than a year. At the end of January, though, after I had tried for months to reach her, she sent me a letter, her first engagement with a member of the media since the scandal. Soon afterward, she published a memoir in Japan, strenuously arguing that she had been misunderstood. "I feel a strong sense of responsibility for the STAP papers," she wrote to me. "However, I want you to know I never wrote those papers to deceive anyone." She insisted that STAP was real.

It seemed that Sasai, too, never lost faith in the discovery, or in Obokata. According to the *Japan Times*, he left a note for her, which said, "Be sure to reproduce STAP cells."

The idea behind STAP originated in Boston about fifteen years ago, in the lab of Charles Vacanti, who recently retired as the chairman of the anesthesiology department at Brigham and Women's Hospital. Vacanti is in his mid-sixties, tall and stoop-shouldered, with short gray hair and an amiable tendency to credit his achievements to good luck. (His bad luck he attributes to ego and naïveté.) A lifelong tinkerer, and one of eight siblings, he spent his adolescence taking apart old cars with his brothers; he now has a collection that includes seventeen vintage motorcycles, most of which he restored himself. Vacanti's father was a professor of dentistry, and his brothers Jay, Martin, and Frank are also physicians.

Chuck, as Vacanti is known, approaches his work with the trouble-shooter's willingness to take a flyer. "If you don't say something really stupid once in a while, you aren't really pushing the envelope," he says. In the late eighties, he was working at Mass General; his brother Jay, a liver-transplant surgeon at Children's Hospital and a pioneer of tissue engineering, was struggling to grow a liver from cells seeded on a scaffold. Bored by the prospect of anesthesiology research, Chuck asked Jay if he could pitch in. He began to tinker, sometimes to outlandish effect, and often with a keen instinct for publicity. In the mid-nineties, he released a picture of a mouse with what appeared to be a human ear growing from its back. "Earmouse"—made by inserting an ear-shaped scaffold seeded with cow cells under the skin of a live mouse—became a sensational meme at the dawn of Internet Bizarre. Oprah covered it; Jay Leno called Chuck in the operating room. Later, after engineering a trachea for a fourteen-year-old girl with a life-threatening tumor, Chuck made a guest appearance on "Grey's Anatomy."

But after a decade Chuck was eager to move into new terrain. Behind his restlessness lay the story of the youngest Vacanti brother, Carl, who has Down syndrome. In tissue engineering, researchers' highest aspirations centered on generating organs, but, Chuck reasoned, patients often don't need an entire new organ. Carl didn't need a brain transplant to live an independent life; he needed a boost in mental function. Chuck envisioned extracting cells from Carl's brain, deleting the chromosome that causes Down's, and injecting him with the altered cells. "You could end up with a mosaic," Chuck ventured. "Part of the brain is his own, part is his but modified. Can you change his intelligence? I don't see why not."

As a preliminary investigation, Chuck decided to perform experiments using stem cells from the brain. He invited his brother Martin, a pathologist, to collaborate. Neither had any experience with stem cells, then a fledgling area of research. "I felt like Don Quixote," Martin told me.

The standard process for isolating stem cells from neural tissue required roughing up the tissue and then sluicing it aggressively through a pipette, a process known as trituration. After a few days in an incubator, for unknown reasons, spheres composed of neural stem cells would appear. For more than a year, Martin tried the protocol on brain tissue, to no avail. Then, on Groundhog Day, 1998, a Canadian television crew arrived to film the laboratory, and Chuck insisted that Martin come up with something to show the cameras. Hastily, he scraped a flat-edged scalpel along a tissue sample, hoping for maximum abrasion, and triturated the results. This time, when he looked at the sample underneath the microscope, he saw a smattering of tiny structures. Curious, and hoping that maybe at last he had stem cells, he took the culture to a specialist at the hospital. The expert dismissed the specks as junk—the detritus of mass cell death. "I was so discouraged," Martin said. "But I thought, It's the weekend, I'll throw it out on Monday."

Martin placed the culture flask in the incubator and left the lab; when he returned a few days later, he saw spheres. Breaking the spheres apart, he saw the specks again. It seemed obvious to Chuck and Martin that the specks were giving rise to the spheres. They began referring to the specks as sporelike cells, because of their diminutive size and their impressive hardiness. In a 2001 paper, they proposed that these sporelike cells lay dormant in all tissues and could differentiate into multiple cell types, giving them "the potential to regenerate tissues lost to disease or damage."

At meetings, when they talked about the work, their colleagues rejected it as nonsense. "There was outrage," Chuck told me. "People said, You guys are crazy, everybody knows this is junk." At a conference, one biologist heckled him, and told him to stick to tissue engineering. Chuck's wife, a schoolteacher, agreed. But Chuck's curiosity only grew. He thought that he could prove his theory with a time-lapse photographic sequence of cells coming together to form spheres. But a camera-equipped incubator would cost tens of thousands of dollars, so, instead, he rigged up one himself, using common lab equipment and a foil party balloon. The images were not conclusive, but they revealed another tantalizing phenomenon: thousands of sporelike cells—too many, he thought, to be explained only by a dormant population. This opened the possibility that the rough process of trituration was not merely segregating the stem cells from the tissue. Maybe the stress was creating them.

