



## The Second Act

After his first turn on the world stage ended in scandal, Woo Suk Hwang has quietly rebuilt his scientific career

**SEOUL**—Watching a pair of German shepherd puppies frolic on the lawn of a research institute, Chang Hyun Choi likes what he sees. Few puppies from breeders have the temperament and trainability required in a police dog, says Choi, an officer with the police canine unit in the city of Busan. The look-alike pups scampering about may well have the right stuff to sniff for bombs and track down missing people: They are clones of one of the country's top police dogs. With clones, Choi says, "there is less chance of rejection" during training. Before driving off, Choi and a couple of colleagues pose for

a photo with the puppies, and with the man who oversaw the cloning: Woo Suk Hwang.

Eight years after Seoul National University (SNU) dismissed him for his central role in one of history's most notorious scientific frauds, Hwang, 61, is in a position many researchers would envy. He heads Soom Biotech Research Foundation, a nonprofit institute with a staff of 40, a \$4 million annual budget, and a new, well-equipped six-story building. His team publishes a steady stream of papers. Devoted dog owners from around the world, as well as the Korean police, seek their services. The institute is applying its

cloning know-how to rescuing endangered species and improving livestock breeds, as well as to fundamental research in developmental biology. And Hwang reportedly hopes to someday resume work with human embryonic stem cells.

Some say that the disgraced icon of science in South Korea has come far on the road to rehabilitation. "For animal cloning, his team is one of the best in the world," says Yang Huanming, chair of the Chinese sequencing powerhouse BGI-Shenzhen. Eventually, Yang predicts, Hwang "will regain respect from the scientific community."

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◀ **Back to work.** Barred from handling human tissue, Woo Suk Hwang concentrates on animal cloning.

Others are not so sure. “I highly doubt that Hwang will gain respect in the scientific community at large, even with his ongoing successes in animal cloning,” says Insoo Hyun, a bioethicist at Case Western Reserve University in Cleveland, Ohio, who once advised Hwang. “[Hwang’s] scientific fraud was simply too great.”

### Meteoric rise and fall

At the start of 2004, Hwang was toiling in obscurity in South Korea, engaged in routine livestock cloning. Then on 12 February, in a paper published online in *Science*, Hwang’s team claimed it had created stem cells from a cloned human blastocyst (*Science*, 13 February 2004, p. 937). From out of nowhere, the group had leapt ahead of dozens of labs worldwide seeking to generate stem cells genetically matched to individual patients; such cells, researchers hoped, would evade immune rejection and be used someday to treat or cure diseases like diabetes and Parkinson’s. Hwang’s team took another apparent step toward this goal with a second *Science* paper, published online on 19 May 2005, describing the creation of 11 embryonic stem cell lines using genetic material from patients suffering spinal cord injuries, a genetic immune deficiency, and diabetes. And in August, the team unveiled in *Nature* the first cloned dog, an Afghan hound named Snuppy.

In 18 months, the once-anonymous veterinarian had become a superstar. Colleagues described his findings as “a breakthrough” and “spectacular.” *Time* magazine named Snuppy 2005’s “Most Amazing Invention.” In South Korea, Hwang became a national hero. The government proclaimed him the country’s top scientist and launched a generously funded World Stem Cell Hub just for him. It issued a postage stamp featuring the expected fruits of Hwang’s research: a silhouetted figure rising from a wheelchair and leaping, with the caption referring to embryonic stem cells. Hundreds of women volunteered to donate eggs for his use.

As fast as he shot to fame, Hwang’s career began to unravel. A May 2004 news report in *Nature* claimed that one of Hwang’s Ph.D. students had said she and another member of the group donated their own eggs for

Hwang’s research, a dubious practice that ethicists feel could reflect lab heads pressuring junior researchers. For more than a year, Hwang denied he’d used their eggs, until a Korean TV broadcast in November 2005 showcased hard evidence from a whistleblower on Hwang’s team. In the days that followed, Korean bloggers started pointing to duplicated images and questionable data in Hwang’s papers. That drew an SNU investigation; on 29 December, the university’s panel reported that none of the 11 embryonic stem cell lines described in the second *Science* paper ever existed.

In their final report on 10 January 2006, the investigators cast doubt on the first



**Better days.** Hwang and Snuppy in 2005. The world’s first dog clone was his only achievement of that era to withstand scrutiny.

*Science* paper as well, stating that the human stem cell line was probably not derived from a cloned blastocyst but rather from an unfertilized oocyte that started developing into an embryo, a phenomenon known as parthenogenesis. The panel concluded that virtually all the images and data in the two papers had been fabricated. Hwang’s sole legitimate achievement was Snuppy: The panel confirmed that the dog really was a clone.

