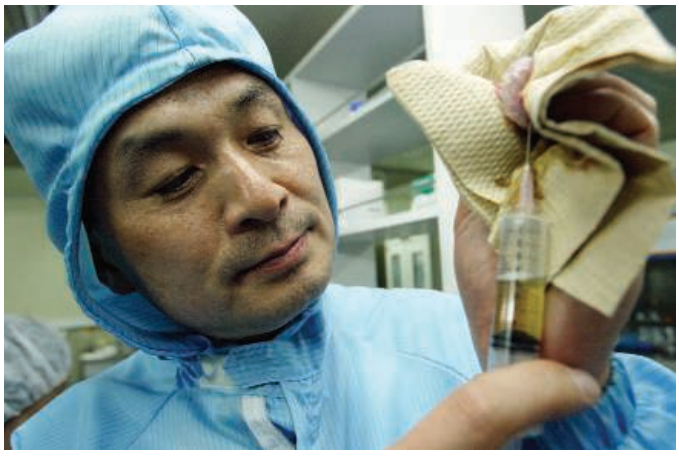
Less encumbered by societal restrictions on embryonic stem cells, scientists in the developing countries of Asia are giving Western researchers a run for their money

Asia Jockeys for Stem Cell Lead

Veterinarian Woo Suk Hwang and gynecologist Shin Yong Moon leapt from obscurity to scientific stardom last February when they isolated embryonic stem (ES) cells from cloned human cells, a world first and a key step toward therapeutic, or research, cloning.

Coming from a region that rarely produces scientific headlines, the announcement by the Seoul National University (SNU) pair stunned researchers around the world. But it was no fluke. Hwang has a long track record of successful animal cloning. Moon is South Korea's leading expert in assisted reproductive technology. The duo were able to draw on the expertise of a dozen co-authors at six institutions. And when Western scientists got their first peek into the SNU lab, they were astounded to see state-of-the-art facilities—and an enviable supply of egg donors.



Spotlight. Woo Suk Hwang (above) and Shin Young Moon grabbed acclaim for South Korea with their breakthrough work with ES cells.

Largely below the radar screen, the emerging economies of South Korea, Singapore, Taiwan, and China are fast becoming major centers for human ES cell research. Like their colleagues in the advanced scientific powers—including Japan, the United States, and many European countries—researchers in the developing countries of Asia are racing to learn how to transform ES cells into human tissues and organs, which could lead to treatments for conditions that are now intractable, such as diabetes, Parkinson's disease, and spinal cord injuries.

But there is one big difference: Unlike their colleagues in the United States and much of Europe, Asian scientists have the full support of their governments. Because obtaining ES cells involves the destruction of very early stage embryos, many Western governments have placed heavy restrictions on the work. But across Asia, there is little of the conflict with prevailing religious and ethical beliefs that has Western countries hesitating (see sidebar, p. 664). Governments are ramping up funding for both basic and applied stem cell work, setting up new institutes, programs, and grant schemes, and providing incentives for private companies to join the effort. Giving these efforts a further boost, the region also has legions of lab workers willing to log long hours, and increasing numbers of expatriate scientists are returning home to work in the flourishing environment.

With all these advantages, Asia's scientists believe that they can be fully competitive in, and perhaps even lead, the race to harness stem cells. "Asia has never dominated [any field in] cutting-edge biology," says Chunhua "Robert" Zhao, director of the National Center for Stem Cell Research in Beijing. "This could be our chance."

Stem cell researcher George Q. Daley of Harvard Medical School in Boston agrees: "I firmly believe they have an advantage." Although recent state funding initiatives in California and Wisconsin (see sidebar, p. 662) should ease some of the constraints hobbling ES cell research in the United States, says Daley, such efforts are no substitute for federal support, which is still restricted.

Asia does face challenges, however. These countries are still building their scientific infrastructures, and many institutions must make do with older equipment. For some groups, geographical isolation and lingering language barriers hinder participation in conferences and complicate scientific publishing. In China, a lack of coordination and a culture of secrecy among scientists hamper progress. Perhaps most pressing, says South Korea's Hwang, the entire region suffers from a dearth of experienced senior scientists to run the new programs.