For cells in the body, stem-ness is a fleeting state—a potentiality that fades as cells begin to specialize. To chart the complex changes, scientists classify stem cells according to their developmental versatility. Embryonic stem cells are considered pluripotent—able to make any cell in the body—and therefore serve as a gold standard by which newly discovered cell types are evaluated. Adult stem cells, as in the lungs and the bone marrow, can produce only cells appropriate to their native tissue. But researchers debate the possibility of "plasticity," the ability of a cell to reprogram, under certain conditions, to an unexpected type.

When Vacanti began his experiments, other researchers had already established that the body harbors reserves of stem cells, which serve as élite paramedic units, responding to chemical sirens issuing from an injury. His new, highly unorthodox idea proposed an additional method of healing: bystanders to a disaster who find themselves capable of heroic feats. "When a certain number of your cells die, other cells turn on a survival mechanism, and they turn into stem cells," he told me. "It's Mother Nature's repair process." In his office, he once showed me what he meant, drawing up his pants leg to reveal his knee, which was laced with white scars, where he had hit himself with a chainsaw while cutting trees near his house. "It's almost healed," he said. "It's just amazing." He believed that the stem cells created by his wound had helped the tissue mend.

In 2002, Vacanti went to Brigham and Women's as the head of anesthesiology, and opened a large tissue-engineering lab. Recognizing that the pursuit of stress-altered cells was well outside his area of expertise, he hoped to hire someone who could help. Several years later, a Japanese colleague mentioned that he had a talented student—at the top of her class in chemical engineering at Waseda University—who was looking for a tissue-engineering project. It was Haruko Obokata.

When Obokata arrived in Vacanti's lab, he quickly recognized her as open-minded and astute. Thinking that she could add credibility and detail to his work on the sporelike cells, he asked her to recapitulate the study, employing the latest techniques in stem-cell research. For the time being, he withheld his hypothesis that harsh conditions could create stem cells. The last thing he wanted was for a graduate student from abroad to return home and develop the idea in someone else's lab. His main concern, he told me, was: "Can we trust Haruko?"

Obokata was a lab director's dream. She applied herself to the study of stem cells with fanatical devotion, and still found time to attend Harvard seminars on a huge range of topics. In the lab, she mastered every machine and method. Lab work is like cooking, and protocols like recipes: the quality of the result depends a great deal on the practitioner. Obokata was possessed of what scientists call "golden hands"—she could get everything to work. "I've never met anyone smarter," Jason Ross, who worked as a research assistant under Obokata and credits her with teaching him everything he knows about biology, told me. "Everyone saw how gifted she was. There are not many Harukos out there."

Though Obokata's English was good, she wanted to improve her accent, so Ross read "Curious George" books to her, and in return she made him shabu-shabu. She loved the United States; in Japan, she told him, female researchers were second class, expected to give up the microscope when a male—even an undergraduate—needed it. Yet she was deeply Japanese. When visitors came to the lab, she would take her gloves off and bow. Ross said, "I called her Princess Haruko."

Obokata decided to base her Ph.D. on the sporelike cells, and she performed a series of experiments to test their capabilities. Vacanti's data suggested that they might have limited versatility, like adult stem cells. Obokata, though, reported coaxing them into forming teratoma, complex tumors that provide strong evidence of pluripotency. Her adviser later told Vacanti that it was the best thesis he had ever read.

Having determined that Obokata was loyal, hardworking, and proficient, Vacanti decided to reveal his theory about conversion to stem-ness. When she expressed enthusiasm, he hired her as a postdoc and tasked her with designing experiments to explore the idea. First, she had to nail down a protocol for making spheres. Martin had starved the cells, frozen them, and deprived them of oxygen, but he got the best results from mechanical stress—squeezing them through a pipette. Like garage work, this method was hard to standardize, and hence to reproduce. How many micrometres was the tip of the pipette? How many minutes did one sluice for, and at what pace? Listening to an iPod or not? Eventually, Obokata—a chemist—discovered that she got the most consistent spheres by bathing the cells in a solution of adenosine triphosphate, a cellular fuel that also happens to be mildly acidic. The acid stress would kill off most cells, but the survivors, sustained by the ATP, would flourish. These cells, as she described them, had extraordinary qualities. Researchers testing for stem-ness often use cells engineered to glow green when they are in a state of high developmental potency. Obokata's spheres glowed vividly.