Hwang did not challenge the SNU panel’s findings. During a 12 January news conference broadcast on national TV, he tearfully admitted that both *Science* papers were bogus and pointed the finger at junior researchers, who he claimed had deceived him. *Science* retracted both papers in a notice posted online on 12 January.

SNU dismissed Hwang in March 2006. In October 2009, a South Korean court found him guilty of embezzling research funds and of illegally buying human eggs. Completing his downfall, an appeals court upheld the conviction in December 2010 and sentenced him to 18 months in prison. The sentence was suspended for 2 years, and he did not serve any jail time.

### Starting over

As the disgraced researcher faded from view, a small band of supporters rallied to his cause. “I thought there was going to be no chance of helping disabled people and many other patients if we lost him from the scientific community,” says Byung Soo Park, a Korean electronics industry businessman and philanthropist who chairs the Sooam Foundation, which is separate from the research foundation and provides scholarships for Korean students. Park had known Hwang before he became famous. In 2000, on a mission to war-ravaged East Timor that Park organized, Hwang offered advice on improving cattle breeds and later hosted East Timorese scholars for training at SNU. “I was deeply touched and inspired by his effort and commitment,” Park says.

With the ax about to fall on Hwang at SNU, Park raised \$3.5 million and in July 2006 helped launch the Sooam Biotech Research Foundation to allow Hwang to continue his research activities. Many members of his group remained loyal to Hwang, a charismatic figure who inspired staff members through his long hours in the lab and dedication. “I believed that the team could prove it had the cloning technology” described in the *Science* papers, says Yeon Woo Jeong, a veterinarian who was among a couple dozen members of Hwang’s SNU lab to decamp to the fledgling institute.

At Sooam, barred by the government from working with human eggs and stem cells, Hwang returned to his roots in cloning livestock. But he soon had a chance to build on his one real accomplishment. After the birth in 1996 of the first cloned mammal, Dolly the sheep, U.S. billionaire John Sperling had bankrolled a venture to clone dogs—specifically Missy, a collie-husky mix owned by his friend Joan Hawthorne and her son Lou (*Science*, 4 September 1998, p. 1443). The Missyplicity Project and related pet cloning efforts ended up producing several cat clones, but no dogs.

In cloning Snuppy, Hwang's SNU group showed that it had mastered the complexities of dog cloning. Doing so requires synchronizing the reproductive cycles of egg donors and surrogate mothers, harvesting eggs at the right moment, and figuring out where in the reproductive tract to insert cloned oocytes—riddles that had all proved trickier to crack in dogs than in other cloned species. In early 2007, the Missylicity Project sent Sooam tissue from Missy, who had died in 2002. Sooam promptly succeeded in cloning her. “The first surrogate got pregnant” and produced a pup that December, says In Sung Hwang, a Sooam researcher not related to Woo Suk Hwang.

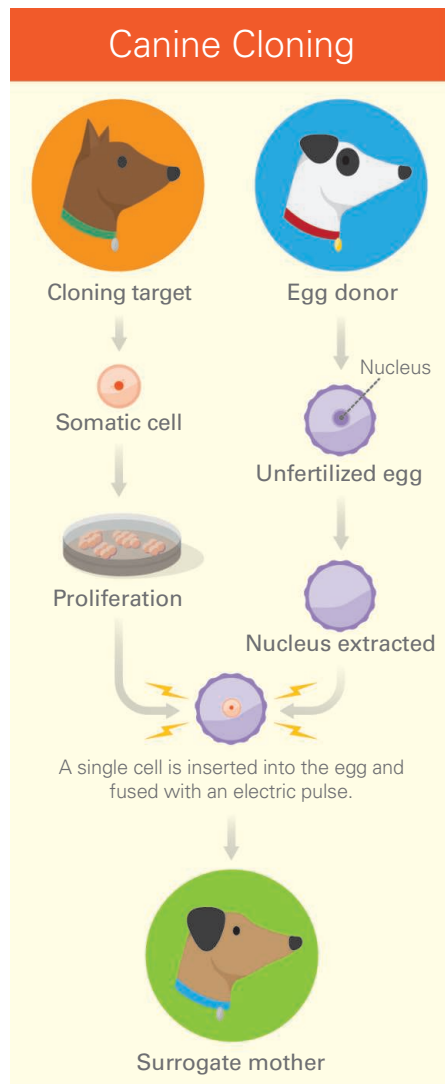
Fresh off that success, Lou Hawthorne started marketing dog cloning services through BioArts International, a business venture he set up to invest in biotechnology, with Sooam doing the cloning. BioArts gave up on dog cloning in 2009, citing the tiny market, the unpredictable results of cloning, and other issues. But determined pet lovers continued to find their way to Sooam.

