

CLONING COMEBACK

Ten years ago, Woo Suk Hwang rose to the top of his field before fraud and dodgy bioethical practices derailed his career. Can a scientific pariah redeem himself?

BY DAVID CYRANOSKI

The Sooam Biotech Research Foundation nestles on a wooded hillside in Guro, a district on the southwestern outskirts of Seoul. Spartan, quiet and cold on this winter day, the grey-white exterior belies the buzz of activity within.

A door just off the foyer leads to a corridor of canine chaos. In stalls to the left, Tibetan mastiff and Australian shepherd puppies are cavorting. A Yorkshire terrier dances back and forth on its hind legs. And an adult mongrel howls with separation anxiety, only calming down when the two beagle pups that she gave birth to are returned to her pen. She doesn't know that she is just a surrogate mother, nor that the pups are highly unusual dog clones, engineered to show the symptoms of Alzheimer's disease.

The right side of the corridor houses a wall-sized window that looks onto an operating theatre. Inside, Woo Suk Hwang, in a blue surgeon's gown, cap and mask, is working on a bitch in labour. He greets his visitors through a microphone headset and then explains that this is an emergency: one of the puppies is stuck in the cervix. He makes an incision and carefully probes the dog's womb until the whitish sausage of a puppy emerges. After it is wiped down, Hwang holds it to his ear, listening for sounds of breathing. He then gently massages the groggy pup into consciousness and goes back for the last one. Minutes later he announces: "We have saved all three cloned dogs." Hwang brims with pride.

Eight years ago, few could have imagined watching such a jubilant scene. Hwang, a

world-famous cloning researcher, had just plummeted from the pinnacle of scientific success, when it became clear that he had committed fraud in two articles^{1,2} describing stem-cell lines derived from cloned human embryos. There had been gross ethical lapses in the way Hwang had collected the human eggs for his experiments, and the papers were found to contain fabricated data. They were eventually retracted. It was one of the most widely reported and universally disappointing cases of scientific fraud in history. In January 2006, Un-chan Chung, then president of Seoul National University (SNU), where Hwang had done the work, called the episode "an unwashable blemish on the whole scientific community as well as our country".

If the stain cannot be washed away, perhaps it can be stamped out of memory by hundreds of paws and hooves. With private funding from steadfast fans, Hwang opened Sooam in July 2006. He has since cloned hundreds of animals — dogs, cows, pigs and coyotes. His goals include producing drugs, curing diabetes and Alzheimer's disease, providing transplantable organs, saving endangered species and relieving grief-stricken pet owners. He has a raft of publications in respectable journals, collaborations within and outside South Korea, and increasing institutional support from government agencies. It is hard to square this image with the pictures of Hwang released by the South Korean media in 2005. Shattered by the controversy, he was photographed in a hospital bed, unshaven and reportedly suffering from exhaustion.

Today Hwang plays down his involvement in the fraud. He retains a base of ardent supporters,

mostly in South Korea. And he maintains, contrary to scientific consensus, that he really did create the first line of cloned human embryonic stem cells. He has even had success in getting some legal recognition of that claim.

In December, he welcomed reporters into Sooam to tour the facilities and see him deliver some cloned puppies, but he declined to comment for this story. Maybe "in a couple of decades", he wrote by e-mail.

CLONING FOR COUNTRY

A veterinarian by training, Hwang rose to fame in South Korea in the late 1990s by cloning animals — and by developing important allies (see "The rise and fall and rise of Woo Suk Hwang"). He asked then-President Kim Dae-jung to name the first cloned beef bull, and he promised a national agricultural boom centred on cloned cattle.

His popularity in South Korea grew, and in 2004 he shot to international fame when *Science* published a paper¹ in which he claimed to have created an embryonic-stem-cell line from a cloned human embryo — something that several groups had been trying to do. Hwang's success seemed to offer an endless supply of versatile cells genetically matched to the cell donor. Through this process, often called therapeutic cloning, it was hoped that doctors could rejuvenate failing tissues or organs, or that cells derived from people with virtually any disease could be used for research and drug screening. The following year, his group published a second paper², describing the development of 11 more such lines, making the process so routine that clinical application seemed imminent.



2005



2013

Snuppy, the first cloned dog (left), was one of Woo Suk Hwang's successes. Today (right) Hwang regularly delivers cloned animals at an institute near Seoul.

But even as his star was rising, cracks were beginning to show. In May 2004, one of Hwang's graduate students told *Nature* that she had donated eggs for experiments in the first paper (see *Nature* 429, 3; 2004). It was a controversial assertion: many bioethicists worry that, in such a situation, students might feel pressure to endure a risky and uncomfortable procedure.