The atmosphere in the lab was giddy and intense, with Obokata working at all hours, and fantastic data coming in day after day. Koji Kojima, a Japanese surgeon who ran Vacanti's lab, urged Obokata to get more sleep, but she was single-minded. Her lab notebooks were dashed off and incomplete, and she often left her work space a mess. "Please clean up!" Kojima exhorted her. But, he said, "she didn't care. She was just so focussed." Throughout, Obokata maintained her humble, pleasing affect; her goal, she told Vacanti, was to make him smile. With their stress-altered cells, Vacanti and Obokata thought they had made a discovery significant enough to publish in a top-tier journal. He teased her, "You'll be the most famous female scientist in Japan."

"Giddydown."

Nature was founded a hundred and forty-five years ago, in England, at a moment when scientists were seeking to invest an often shambolic group of quasi-amateurs—the nineteenth-century "men of science"—with authority. In the course of its history, it has acquired a reputation for presenting cutting-edge research that advances the sciences; in 2014, the most recent year for which data are available, its articles were cited in academic work more than any of its competitors'. Space is severely limited—around eight per cent of submissions are accepted—and that exclusivity confers significance on what does appear. As a publication, *Nature* defines the frontier; unofficially, it showcases researchers' ideas for funding institutions, private companies, and universities, whose tenure committees use *Nature* credits as a measure of hirability.

To be taken seriously by *Nature*, Vacanti and Obokata felt, they needed a high-profile co-author, someone whose recognized expertise would convey legitimacy. They turned to an old friend of Kojima's, Teruhiko Wakayama, based at Riken's Center for Developmental Biology. Wakayama seemed like an ideal collaborator.

The first person to have cloned a mouse, he was a gentle researcher whose enthusiasm led other C.D.B. scientists to refer to him as a "genuine science boy." Obokata had met him two years earlier, while working on her Ph.D. "Wakayama's office was a mess, and I smelled blood and mice," she writes in her memoir. "I explained my research to him for more than thirty minutes. I was very touched by Wakayama, an authority in cloning technology, who was earnestly listening to me while taking notes."

To Wakayama, the project would have represented an unusual opportunity. His ten-year term at C.D.B. was coming to an end, and he was seeking a university position; a prominent publication could give him a tremendous lift. According to Vacanti, Wakayama "loved the idea and was a hundred per cent confident that he could get the paper published in *Nature*." With the help of his cloning expertise, they hoped to create a chimera, a mouse grown from stress-altered cells injected into a host embryo—a spectacular show of the cells' developmental potency. Wakayama had cautioned Obokata that chimeras were elusive, though; not even embryonic stem cells produced them consistently. She writes, "The production of chimera mice really depends on the skill sets of the person who conducts the experiment."

Obokata says that she took mouse cells that Wakayama gave her, exposed them to acid, and returned them to him. Thrillingly, he began to produce chimeras. But, according to the memoir, he refused to teach her how, lest she take the technology and leave him behind. If his chimeras showed signs of abnormality, she writes, "he said, 'Let's just say the mother mouse ate the baby,' and that data was not used." (Wakayama would not comment on this, and declined requests for an interview.)

In the spring of 2012, Vacanti, Obokata, and Wakayama made their first submission to *Nature*. The journal rejected their manuscript, arguing that they had failed to prove that the cells had converted: perhaps they had simply isolated other stemlike cells within the tissue, or perhaps the samples had been contaminated with embryonic stem cells. Reviewers at Cell and at Science concurred. “The bar to say you’ve demonstrated your hypothesis is correct is very high for those journals,” Vacanti says. “It’s a lower bar for other journals. Do you decide to try to jump over a lower bar or do you jump higher?”

The researchers’ ambitions were incited when, that fall, a Japanese biologist named Shinya Yamanaka, who had developed a rival technique for turning mature cells into pluripotent stem cells, won the Nobel Prize. Yamanaka’s method—based on manipulating gene expression—had initially been met with astonishment, but it soon fuelled a rapidly growing billion-dollar industry. The process was laborious and potentially clinically unpredictable, though. The C.D.B. team thought that their discovery might compete with Yamanaka’s—even make it obsolete.

But, even as expectations rose, fundamental tactical differences emerged. Wakayama began to argue that it was essential to create a stem-cell line—a population of identical cells that can proliferate indefinitely. In addition to the potential commercial benefits, the ability to form a stem-cell line is a feature of pluripotent cells, and might provide a key piece of evidence to skeptical reviewers. While working on the chimeras, Wakayama had taken some of the cells that Obokata gave him and placed them in a culture. The cells, he said, had multiplied. Obokata was taken aback; she had never seen STAP cells exhibit a tendency to proliferate. When she expressed surprise to Wakayama, she recalls, he said, “I am using special methods. It won’t be easy for the rest of the world to catch up with me.’ ” As Wakayama pondered a patent for his stem-cell line, Obokata writes, he proposed a split of the proceeds: fifty-one per cent for himself, thirty-nine per cent for her, and five per cent apiece for Vacanti and Kojima.