In 5 years, the institute has cloned about 200 pet dogs, charging \$100,000 each time they are successful. (To prove that the puppies are genetic copies, the institute says it has an outside lab perform a genetic analysis on the original dog and the clone.) Sooam has also cloned another 200 or so dogs for the police, to preserve rare or valuable breeds, and for research purposes. While producing Snuppy required more than a thousand embryos and 123 surrogates, Sooam now typically needs only three surrogates, each of which gets three embryos, according to In Sung Hwang.

### Mass production

In a clean room at Sooam, Kyung Hee Ko, a technician from Hwang's SNU days, peers through a microscope, wielding manipulators that control needles and probes. With metronomic constancy, she positions a bovine oocyte, sucks out the nucleus, replaces it with a somatic—or mature—cell from the target cow, and then positions the next oocyte. It's essentially the same somatic cell nuclear transfer technique used to create Dolly.

Woo Suk Hwang declined to be interviewed for this article. But in the surgery down the hall, there he is in blue scrubs and a white mask, slicing into the belly of an anesthetized dog and inserting a clutch of cloned oocytes into her oviduct. The dog is sewn up and wheeled out; in all, the procedure takes less than 10 minutes. Then, in quick succession, two pregnant dogs are wheeled in and Hwang performs cesarean deliveries of cloned puppies.



**Recipe for a clone.** Dog eggs must be harvested after they enter the oviduct, rather than taken from ovaries, as is done with livestock. Cloned oocytes must be implanted quickly into surrogates, rather than allowed to mature into blastocysts in culture before implantation.

Sooam had never advertised its dog cloning service. But as a first foray into marketing, last year it launched a contest in which pet owners described on the United Kingdom's Channel 4 why they believe their dogs deserve to be cloned. The winner of a cloned pet will be announced on TV later this year.

One objective of the contest is to “figure out what the public thinks about cloning,” In Sung Hwang says. Some researchers are critical. Robin Lovell-Badge, a developmental geneticist at the MRC National Institute for Medical Research in London, points out that the cloning process in general is inefficient, that clones may not be identical physically to the original because of developmental factors, and that many cloned pups die as

embryos or soon after birth. Surrogates, meanwhile, bear the hardships of pregnancy and losing embryos and newborns. “Is the outcome worth it?” Lovell-Badge asks.

In Sung Hwang responds that Lovell-Badge's impressions of dog cloning are out of date. Experience acquired through cloning hundreds of animals and continual tweaking of the process has dramatically improved efficiency and reduced the number of clones with birth defects, he says. But he agrees that the issue of whether it is right to impregnate surrogates for the benefit of human pet owners “is a moral question that should be answered through discussion.”

The Korean police need no more convincing. They point to a case that began in March 2007, when a 9-year-old girl went missing on Jeju Island. After a futile monthlong search, the Jeju police put their best bomb-sniffing dog, Quinn, through a crash course on searching for human remains. Less than an hour after being put on the job, Quinn found the girl's body in a barn near her home, leading to the arrest of her murderer. The Korean police do not allow working dogs to mate. Hoping nevertheless to propagate Quinn's talents, Jeju's police chief in 2009 asked Sooam to clone the champ. All five clones completed training and were put into service. Three were sent to Incheon, where they work in security at the airport, and two went to Jeju, where one died of a congenital heart defect. The other is healthy and “doing pretty well” working alongside Quinn, says Yong Shik Choi, a Jeju police department dog trainer.

While about one in three puppies from breeders complete police training and enter service, 90% or more of cloned puppies make the grade, claims Yongsuk Cho, Sooam's chief administrator, pointing to data released last May by the Rural Development Administration. Sooam provided more than 30 cloned dogs to police departments last year.

Working on dogs is allowing Sooam researchers to tackle fundamental questions in developmental biology. For example, apparently female puppies born occasionally when cloning a male dog could yield clues to why sexual development sometimes goes awry in human embryos. Sooam molecular biologist Kyu-Chan Hwang (unrelated to the other Hwangs in this story) says the team has determined that the gene on the Y chromosome that controls testes development is sometimes blocked by methylation in cloned canine embryos. He hopes further work in dogs might lead to a better understanding of Swyer syndrome, a rare condition in which a person with a Y chromosome has female genitalia—though no ovaries.