A series of firsts

Asian scientists have been at the forefront of research on cloning and stem cells since its inception. At China's Shandong University, embryologist Tong Dizhou produced the world's first cloned vertebrate, an Asian carp, in 1963. He went on to create the first interspecies clone in 1973, by inserting European carp DNA into an Asian carp egg. But Tong's work remained almost unknown outside China.

Two decades later, in 1994, Ariff Bongso, an in vitro fertilization (IVF) expert at the National University of Singapore, reported the first isolation of human ES cells in the journal *Human Reproduction*. But Bongso was unable to keep the cells growing, so the work attracted little publicity. That changed when two U.S. groups—one led by James Thomson of the University of Wisconsin, Madison, and another by John Gearhart of the Johns Hopkins University School of Medicine in Baltimore, Maryland—almost simultaneously solved the problem of maintaining stable lines of ES cells in 1998 by growing them on "feeder" layers of mouse fibroblast cells. Bongso and colleagues from Monash University in Melbourne, Australia, and Hebrew University in Jerusalem caught up, creating their own stable human ES cell lines in 2000.

Singapore

Singapore was quick to realize the scientific and commercial payoffs of stem cell research. "Given its huge potential, stem cell research has been identified as one of Singapore's niche areas," explains Hwai Loong Kong, executive director of the Biomedical Research Council, a part of Singapore's Agency for Science, Technology, and Research (A*STAR). ES cells became a cornerstone of Singapore's

CREDIT: KIM KYUNG-HOON/REUTERS

Published by AAAS

State of the art. With a 25-person research team, Singapore's ES Cell International is racing to create insulin-producing ES cells to treat diabetes.

$2 billion National Biomedical Science Strategy, announced in June 2000 (*Science*, 30 August 2002, p. 1470).

Kong says A*STAR is spending about $7.3 million per year to support stem cell research, using both embryonic and adult lines, at the country's national labs and through grants to university researchers. But that is only part of the story. Academic groups also get funding from their universities and the Ministry of Education. The amount can't be pinned down, but the National University of Singapore reports that about a dozen groups are working on stem cells. Additional money is coming through venture capital support for start-up companies working to commercialize stem cell therapies and from foreign funders attracted by Singapore's welcoming climate for ES cell research.

Among academics, Bongso continues to set the pace. In September 2002, he and his Australian and Israeli colleagues reported the first propagation of human ES cells without using mouse feeder layers—a key advance because the lines grown on mouse cells probably cannot be used for clinical applications, given concerns about nonhuman pathogens. Bongso and his colleagues have turned over their cell lines and intellectual property to ES Cell International for commercialization. ES Cell owns six of the 22 human ES cell lines currently listed on the U.S. National Institutes of Health's (NIH's) Stem Cell Registry and has supplied more than 140 ES cell lines to researchers around the world, second only to the Wisconsin Alumni Research Foundation.

In March 2002, ES Cell recruited Alan Coleman, former research director of PPL Therapeutics in Edinburgh, U.K., and a member of the team that cloned Dolly the sheep, to head its 25-person research team. The company is banking on its ability to turn stem cells into insulin-producing cells that could be transplanted into patients with diabetes. Robert Klupacs, ES Cell International's CEO, says it hopes to start human clinical trials in 2006. Ronald McKay, a stem cell researcher at NIH, says ES Cell International is definitely one of the teams to watch, as is Singapore as a whole. Although the company has yet to turn a profit, concedes Klupacs, it has been able to support its $6.1-million-a-year research program with grants from Singapore, Australia, and private investors.

Asia's Stem Cell Firsts

1963 First cloned vertebrate (Asian carp)
Tong Dizhou
Institute of Oceanology, Chinese Academy of Sciences, Qingdao, Shandong Province, China
Science Bulletin (Chinese)

1973 First interspecies clone (European carp DNA into Asian carp egg)
Tong Dizhou
Institute of Oceanology, Chinese Academy of Sciences, Qingdao, Shandong Province, China
Acta Zoologica Sinica

1994 First isolation of human ES cells
Ariff Bongso
National University of Singapore
Human Reproduction

2002 First propagation of human ES cells without use of mouse feeder layers ▶
Ariff Bongso
National University of Singapore (plus colleagues from Monash University in Melbourne, Australia, and Hebrew University in Jerusalem)
Nature Biotechnology