Obokata resisted working on the stem-cell line; she wanted to remain focussed on the research she had been doing. When Wakayama pressed her, she grew embittered. In Boston, Kojima heard her screaming while reading her e-mail. He recalls that she shouted at the computer screen, “No! I don’t want to do it!” Kojima asked her what was going on. “Dr. Wakayama e-mailed me so many times," she told him. "Like, 'Did you do this assay? Did you do this experiment?' Anything related to the stem-cell line, he forces me to do. I don't want to, because I don't know how to make it. I tried. I couldn't." In spite of their differences, Obokata writes, when Wakayama was offered a position at the University of Yamanashi he urged her to go with him.

But, at C.D.B., Yoshiki Sasai, the brainmaker, had taken a particular interest in her work. After she presented her data on stress-altered cells, he grew convinced that, with his guidance, the research would be accepted by *Nature*. Not only did he know the editors well; he also had an instinct for how to frame the findings in the larger conversation about stem cells, embryology, and cell fate. Sasai offered to host her in his lab and shepherd her through the publication process. Around this time, he came up with the acronym STAP.

"We're watching some Danish television show and convincing ourselves that it's superior to anything on American TV."

Obokata advanced quickly at C.D.B., but she fit in awkwardly. She was more American now, and seemed impatient with the stringent hierarchy of a Japanese research institution. The environment could be gossipy. The postdocs complained about her: the perfume she wore was overbearing, her blouses were too low-cut. Instead of a lab coat, she had taken to wearing a *kappogi*, the square-necked smock typical of a Japanese housewife. She tended to get along well with older men in positions of authority, but her peers learned to keep a wary distance. To other members of the lab, Sasai appeared dazzled by Obokata, whom he referred to as a genius. When not in close consultation with her, he was sealed away in his office, rewriting the STAP paper. "If he wants to neglect his own research and spend time on hers, no one can say anything," one C.D.B. researcher said.

Obokata's data were closely guarded—other lab members knew only that she was working on a radical new way to make stem cells. Even Vacanti was excluded from the day-to-day progress. He wrote to Obokata seeking updates, and got responses from Sasai. "Haruko has been so busy over the past two months and, from what I see, got exhausted time to time," he wrote. "I hope that you may understand such a situation and kindly help her concentrate." When Obokata did find time to respond to Vacanti, she signed her notes, "With a lot of love," and reassured him that she just wanted to see him smile.

In the lab, Obokata and Sasai were working to persuade the journal that what they had were genuinely reprogrammed cells. As they revised the paper, they described an experiment in which they took cells that had an incontrovertible marker of maturity and got them to express the signals of embryonic stem cells—the cellular equivalent of looking at a sonogram and seeing an unborn child with a faded tattoo. Using special equipment in Sasai's lab, Obokata also made a time-lapse video of mouse cells apparently being transformed by STAP; in the footage, the cells go from gray to green, and then aggregate into luminous clusters. With the new data, they re-submitted to *Nature*, incorporating a revised protocol, in which the mild stressor ATP was replaced with the harsher hydrochloric acid. They also included a separate paper describing Wakayama's stem-cell line. In December, 2013, *Nature* finally accepted.

As the publication date drew near, the correspondence took what Vacanti felt was an ominous turn. Sasai wrote him a note seeming to credit Obokata with the entire concept. "With a magic spell that Haruko discovered, the chain of 'epigenetic curse' of differentiation is unexpectedly broken," he wrote. "Under your admirably generous support, Haruko unveiled it with her God-given ingenuity and developed the research to this highest level." Vacanti began to fear that he and his team would be erased from the scientific story of the century. When *Nature* held a press briefing and included only Obokata and Sasai, he was distraught. "I felt like all the air went out of the balloon," he told me.

The papers created an international sensation, and in Japan Obokata became a celebrity—an icon of the country's future preëminence in the sciences, and of the new Japanese woman. She played the part winningly. In her free time, she told a newspaper, "I spend normal days just like others, such as looking after my pet turtle and going out shopping." She said that she thought about her research non-stop, even "when I am on a date with my boyfriend." *Kappogi* sales spiked. Vacanti, in spite of his concerns, joined in the adulation. A week after publication, he sent her an e-mail. "You deserve all of the attention that you are receiving," he wrote. "I tell everyone that you are the most intelligent, hardest working, nicest, most creative and driven scientist I have ever had working in my lab. Also, the most beautiful."

But, by the time the news cycle finished, Vacanti's fears had been realized. He had vanished from Obokata's narrative. *Nature's* news site carried a recording of her talking about how she had come up with STAP. Like Archimedes, she described her eureka moment as having taken place in the bathtub, when she started to wonder if mammalian cells responded to stress by producing stem cells. "I tried everything I could think of," she says. "Squeezing cells through a pipette, starving cells, and so on." Martin Vacanti called his brother. "Chuck, have you listened to her description of the eureka moment?" he said. Chuck hadn't. "She gave the same description I give about the sporelike cells," Martin said. She was using his eureka moment.

