

STEM CELL RESEARCH

South Korea Picks Up the Pieces

Korean scientists are moving beyond the Hwang scandal with a new strategy for the country's stem cell research

SEOUL—Woo Suk Hwang, the would-be stem cell pioneer, is leaving an ironic legacy: South Korea is more determined than ever to become a force in worldwide stem cell research, and he won't be playing a role. Over the last several months, as public prosecutors were unraveling how Hwang and his team at Seoul National University (SNU) fabricated data to make it look as though they had created patient-specific stem cells, a task force of scientists and public officials has been working on a strategic plan to guide the country's future stem cell efforts. The plan's bold goal is for the government to spend \$454 million over the next 10 years in the hope of having Korea emerge as one of the top three global leaders in stem cell research.

Commissioned by the government and due to be unveiled in Seoul this week, the plan calls for developing a stem cell research infrastructure, attracting more scientists to the field, and providing even more money than what had been promised when the country's hopes and funding were centered on Hwang. (According to media reports, Korea's Ministry of Science and Technology budgeted \$28 million for stem cell research last year.) "It's a national plan to do stem cell research more effectively and systematically," says Dong-Wook Kim, a stem cell researcher at Yonsei University in Seoul, who led the task force. The funds will likely be spread in a more balanced way across institutions and between research on both embryonic stem cells—the focus of Hwang's efforts—and adult stem cells, which have been tested in a Korean clinic for treating heart attack patients and are envisioned here for possible use in treating neurological and other disorders.

In contrast to the breathless anticipation that surrounded Hwang's work, the plan will have

"a long-term perspective, not a focus on short-term results," says Youngsook Son, a Seoul researcher working with adult stem cells at the Korea Institute of Radiological and Medical Sciences, who was among the 50 scientists on the task force. The researchers hope to convince the Korean public of the value of continuing an aggressive research program even while giving a more sober assessment of the potential benefits of stem cell therapies and when they will reach the clinic, as well as Korea's place in global stem cell research efforts. And most important, "we will forget Hwang, and we will move on," declares Il-Hoan Oh, another task force member at the Catholic University of Korea in Seoul.

Taking stock

The task force's first job was a realistic assessment of Korea's strengths and weaknesses in stem cell research, irrespective of Hwang's claims. Kye-Seong Kim of Hanyang University in Seoul, who headed a subgroup on human embryonic stem cells (hESCs), says there was no question about the coun-



Bright spot. Kye-Seong Kim is one of a small number of Korean researchers studying the basic biology of human embryonic stem cells (above).

try's greatest strength. "Maintaining and establishing stem cells is where Korea is competitive," he says.

Korean researchers got off to an early start, thanks to a rivalry among Korean fertility clinics. In 1998, James Thomson and colleagues at the University of Wisconsin, Madison, reported the first stem cell line derived from human embryos (*Science*, 6 November 1998, p. 1145). Within less than 3 years, four Korean groups, all affiliated with fertility clinics, had duplicated the feat. "We were all competing but still cooperating, sharing information for producing human embryonic stem cells," recalls Hyung Min Chung, a cell biologist at Pochon CHA University College of Medicine, which is affiliated with one of Korea's largest obstetrics and gynecology hospital chains. Rival MizMedi Hospital, which produced hESC lines by the end of 2000, subsequently got a grant from the U.S. National Institutes of Health (NIH) to prepare those lines for worldwide distribution, says MizMedi chair Sung-il Roh. Those two groups, plus the Seoul-based Maria Biotech Co., are among the 15 groups on NIH's Human Embryonic Stem Cell Registry, which lists stem cell lines created before August 2001 and thus eligible for use in federally funded research in the United States. A group led by in vitro fertilization specialist Shin Yong Moon at SNU Hospital derived its own hESC lines in September 2001.

These clinics are continuing to push their advantage. For example, Chung says Pochon CHA has 1000 donated human embryos, left over from in vitro fertilization treatments, and scientists there plan to derive 100 hESC lines over the next 10 years. Unlike the original hESC lines, these will not be grown on animal feeder cells and thus should be suitable for clinical use, he says.

Progress has been slowed, however, by the Hwang debacle, as two of the original labs are now under a cloud. Hwang recruited both Moon and MizMedi to his team for the stem cell know-how he needed to attempt therapeutic cloning. Earlier this year, SNU suspended Moon for 3 months for "failing to uphold the principles of academic honesty and integrity," according to an SNU press release; Seoul public prosecutors later cleared him of any legal wrongdoing. Then last month, the prosecutors charged that one of the MizMedi researchers seconded to Hwang's team, Sun Jong Kim, was heavily involved in the fraud and indicted him for destroying evidence and obstructing research work. Roh says he is rethinking the direction of their research; Moon could not be reached for comment.