2003 First isolation of embryonic stem (ES) cells from cloned human cells
Woo Suk Hwang and Shin Yong Moon
Seoul National University
Science

The U.S.-based Juvenile Diabetes Research Foundation (JDRF) is also supporting stem cell research in Singapore. It provided a $600,000 grant to Bernat Soria of the University Miguel Hernandez de Elche in Alicante, Spain, to set up a lab in Singapore in 2002 to continue work he was prevented from doing in his native country. In February 2000, Soria reported that his group had differentiated mouse ES cells into insulin-producing cells that had alleviated diabetes symptoms in mice. He has been extending that work to humans in his Singapore lab. Although the Spanish government has since relaxed its restrictions, Soria plans to keep a lab in Singapore. "The Asia-Pacific is playing a very important role in this research," he says.

JDRF is also putting up half the cost of a $3 million fund—the other half is coming from A*STAR—to support other Singapore-based stem cell researchers working in a number of fields, as part of a new, competitively reviewed grant scheme. The founda-

CREDITS (TOP TO BOTTOM): ES CELL INTERNATIONAL; D. NORMILE/*SCIENCE*

Published by AAAS

U.S. States Offer Asia Stiff Competition

Proposition 71, the $3 billion initiative designed to catapult California into position as the world leader in research involving human embryonic stem (ES) cells, is having a seismic effect across the United States. A few states—notably Wisconsin and New Jersey—are trying to become counterweights to California. Others are proposing more modest measures to make their states more attractive to stem cell researchers. Many legislators are trying to float initiatives despite substantial obstacles, such as big budget deficits. But if they don't take action, "states that have made significant investments in biomedical research"—Maryland and Massachusetts, to name two—"are genuinely concerned they are going to lose intellectual capital and resources," says Daniel Perry of the Coalition for the Advancement of Medical Research in Washington, D.C.

Wisconsin—where the first human ES cell line was derived in 1998—is moving decisively. The state is poised for a massive new investment of $750 million in stem cell and other biomedical research over the next few years, including more than $500 million in new facilities and research support for scientists at the University of Wisconsin, Madison. Post–Proposition 71, a planned $375 million public-private research institute, the Wisconsin Institute for Discovery, has gained impetus.

In New Jersey, acting Governor Richard Codey is pursuing a regional approach. He has proposed allocating $150 million from unspent bond income to construct the New Jersey Institute for Stem Cell Research, a joint project of Rutgers University and the University of Medicine and Dentistry of New Jersey. Codey wants a ballot referendum next November to raise $230 million to bankroll research grants over the next 10 years.

In Illinois, members of the state Senate failed narrowly in November to pass a bill that would have allowed state funding for ES cell and nuclear transfer research. Now state Comptroller Daniel Hynes has designed a California copycat initiative: a statewide referendum in 2006 on a billion-dollar bond initiative. The Illinois Regenerative Medicine Institute would be created from the sale of $100 million in bonds per year for 10 years—repaid through a 6% tax on cosmetic plastic surgery.

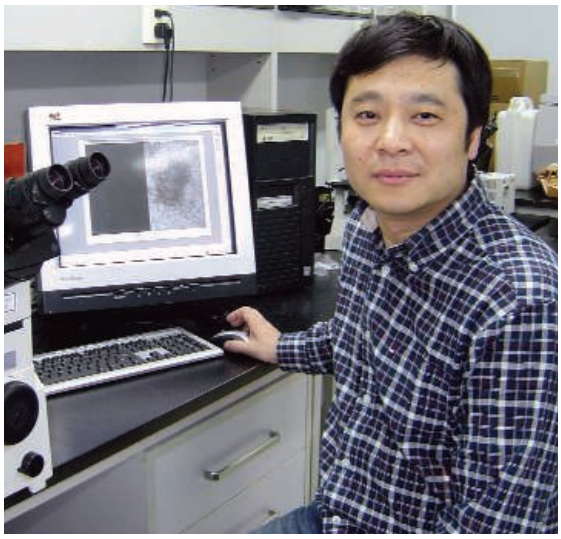
States' rights. New Jersey's Richard Codey is one of several governors trying to lure stem cell research to his state.

tion is investing in Singapore, says Chief Scientific Officer Robert Goldstein, "because there is excellent science, a good environment, and really strong support for work that can't be done in [the public sector in] the U.S.," including deriving and working with new stem cell lines.