The primary *Nature* paper described a captivatingly simple procedure: a seven-day transit from hydrochloric-acid bath to reprogrammed cells. If the results seemed surprising, they were no more so than Yamanaka's had been. Christof Niehrs, the biologist, said, "I didn't think it was out of this world. I thought, Why not?" Around the world, laboratories started attempting to replicate the findings.

Reproducibility has been an essential step in the scientific process since the Enlightenment, and it is currently the subject of a great deal of angst in American science. In 2012, a former research director at the pharmaceutical company Amgen reported that he and his colleagues had attempted to reproduce the findings of fifty-three prominent papers. Only six panned out—a validation rate of eleven per cent.

Many people believe this is partly the fault of the scientific journals. Along with the influential role that *Nature* has in shaping the trajectories of ideas, technologies, and careers, it is essentially a commercial enterprise. The editors like big stories, and for the right ones they take risks. Some observers complain that incentives to publish have a distorting effect, causing scientists to oversell data; a cutthroat culture sometimes leads researchers to publish intentionally incomplete or vague protocols. The perceived conflict between good science and prestige has become so pointed that, two years ago, Randy Schekman, a Nobel Prize-winning biologist, announced in the *Guardian* that he would no longer publish in *Nature*, *Cell*, or *Science*, which, he wrote, "aggressively curate their brands, in ways more conducive to selling subscriptions than to stimulating the most important research."

"It's alive! Alive!!"

Discontent among scientists—especially the younger and more professionally vulnerable—has created an online community dedicated to questioning major publications by prominent researchers. In 2012, a neuroscientist named Brandon Stell founded PubPeer, a forum where anyone can analyze and discuss scientific papers, as a corrective to what he sees as the flaws in today's clubby scientific culture. Stell told me he looks forward to a day when the journals are obsolete. "Scientists are using whether a paper appears in *Nature* or *Science* or *Cell* as evidence of whether a paper is good," he said. "Instead of looking at papers themselves, academics look at publication history to decide who gets promotion. If *Nature* isn't looking at the data, either, our careers are just random."

The STAP papers, based on electrifying claims from a team of well-known collaborators, were juicy material for PubPeer. They were posted right away, and immediately began eliciting comments. Within two weeks, an anonymous user had noticed that two of the images in the secondary paper—one purporting to show a placenta made using STAP cells and the other a placenta derived by a contrasting technique—appeared nearly identical. As outrage grew on the Internet, Vacanti found himself unprepared. Not long after the papers were published, he got a call from a blogger. He told me, “I wasn’t even sure what a blogger was.”

Among the establishment, too, the sense of excitement and possibility quickly gave way to doubt. George Daley, a prominent Harvard scientist and the director of stem-cell transplants at Boston’s Children’s Hospital, told me, “My network of colleagues around the globe were e-mailing each other saying, ‘Hey, what’s going on? Have you gotten this to work?’ Nobody had.”

Daley is fifty-five, with a crisp, friendly confidence and a deep sense of order. When I met him at his home, a Greek Revival in Cambridge, he served me bagels and coffee; it seemed as though every time he used a knife he sprang up to wash it and his hands. Daley came of age as a scientist in the lab of David Baltimore, a Nobel laureate who was investigated by the National Institutes of Health and temporarily derailed professionally for standing by a colleague accused of research fraud. The investigators, Daley told me, were “self-appointed watchdogs,” who relentlessly pursued the accusations “until they did find the inevitable inconsistencies and flaws within the project.” After a decade, Baltimore’s colleague was cleared of charges of misconduct, but the tarnish on her work remained. “I appreciated the frailty and nebulousness of some of the data, and yet what David was trying to protect was the scientific process—that there’s a process, and the process shouldn’t be subject to some kind of assault from the outside.”

Science, Daley believes, must be policed from the inside. A decade ago, the South Korean biologist Hwang Woo-suk astonished the world by reporting in *Science* that he had cloned a human embryo and had made a stem-cell line from it. Daley, analyzing the genomes, was able to demonstrate that the data were invalid. (Hwang, who is now prohibited by the South Korean government from practicing embryonic-stem-cell research, has never admitted to fraud, instead blaming underlings for deceiving him.) Daley takes no pleasure in pointing a righteous finger at fellow-researchers whose data have come under scrutiny. But, he told me, "the process is protected best by a culture that admits fallibility—identifies it as quickly as it can be identified and corrects it through a nonpunitive set of mechanisms."

When the confused reports about STAP began to circulate, Daley sent one of his best graduate students to Vacanti's lab to see if he could learn the technique. The student reported that the treated cells indeed glowed green, but that the only phenomenon at work was auto-fluorescence: cells' tendency to emit light as they are dying, a possibility that Vacanti's researchers seemed oddly not to have entertained. He told Daley that he thought they didn't know what they were doing. Subsequent tests, Daley said, had shown signs of pluripotency so weak as to be insignificant, not even close to the gold standard of embryonic stem cells. Without a reproducible protocol, all the elaborate experimental proofs that C.D.B. had presented became suspect. Daley, along with a team of international collaborators, began to prepare a paper, for publication in *Nature*, that would establish that STAP was a mirage.