Hwang denied the charge and the student recanted her statement. But in November 2005, amid increasing evidence, Hwang admitted that he had lied (see *Nature* 438, 536–537; 2005). Two students had donated eggs; Hwang even drove one to the clinic, where she donated her eggs before returning to the lab to try to make cell-line clones of herself. Hwang had also paid donors for eggs used in the 2004 paper, contradicting what the paper said. And he continued to compensate donors even after a South Korean bioethics law came into effect in January 2005 banning the practice.

Hwang's triumphs soon unravelled further. In January 2006, an SNU investigation committee announced that both of his human-cloning papers were fraudulent. The committee found that the cell line reported in 2004, called NT-1, was not produced by cloning and was probably a product of parthenogenesis — the 'virgin birth' process by which an egg starts embryonic development without the contribution of sperm. The 11 stem-cell lines claimed to be patient-specific clones in the 2005 paper turned out to be normal embryonic-stem-cell lines from a fertility hospital that had been relabelled. Images and graphs in both papers were fabricated to give the appearance of clones. "The research team of Professor Hwang

does not possess patient-specific stem cell lines or any scientific bases for claiming having created one," the report concluded.

Hwang's empire crumbled. He was expelled from SNU in March 2006. The Seoul Prosecutor's Office raided his laboratory and launched a massive investigation.

Hwang took responsibility for poor oversight of his lab, but maintained that he had been duped by a co-author. During the inves-

THE EPISODE DREW ATTENTION AND INTEREST FROM GOVERNMENT AND ORDINARY PEOPLE.

tigation, one co-author admitted to switching stem cells without Hwang's knowledge, but Hwang also admitted to ordering subordinates to fabricate data. A complicated web of blame emerged in which Hwang admitted being involved in fraud but still maintained that the achievement was real.

Data fabrication is not illegal in South Korea, but knowingly using bogus articles to get funding is. The Prosecutor's Office charged Hwang with fraud, embezzlement and bioethics violations, and a three-year court case ensued. In 2009, the court threw out the fraud charge, saying that the companies involved gave the money knowing that they would not benefit from the donation. Hwang was, however,

convicted of violating the country's bioethics law and of embezzling government funding. He was sentenced to two years in prison. The term, later reduced to 18 months, is still under appeal in court. But even if Hwang loses his appeal, as long as he doesn't break the law during his probation, he will not spend any time in jail, says Sean Hayes, a partner at IPG Legal in Seoul.

DOGGED PURSUIT

Despite his legal troubles — and the widespread belief that his career was over — Hwang continued to work, thanks to the supporters who amassed US\$3.5 million to launch Sooam. About 15 scientists followed Hwang from SNU, and around half of those remain today among Sooam's 45 staff. His team now creates some 300 cow and pig embryos per day, and delivers about 15 cloned puppies per month.

Hwang has long been interested in cloning dogs. He reported³ the world's first cloned puppy in 2005 — a claim upheld by the SNU investigation. Since 2006, Sooam has cloned more than 400 dogs, mostly pets. Customers, the majority of whom are from the United States, pay about US\$100,000 for the service. Sooam has begun supplying dogs to the Korean National Police Agency in Seoul in the hope that clones of proven service animals will quickly learn their trade as sniffer dogs. And last year, it launched a contest for a UK dog owner to have a dog cloned for free — which would make it the first cloned canine in the country.

Although Sooam could make more money from cloning pets if it cut prices and increased production, the non-profit organization wants to be more than a dog-cloning factory. "It's just a

THE RISE AND FALL AND RISE OF WOO SUK HWANG



FEBRUARY 2004

Woo Suk Hwang describes the first stem-cell line, NT-1, derived from a cloned human embryo.

MAY 2005

Hwang's group publishes a second paper reporting 11 further human embryonic cell lines.

AUGUST 2005

Hwang's group is the first to clone a dog.

NOVEMBER 2005

US collaborator Gerald Schatten splits with Hwang, citing ethical problems in getting human eggs.

DECEMBER 2005

Pushed by increasing evidence, Seoul National University (SNU) launches an investigation.

JANUARY 2006

Hwang's human-cloning research is deemed fraudulent by SNU. His dog-cloning claims are upheld.

side project to get research funding for our other projects," says Insung Hwang, a scientist at the institute who agreed to speak about research at Sooam. He is no relation to Woo Suk.

Using cloning technology, Sooam is creating cows that produce the human interferon protein, which can be used for treating a number of human diseases, in their milk⁴, and pigs that are genetically tweaked so that their organs might be suitable for transplantation into humans⁵. Sooam researchers have also created new models for diabetes by putting genes that cause symptoms of the disease in mice into cloned pigs⁶ and dogs⁷. Likewise, says Insung Hwang, a transgenic beagle at Sooam that carries a gene related to Alzheimer's disease shows hallmarks of the disease. Researchers at the institute have cloned this beagle 18 more times and are waiting to see whether these dogs also develop the symptoms.