China

Although numbers are hard to verify, China may be home to the largest stem cell program in Asia. The government does not release statistics, but Pei Xuetao of the National High Technology Research and Development Program's stem cell division estimates that China has "about 300 to 400" Ph.D.s working on all types of stem cells in more than 30 scientific teams across the country. Perhaps 80 of them work with embryonic cells, a proportion that is growing.

As opposed to Singapore's coordinated national plan, China has a host of overlapping initiatives from the central government, cities and provinces, private enterprise, and even semiprivate venture capital funds created by government agencies and the military. Pei pegs the total 5-year research budget at "more than" $24 million. (Dollars go further there than in the West, given China's vastly lower labor and material costs and its allocation of almost 100% of funding to research, with little overhead.)



Coming home. Deng Hongkui left his lab in New York for new digs in Beijing's Peking University.

Perhaps more important than funding levels, says Xiangzhong "Jerry" Yang of the University of Connecticut, Storrs, is that China has one of the most supportive environments for embryo research anywhere in the world. Issued in December 2003, Chinese regulations are quite "liberal," says Yang. There is a strict ban on human cloning for reproductive purposes. But for research cloning, the guidelines include little more than a requirement that scientists comply "with the principle of informed consent and informed choice" when obtaining embryos from IVF clinics or fetal tissue from aborted fetuses. They also include a directive for institutions to monitor compliance. Wang Yu, the Ministry of Science and Technology's vice director of rural and social development, says the guidelines are "aimed at pushing forward our country's stem cell and therapeutic cloning research."

The competition among groups and the government's reluctance to reveal information make it difficult to judge China's progress. But there is one sign of success: the growing number of foreign-trained Chinese scientists who are leaving comfortable positions in Europe and the United States to work in their native land. Sheng Hui Zhen, an ES cell researcher at Shanghai Second Medical University, says that "most major teams" in the field now have U.S.- or Europe-trained scientists in senior positions.

Sheng is a prominent example. She spent 11 years at NIH before relocating to Shanghai in 1999, where she leads a 50-person team, funded mostly by the city. The group is attempting to create functioning human ES cells by inserting the nucleus of adult human skin cells into rabbit eggs from which the nuclear DNA has been extracted. Sheng reported initial success in August 2003 in *Cell Research*, a peer-reviewed journal backed by the Chinese Academy of Sciences, but so far, no other lab has reported duplicating her work.

The popular press described the work as a "cross-species clone," sparking intense ethical debate in the West. But Sheng dismisses talk of chimeric animals, noting that the only rabbit DNA in the cells is mitochondrial. Her goal, she says, is to design an alternative to human eggs for use in therapeutic cloning. She suspects that when such work becomes feasible, the procurement of eggs, which are