Hwang's team also clones prize livestock and uses the technique to generate transgenic cows that produce human drugs in their milk and transgenic pigs for xenotransplantation of organs into humans. Such work accounts for most of the 45 or so papers Hwang's team has published since 2006, including in respected journals such as *PLOS ONE*. These applied efforts also attract government grants—from Gyeonggi province, the city of Seoul, and the Rural Development Administration of Korea—which cover about 80% of the institute's annual budget.

### To the rescue

Hwang's team is trying to extend their cloning know-how to endangered and extinct species. The scheme for both involves obtaining DNA for the species to be cloned and inserting it into the egg of a closely related living species to create an embryo that can be implanted into a surrogate. Interspecies somatic cell nuclear transfer has worked in seven species to date, including the Boer goat, a wild sheep known as a mouflon, two species of wild cats, and a gaur, an endangered wild ox native to Southeast Asia, according to a paper that appeared online on 13 September in *Cellular Reprogramming*. Hwang had a hand in creating the remaining two beasts in this menagerie—a gray wolf, reported in *Cloning and Stem Cells* in 2007, and coyotes, described online in *Reproduction, Fertility and Development* in December 2012. (Coyotes are not endangered, but Sooam wanted to develop expertise in interspecies cloning.) The team is now working on the endangered *Lycaon pictus*, or African wild dog. In a near miss, a *Lycaon* fetus in a surrogate dog mother died 2 weeks shy of expected delivery.

A more quixotic quest may be Sooam's project to revive the woolly mammoth. The team hopes to produce a clone using DNA from frozen mammoth remains and the eggs and womb of an elephant. Working with North-Eastern Federal University in Yakutsk in Russia, Sooam has sponsored two expeditions to hunt for mammoth remains preserved for thousands of years in Siberian permafrost.

"Cloning the woolly mammoth using the approach envisaged by the Sooam team is with all certainty never going to work," says Love Dalén, a paleogeneticist at the Swedish Museum of Natural History in Stockholm. Even in the best preserved mammoth samples, he says, "the nuclear genome is fragmented into some 50 million pieces. There is simply no way such a fragmented genome would be viable if transferred into an elephant cell." Sooam's In Sung Hwang acknowledges that the project is "a long shot."



**Reporting for duty.** Korean police officer Chang Hyun Choi says clones like this one make good police dogs.

The chance to work on everything from dog cloning to mammoth resurrection has attracted a cadre of young researchers willing to ignore Hwang's past. "Of course, there was a little bit of hesitation" about joining Sooam, says In Sung Hwang, who started at the institute in February 2010 after earning a master's in biomedicine at Duke University. However, he says, "I could see potential in what

Hwang's fraudulent papers, he says, "were a setback to the field at a time when human embryonic stem cell research was vulnerable and under attack from political opponents here in the U.S." Nonetheless, Daley is sympathetic. "We are all flawed and imperfect, and I believe everyone deserves a chance at redemption," he says.

Jeong-Sun Seo, a geneticist at SNU's College of Medicine, sees little chance that Hwang can achieve his ultimate goal: working on human cloning again. Many in the Korean scientific community oppose allowing Hwang to resume work with human material because of his past ethical lapses and his use of massive numbers of eggs to get a few viable embryos, Seo says. This approach may be acceptable in animals, he adds, but it would be problematic if applied to humans.

The Korean health ministry has turned down two applications from Sooam to work on human stem cells. And Sooam's Jeong notes that any in-depth stem cell research would require collaborations with hospitals, physicians, and biomedical researchers that will be difficult to forge. "There are a lot of



**Resurrection team.** Hoping to clone a woolly mammoth, Hwang (second from left) and colleagues have ventured twice to northern Siberia in search of well-preserved remains of the extinct beast.

was being done here." Hanna Heejin Song, who studied veterinary science in Hungary and joined Sooam in 2012, had no qualms. "In Korea [animal cloning] really happens, and it's really good, so why not be in my own country?" she asks.

Established scientists are more skeptical. "Hwang's rehabilitation faces an uphill climb," says George Daley, a stem cell researcher at Harvard Medical School in Boston and Boston Children's Hospital.

limitations on what we can do," says Jeong, who blames "prejudice" against Sooam because of Hwang's past.

According to In Sung Hwang, Woo Suk Hwang "still has dreams about [human embryonic] stem cell research." Woo Suk Hwang has risen further from his disgrace than many predicted, but those dreams are unlikely to come true.

—DENNIS NORMILE

With reporting by Mi-Young Ahn.