Sooam's ambitions don't stop there. In March 2012, the centre began a collaboration with the Institute of Applied Ecology of the North, part of the North-Eastern Federal University in Yakutsk, Russia. They have joined forces to try to clone a mammoth from ancient tissue dug from permafrost. The project has received great fanfare, but Insung Hwang admits that it is a long shot. "The chances are very small," he says.

Sooam is also expanding its repertoire of species. It has already cloned coyotes (*Canis latrans*)⁸ using dog eggs and dog surrogates, and it now hopes to build on that work to clone the African wild dog (*Lycaon pictus*), one of the most endangered carnivores in Africa.

Under Woo Suk Hwang's guidance, the institute has published more than 40 papers documenting cloning successes and technical improvements to the cloning process. "His group is making important yet incremental progress towards long-term goals," says Cindy Tian, a cloning and reproductive biology researcher at the University of Connecticut in Storrs.

The fact that Hwang is being published in peer-reviewed journals is a sign that he is

becoming accepted once more. Insung Hwang says that researchers he meets often bring up the fraud and "some reviewers are a little hesitant" to take Sooam manuscripts seriously, but overall, they are treated fairly. Tian, who edited two of Woo Suk Hwang's papers for *PLoS ONE*, says that his "designs are sound and the conclusions are supported with good data". She adds that "it is very unlikely a 'come-back fraudster' would do the same trick again", and that because Sooam work is likely to be closely scrutinized, the researchers there are bound to be on their best behaviour.

Woo Suk Hwang's greatest coup in terms of

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regaining legitimacy was establishing a partnership in March 2013 with BGI in Shenzhen, China — the world's largest sequencing facility and a powerhouse in scientific publishing (see *Nature* 464, 22–24; 2010). Together, they plan to look at modifications of chromosomes that determine how genes are expressed, a field called epigenetics. Analysing the variation between clones and how that may contribute to, for example, different coat patterns in dogs could be a powerful tool for such work.

Yang Huanming, BGI's co-founder, says that he was impressed by the level of involvement from Woo Suk Hwang after watching him deliver a litter of cloned pups. "Personally, I like him, how hard he works, and how passionate he is for science," Yang says.

Woo Suk Hwang has also earned support from the Korean government. Roughly 50% of the funding for Sooam now comes from

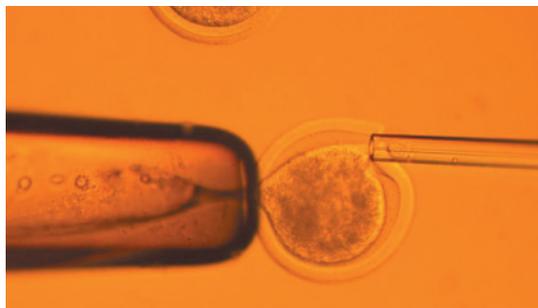
government grants, which includes 3 billion won (US\$2.8 million) over three years from Gyeonggi province, Seoul's neighbour, for two cow-cloning projects, according to Insung Hwang. In 2012 and 2013, the Rural Development Administration contributed nearly 190 million won for the interferon project and 140 million won for transgenic animal models of metabolic disease.

But some scientists remain wary. "If you fabricated data once, how would one know that you will not do it again?" asks Hans Schöler, a stem-cell biologist at the Max Planck Institute for Molecular Biomedicine in Münster, Germany. Looking at the unlikely bid to clone a mammoth, Jeong-Sun Seo, director of the Genomic Medicine Institute at SNU, feels a sense of *déjà vu*. "I am afraid that it seems to be just show," he says. Seo says that he is not opposed to Woo Suk Hwang getting grants for animal cloning, but he draws the line at research into human cloning. Hwang "doesn't know the trends in stem cells. He should stick to his strong animal-cloning technology," Seo says.

LINE OF INQUIRY

Nevertheless, Woo Suk Hwang intends to return to human therapeutic cloning. But he may be trying to ride a wave that has already passed. A competing technology — induced pluripotency, discovered in 2006 — creates stem cells from adult cells, skirting the difficulty of sourcing human eggs and the controversy of embryo destruction. Even the announcement⁹ last year that a human stem-cell line had finally been created from a cloned embryo got a more muted reception than the carnival that greeted Hwang when he announced his now-discredited paper.

In 2007, the Korean health ministry gave Sooam approval to do research using human embryos. However, approval to start specific human therapeutic cloning projects has so far been denied twice. Insung Hwang says that no explanation was given, but he thinks that

**JULY 2006**

Sooam Foundation starts up, with US\$3.5 million from Hwang's supporters.

2007

The Korean health ministry grants Sooam the right to do human-embryo and cloning research.