A few weeks after the problems with the placenta images were revealed, a Japanese blogger uncovered two images, supposedly documenting STAP, that were evidently identical to those in Obokata's dissertation. Soon, the blogger also discovered that, in a section of her thesis about the characteristics of stem cells, Obokata had cut and pasted long passages from the National Institutes of Health Web site. In her book, Obokata says that she was hurrying to finish her thesis before the deadline, and accidentally bound and submitted a draft rather than the final version. But Vacanti says that when he confronted her about the plagiarism she said that it was common at Waseda, and that a faculty member had told her that no one reads the theses anyway.

As the questions mounted, Vacanti says, he called Obokata and said, "Haruko, I have to know, because people are losing their careers on this. Is any of this data fabricated?" She assured him that everything was legitimate. He recalls that she said, "If I was going to fake this, I wouldn't have spent hours and hours collecting data." Vacanti thought that she was too smart to cheat so brazenly, and certainly too smart to get caught.

Delusion and fraud exist along a spectrum of deceit—first you fool yourself, then others—and one measure of a scientist is his ability to see that he is mistaken. For a long time, as a cautionary reminder, George Daley saved a voice mail from an American collaborator of the discredited biologist Hwang Woo-suk, swearing that he had seen the science work with his own eyes.

"If you could eat only one type of grass for the rest of your life, what would you choose?"

JANUARY 20, 2014

Daley believes that the problems with STAP began with misinterpretation. An artifact—a green glow—was taken by scientists working outside their area of expertise to be a phenomenon. From that point, the thrilling "observation" was privileged and protected, given more credence than contradictory signs. On two occasions, in a spirit of collegiality and damage control, Daley tried to explain to Vacanti where he had erred, to no avail. "Vacanti was so convinced that he was right," Daley told me. "This is why scientific method was invented—to prevent us from falling victim to our biases."

Two weeks after the STAP papers were published, Riken opened a preliminary inquiry. Initially, Wakayama defended Obokata, claiming that he had also made STAP cells. But as the probe grew into a full-blown investigation he abruptly recanted, suggesting that Obokata might have defrauded him.

For several months, on orders from the investigators, Obokata attempted to replicate her data, under twenty-four-hour video surveillance. In the room where she worked, she told me, even tiny nail holes in the walls were filled in. "Riken started treating me like a criminal," she recalled. "I was forced to wear clothes with no pocket, and furthermore I had an apron tied on by surveillance agents every day. That apron felt so heavy as if it were a leaden prisoner's uniform. I could not even pick up reagent bottles freely. Also, I was not allowed to analyze re-created STAP cells by myself. Therefore, I could not even know whether my experiments went well or not. All I could do was to perform the same task over and over every day." As months passed with no satisfying results, her health failed. The Japanese press was merciless. At one point, Vacanti visited her in the hospital, where she was being treated for depression, and had to make special arrangements to avoid a vanful of reporters who had been following him.

In July, 2014, the papers were retracted. A month later, Sasai hanged himself. Obokata seemed devastated. Kojima told me, "Haruko was crying, 'His wife and his family, his kids hate me.' " Though she was Sasai's favored protégé, she did not attend his memorial service. Not long afterward, Riken announced that its replication efforts had failed. Obokata resigned and disappeared from public view.

Last September, *Nature* published Daley's paper about STAP, which documented the failed attempts of seven labs to validate the claims of Obokata and her collaborators. His analysis points to serious flaws in the data. One of the basic pieces of evidence that the STAP process had worked was the green glow emanating from the altered cells. Researchers agree that this characteristic glow should be evident only when viewed through a green filter. But Daley and his collaborators noted that it was visible with both red and green filters—the sign of auto-fluorescence. The paper also noted that, while the original cells from Wakayama's mice were female, the STAP cells were male, "a clear inconsistency." A paper by a team from Riken, which appeared in the same issue, offered a good, if deflating, explanation for the chimera supposedly made up of STAP cells: genome analysis showed that the injected cells were actually a mixture containing embryonic stem cells.

Because these were scientific papers, the authors stopped short of speculating about who was at fault. But, in conversation, Rudolf Jaenisch, one of Daley's co-authors, felt no constraint. "Clearly, Obokata gave Wakayama a mix of cells," he told me. "He believed her and injected them, and he got beautiful chimeras—exactly what you expect if you are injecting embryonic stem cells."

Writing to me, Obokata insisted that she had been made a scapegoat. “All Japanese media reported and concluded that ‘Dr. Wakayama is a victim, and Obokata is an absolute scoundrel,’ ” she wrote. “Most of people believe this story, because it’s the most simple, interesting, and enjoyable story for Japanese people.” She suggested that it would have been impossible to fool Wakayama, a respected expert on cell biology, or even to independently gather the materials to produce fake samples. “There was no way for me to obtain any cells except from Dr. Wakayama’s lab,” she wrote. “All the experiments were under the supervision of Dr. Wakayama. All mice and cells were under the control of Dr. Wakayama.”