The task force also concluded that Korean researchers have an edge in somatic cell nuclear transfer (SCNT), or cloning—Hwang's specialty. Hwang attributed much of his success in cloning cows and Snuppy, a dog, to a technique that involved gently squeezing rather than sucking the nucleus out of cells. An investigation into Hwang's research by SNU concluded that he did not develop this technique, but that he had refined it; a half-dozen other Korean institutions have used it to clone dozens of pigs and cows.

Korean researchers are also competitive in research on adult stem cells, the task force concluded. Although they are less malleable than embryonic stem cells, adult stem cells, found in many tissues and organs throughout the human body, can renew themselves as well as differentiate into the specialized cells of those tissues and organs. Bone marrow has long been a source of stem cells for therapies for blood diseases and certain cancers. Recently, groups throughout the world have been experimenting with other adult stem cell therapies in humans.

In 2003, SNU cardiologist Hyo-Soo Kim led what is so far the country's only large randomized adult stem cell clinical trial. He treated heart attack patients with their own peripheral blood stem cells to try to promote the growth of new blood vessels and heart muscle. A group in Germany had done a similar trial using bone marrow stem cells, and Kim's group wanted to try something less invasive. The team first used a drug called G-CSF to induce the patient's bone marrow to overproduce peripheral blood stem cells, which they harvested and then injected into the patients' hearts.

The trial was halted early because 7 of the 10 patients treated with G-CSF suffered a rearrowing of previously blocked arteries in the area around an inserted stent. Kim is optimistic that the side effect can be minimized, and he notes that patients treated with stem cells showed a measurable, although minor, improvement in heart function. The team published a brief report on the trial in *The Lancet* in 2004, and a more complete paper is now being prepared. "We believe that only a small percentage of the stem cells clung to the heart tissue," says Kim, who is trying to "prime" cells with chemicals and proteins so that a greater percentage will

lodge in the heart and, he hopes, grow into replacement tissue.

The task force highlighted one major weakness of the Korean research community: its limited expertise in cell, molecular, and developmental biology. This hinders efforts to understand and ultimately exploit stem cells'



Uncertain legacy. Construction has stopped on the building once intended for disgraced cloner Woo Suk Hwang (*bottom*); the space intended for his Stem Cell Hub (*above*) will be used for gene therapy.

magical ability to both self-renew and differentiate into all the specialized cells of the body. "Japan, the U.S., the U.K., and other countries in Europe are leading in this field," admits Hanyang's Kim, whose own work is one of the bright spots. He led a team that recently identified 36 novel microRNAs apparently involved in regulating hESC development. Their report in *Developmental Biology* in May 2004 was among the journal's top 10 most frequently downloaded papers for the past 2 years. "I'm really proud," he says. He's now working on elucidating the functions of these microRNAs.

A fresh start

The task force spelled out a new research agenda that aims to capitalize on the country's strengths and take advantage of new opportunities, says Yonsei's Kim. All grants will be competitively reviewed to avoid "concentrating funding on one person," says Catholic University's Oh. Priority areas include:

- characterizing stem cells and directing differentiation,
- improving techniques to isolate and expand adult stem cells,
- developing new culture methods suitable for clinical use,
- exploring alternatives to SCNT for producing patient-specific stem cells,
- verifying the safety and efficacy of transplanted stem cells in animals and humans, and
- applying stem cells to drug development.

The plan also calls for establishing common-use facilities such as a stem cell bank, sponsoring international collaborations, and strengthening training programs. Kim expects the government to implement these recommendations in 2007.

In the aftermath of the Hwang scandal, the task force, which included bioethicists, also called for "a heightened awareness of ethical issues," says Oh. For instance, the group urges more stringent requirements to confirm the efficiency of therapies in animals before trying them in humans. Meanwhile, research on human therapeutic cloning is on indefinite hold, Hanyang's Kim notes, although not because of this report. He explains that groups attempting therapeutic cloning will need permission from the national bioethics review board set up last year, which has yet to decide the criteria for granting permission.

Finally, the task force recommends frank communication between researchers and the public. "Many people in Korea and probably even most of the young officials in the government really believed that Korea was one of the most prominent and leading countries in the world in stem cell research," says Hanyang's Kim. Instead, "we were leading in a small part of stem cell research," he says. Researchers here say the public and patients alike must be given realistic assessments of the expected results of experimental stem cell therapies. SNU's Kim says the goal for his stem cell therapy for heart attack patients is to improve damaged heart function by 10% over what it would be without treatment. "That would be noticeable by patients," he says, but still far short of fully restoring their hearts.

Stem cells are "not a miracle cure; only God can make miracles," says Kook In Park, a stem cell biologist at Yonsei University. It may help get his message across that the Hwang-inspired postage stamp showing a patient rising from a wheelchair thanks to stem cell therapy is no longer on sale.

—DENNIS NORMILE

With reporting by D. Yvette Wohn in Seoul.