OCTOBER 2009

Hwang is found guilty of embezzlement and bioethics violations. Appeal continues.

2011

Canada grants Hwang a patent for the NT-1 cell line.

2012

Sooam scientists clone a coyote using a dog egg-cell donor and surrogate mother.

2013

Court tells the Korean Centers for Disease Control and Prevention to register the NT-1 cell line.

ongoing efforts to prove that the NT-1 cell line was in fact derived from an authentic clone could pave the way to future approvals.

Woo Suk Hwang has made some progress in convincing official bodies of NT-1's authenticity. In 2012, a Seoul court ordered the Korean Centers for Disease Control and Prevention to register the cell line — although this does not indicate its origins. The agency had initially refused on the grounds that eggs used in the experiments had been obtained unethically because donors were paid. But it was forced to relent because the eggs used to make NT-1 were obtained before the bioethics law banning the practice came into effect.

In 2011, Canada issued a patent to Sooam that refers to NT-1 as a cloned cell line. And Insung Hwang says that other patents are pending from some half a dozen of what he considers to be the “most symbolic” countries.

Getting recognition for NT-1 from the scientific community will be difficult, however. The paper in which NT-1 was reported¹ was clearly fraudulent and has been retracted. And SNU's finding that the line was a product of parthenogenesis has been backed up by an analysis¹⁰ by George Daley, a stem-cell biologist at Harvard University in Boston, Massachusetts. He looked at thousands of DNA sites in the cell line and found that the chromosomes had recombination patterns strikingly similar to those of mouse parthenotes — evidence that Daley calls “unequivocal”.

But a 2011 study¹¹ by Eui-Bae Jeung of Chungbuk National University in Cheongju, South Korea, argues that NT-1 does come from a true clone. This analysis is based on the similarities between the way the genes are methylated and expressed in the cell line and in cells from the nuclear donor.

Mahendra Rao, director of the US Center for Regenerative Medicine in Bethesda, Maryland, says that both analyses have their ambiguities. He says he believes that Daley's data are stronger, but that “more evaluation is required”.

The most convincing evidence against NT-1 being a real clone might be that from Woo Suk Hwang's own lab. In 2003, when the researchers were preparing the paper, several tests indicated that NT-1 might be a parthenote, according to team leader Young-Joon Ryu. The Seoul prosecutor's report notes that another researcher, Sung Keun Kang, a former SNU professor and a right-hand man to Hwang, went back and altered the test results.

Many stem-cell scientists see Woo Suk Hwang's failure to publish NT-1 as a parthenote as a missed opportunity¹². “He could have made a career studying parthenogenetic activation,” says Schöler.

SECOND CHANCES

Among the public, opinions of Woo Suk Hwang are mixed. His actions have left many patients feeling betrayed — although some continued to support him with fervour. Susan Fajt, who was paralysed in a car accident and whom Hwang pledged to make walk again, continued to believe him after the fraud was revealed. “I talked with him for four hours. He had tears in his eyes. I don't think he would mislead anybody,” she said in 2006. Fajt died in 2010.

But the scandal did not seem to have as disastrous an impact on support for stem-cell research worldwide as had been feared. Some in South Korea even credit the episode as partly responsible for a recent boom in stem-cell funding in the country (see *Nature* <http://doi.org/qv5>; 2012). “It was helpful,” says Hyo-Soo Kim, a stem-cell scientist at SNU Hospital. “It drew attention and interest from government and ordinary people.”

South Korea has now approved more stem-cell treatments than any other country. One such therapy, which uses stem cells derived from umbilical cords to tackle osteoarthritis, was approved in 2012 and is made by biotechnology firm Medipost in Seoul. Antonio Lee, chief executive of the company's US subsidiary, notes

that immediately after the scandal the firm had trouble enrolling patients, “but at the same time it raised awareness among the general population about the potential of stem cells”.

Overall, the case did not lead to a major erosion of public trust, says Bernd Pulverer, head of scientific publications at the European Molecular Biology Organization in Heidelberg, Germany, although it did raise important questions about how the problems went undetected for so long. “One clear issue that emerged was the danger of focusing such intense expectations to perform, and to funnel so much funding to one individual,” he says. “At some point, it was clear that the stakes were simply too high for Dr Hwang to fail.” For the research enterprise as a whole, he adds, “I am not sure anything changed fundamentally”.

For Woo Suk Hwang, once at the centre of so much media attention, things have undoubtedly changed. In Sooam's chilly cafeteria he dines with a thick jacket on, chatting quietly to a handful of staff. He will greet a journalist and shake hands, but he does not want to talk about what happened. Hwang is increasingly surrounded by people who indulge him in that — offering a space for his ambitions to expand without constant reminders of his failures. When lunch is finished, he steals away, back to his ever-multiplying dogs and his hopes for redemption. ■

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