The dispute over culpability continues. Wakayama would not comment on Obokata’s statements, and he has not responded to her book. After its publication, a spokesperson for the University of Yamanashi, where he now works, declared, “We are not even issuing a press release saying that we are not commenting on this.” But, in an earlier newspaper interview, Wakayama hinted that Obokata might have smuggled mice into C.D.B. The laboratory, he said, “cannot prevent scientists from bringing in something in their pockets.” Last week, the *Japan Times* reported that Obokata had recently submitted to questioning by the police in response to an allegation by another former Riken researcher that she stole embryonic stem cells from a lab at C.D.B. Obokata’s lawyer says that the allegation “significantly contradicts the facts.”

Researchers I spoke to debated the possibilities endlessly, as if in a scientific game of Clue. But, even after multiple exhaustive investigations, there is no conclusive proof of who was at fault. Riken’s final investigation, published a little more than a year ago, noted that the samples in the study had very likely been contaminated by embryonic stem cells—but it did not present an over-all theory of the case. Its findings implicated both Obokata’s sloppy record keeping and her mentors’ lax oversight; in some instances, there were no original data to back up her figures and images, and in others no evidence that the experiments had been conducted at all. Yet it also alluded to systemic problems that were relevant far beyond the walls of C.D.B. “We cannot help but think that these failures to follow up when there were questions may have been due to the sense of urgency to publish rapidly," the report stated. "Responsible and fair research is not measured by the impact factor of published papers, the amount of research funding, or even the number of Nobel Prizes, but by the joy of unraveling the mysteries of nature and the mind to contribute to society."

"You, you, you, you, you, you, you, you, you..."

MAY 22, 2006

In the aftermath of the STAP affair, Riken cut C.D.B.'s funding by forty per cent and closed many of its labs. "The problems with the STAP publications have pierced the scientific community like an arrow in the side," the Riken report concluded. "We may pull out the arrow, but it will take the collective effort of the community as a whole to heal the wound and restore its health."

Not long ago, Waseda University stripped Obokata of her Ph.D. One of the few people from her Boston days she still communicates with is Jason Ross, who is now a medical student. She never says where she is, and mainly answers his e-mails with a perfunctory "Thank you for thinking of me. Lots of love, Haruko." To me, she lamented the unforgiving nature of Japanese society: "There is no second chance for failures. I am socially killed and my future is gone." She admits that she made mistakes preparing the papers but defends her honor and her intentions. "I am ashamed of callowness as a scientist. I had just been dreaming to be a scientist who makes contribution to the development of human society." She added, "My Ph.D. is forfeited, but I still dream of doing laboratory work every night."

At the end of July, Vacanti invited me to Boston. Because of the embarrassment around STAP, he had taken a sabbatical from his chairmanship, and would soon retire from his position. His lab would eventually run out of money, and then close. But his faith in the basic principles of STAP was unshakable. "I will go to my grave still being absolutely certain that it's correct," he said.

For all his conviction, Vacanti looked drawn. His gray hair was a close-shaved stubble, and he was wearing a short-sleeved shirt and khakis. A few weeks earlier, he had undergone a stress test—"It's difficult to differentiate chest pain from anxiety from chest pain from angina." (He had a triple bypass in 1996.) He regretted that the protocol as published had been so spare, and that the implications had been made to sound so sweeping. He said, "The point of the paper was that with any severe, sub-lethal stress—lethal enough that it kills, say, seventy or eighty per cent of the cells—the surviving ones will convert. It came out sounding like 'Acid treatment causes conversion.' But the point was that the harsh environment was supposed to mimic the chemical environment that you have in normal injury and wound healing."

In the year since the papers' retraction, he and Kojima had tweaked the procedure, making small adjustments to the media and returning to the original chemical stimulus, ATP, which also fuelled the cells, instead of the hydrochloric acid indicated in the publications. For months, they had tried to make a teratoma, the first major step to indicating pluripotency.

Now we walked over to Vacanti's lab to see the results. He wasn't optimistic. Before my arrival, he told me, he had called an emergency phone meeting with Kojima and his brother Martin. "I said, 'We have to have something to demonstrate that this is indeed real or we're going to look really stupid.' " As it happened, he said, just a few days before, he had seen the best-looking spheres in many months. They had tested positive for the embryonic-stem-cell markers Oct4 and Nanog, calculated by a machine that is not subject to the vagaries of auto-fluorescence. He had broken the spheres apart and placed the cells in a medium that encouraged the growth of neurons. The new plan was to test them for a protein called nestin, which, he said, would show that a mature skin cell had been transformed into a neural stem cell—taken back down to the root and up another branch.

Vacanti's lab was largely empty, except on the days when an artist collaborator of his came in to work on a replica of van Gogh's ear, made from a descendant's DNA and a mold of the actual appendage. Kojima, the stalwart, was at his desk. On the outer wall to his office was a poster charting the developmental pathways of cells; at the center, over the most powerful cell, a lab worker in the Obokata days had pasted a sign that said "STAP." Scattered around the lab were several pipette calibrators bearing the name "Haruko."

Compact and taciturn, Kojima looked up and said "Good data" before saying hello. The nestin levels were fifty to sixty times as high as the last time he had checked. "Ha!" Vacanti said, jumping up and down and cheering.

"It's only one sample," Kojima said.

"Doesn't matter," Vacanti replied cheerfully. "One's good for me."

In the progress of their research, they were all the way back to 2008, before Obokata, but Vacanti still saw a cause for celebration. After calling his brother, he decided that it was time for lunch and a glass of wine; Kojima came along, and Vacanti kept exhorting him to make merry. "I'm excited," Kojima said. "But I need correct data, otherwise—" He chopped his hand through the air.

Vacanti was reluctant to ruin a good day, but eventually he couldn't put off looking at the teratoma slides any longer. Back in the lab, he sat down at the microscope and examined them for a long time. I stole a glance: a view of pink bubbles and marbled swirls like the endpapers of a seventeenth-century Venetian book. After a while, Vacanti concluded that the cells had failed to form new tissues; the only tissues evident had clearly come from the host mouse. Months of work, without producing evidence of pluripotency. But he didn't dwell on that troubling thought for long. "Koji, you know what I was thinking?" he said. "We had Oct4, we had Nanog, we had nestin. Let's never do another test. Let's let it be someone else's problem!"

"The killer had to be a man. Not only is the knife still bloody—it wasn't even put in the sink."

JANUARY 4, 2010

The STAP papers were defeated by flaws that were at best irreparable and at worst unconscionable; pursuing their ideas, however tantalizing, might be scientific and professional folly. But basic biological mysteries persist. In the early two-thousands, staff members at Walter Reed Medical Center began to notice a bizarre phenomenon among the casualties returning from the wars in Iraq and Afghanistan. Many of the most severe injuries were due to blasts from I.E.D.s, grenades, and other bombs. Sixty to seventy per cent of those injuries exhibited heterotopic ossification: the wounds had bone growing in the soft tissue, where it didn't belong. "Everyone thought, Jeez, what is going on here?" Leon Nesti, an Army hand surgeon, told me. "This is odd."

In the tissue of patients who were growing rogue bone, Nesti discovered some two thousand times as many stem cells as he expected to find. The cells seemed to have local origins, and he speculated that they were induced by the injury. "I think something in the trauma makes them more plastic," he told me. But the lingering taint of the STAP affair has made it more difficult to mount an ambitious inquiry. "If I ever said to a group of hard-core scientists, 'Hey, I think STAP cells are real and I'm going to start working on that,' they would laugh at me," Nesti told me. Rather than focus his studies on showing that the cells have capabilities similar to embryonic stem cells, he is trying, less controversially, to show that they have regenerative abilities. Those cells might have been trying to grow new bone.

The progress of science requires bold ideas; it also requires patient, plodding work on small problems. Scientists grope their way forward, making false starts, hitting dead ends, and falling through trapdoors, all the while struggling to stay both radically open to insights and ruthlessly skeptical of them. Vacanti stumbled out of anesthesiology into stem-cell research, with a far-reaching and sensational conjecture about basic cell capability; honed by Obokata, the notion seduced some of the most respected biologists in Japan, and, in Sasai's case, destroyed one of them. But, as many people told me, in spite of all that was tragic and regrettable, the scientific process had worked. Error had been routed, and now science could advance. Daley saw it as a bracing corrective to a frenzied and speculative culture in his field. "Stem-cell scientists are likely to be more circumspect about their own work, and more skeptical of others," he wrote to me. "This is healthy for science."

A year ago, I spoke with Frederic Michon, a developmental biologist in Helsinki who had been attempting to replicate STAP, focussing on mechanical stress rather than on the acid stimulus. At the height of the scandal, he had produced some seemingly favorable preliminary results, but, in the vexed climate, he carried out his experiments cautiously. He and his researcher called their procedure SIP, for stress-induced plasticity—a name that suggested the cells had un-become what they were, without yet becoming something else. He told me that he felt he needed to repeat the experiment at least fifty times before seeking to publish it.

When I called Michon recently to see how the research was progressing, he said that he had stopped working on SIP. The method was hard to nail down—sometimes it worked and sometimes it didn't—and it was too expensive to continue on a path so uncertain. On the plus side, he found it easier now to discuss his findings with colleagues. "People are generally admitting that there is something interesting," he said. "Here we have cells that are stressed enough to lose their identity and start to be something they are not supposed to be." Michon envisioned the possibility of finding, in the wreckage of the STAP case, the inspiration for more modest, thoughtful work on the question of how the body heals itself. "In STAP, people got extremely pissed off about the letter 'P' "—for pluripotency—"while the letter 'S' "—for stimulus—"was the most interesting," he said. ♦

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