CREDITS (TOP TO BOTTOM): MIKE DERER/ASSOCIATED PRESS; YAN SHEN

Published by AAAS

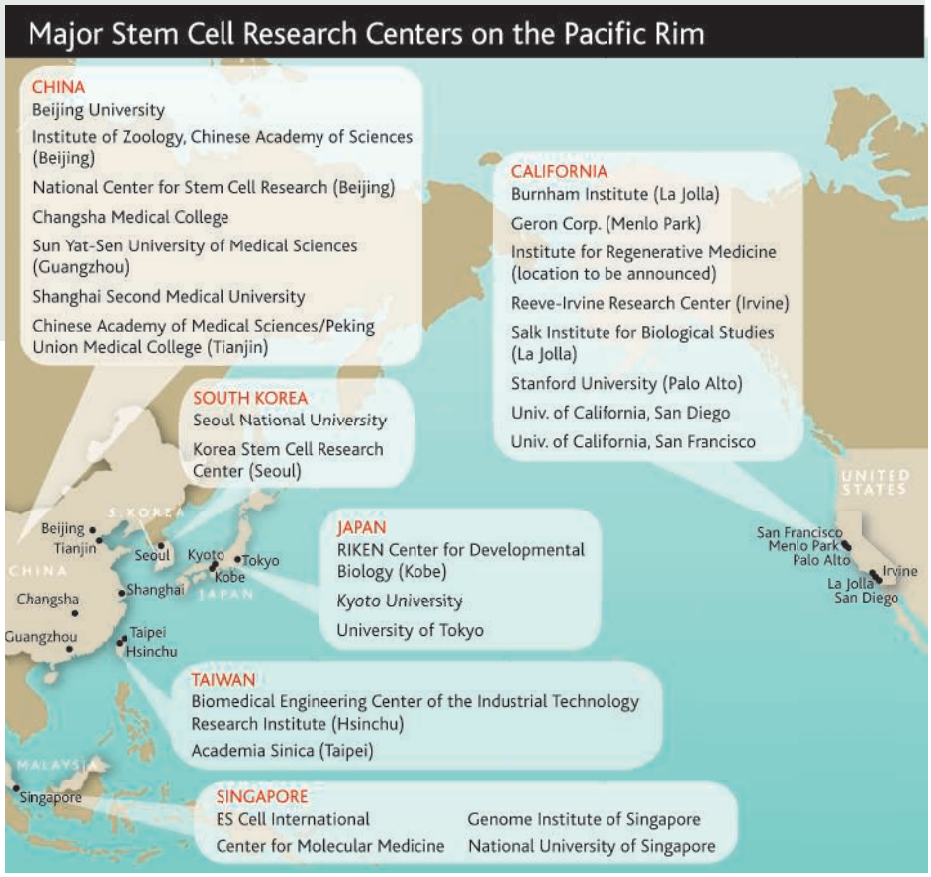
Other states are eyeing various strategies to beef up their stem cell capacities. In Maryland, legislators are readying a proposal that would use tobacco-settlement money to open up $25 million annually for stem cell research starting in fiscal year 2007. Florida is poised to become a major player now that the California-based Scripps Research Institute plans to open its first branch in Palm Beach County. And a private group, Cures for Florida, is campaigning for a $1-billion-plus state ballot initiative for ES cell research.

Legislators in Massachusetts are chafing to get into the stem cell game, but because of the state's large Catholic population, recent pro-research measures have been quashed by the legislature. But Democrats, who are angling for the support of Republican Governor Mitt Romney, have vowed this year to push legislation to promote stem cell research through measures such as tax incentives. And in New York earlier this month, three legislators proposed a 10-year, $1 billion bond initiative that would finance the New York Stem Cell Research Institute.

On the flip side, a number of states are attempting to close the door on research with human ES cells. Nebraska, South Dakota, and Louisiana have forbidden such research. Laws prohibiting nuclear transfer (therapeutic cloning) have been passed in Michigan, Arkansas, Iowa, North Dakota, and South Dakota. Missouri is contemplating one, although scientists are warning that the state will pay a price if it adopts such a ban. The Stowers Institute for Medical Research in Kansas City, a major contributor to the biological lifeblood of the state, has said it "would be forced" to build a planned second facility outside Missouri if the measure passes.

Perry sees the state initiatives as evidence that the center of gravity in research may be shifting away from the federal government. "After generations in which a single NIH" ruled the biomedical research roost, "it's almost like the breakup of the Roman Empire."

–CONSTANCE HOLDEN



difficult and expensive to obtain, may be the weak link. "My Chinese lab does not have everything my NIH lab had," says Sheng. "But here I can work on this important problem, and there I couldn't."

Some Chinese scientists have received backing for research that astonishes their former Western colleagues. Trained in Minnesota, Zhao of the National Center for Stem Cell Research in Beijing is working on stem cells from the bone marrow of aborted fetuses—work that cannot be done with federal funding in the United States and that many states have banned outright. "We have the freedom to look at these problems from many angles," he says.

South Korea and Taiwan

To date in South Korea, the private sector has taken the lead in stem cell research. Three of the four groups that have established ES cell lines are at private IVF clinics, and for their breakthrough work, SNU's Hwang and Moon relied on a culturing technique developed at one of them. Figures for private sector spending are not officially tallied, and Hyun Soo Yoon, director of research at Seoul's MizMedi Hospital, which has a team of 18 scientists and technicians working full-time on stem cell research, also declined to disclose his group's budget.

Now the South Korean government wants to capitalize on the advances made by Hwang and Moon. At Hwang's home university in Seoul, the government is spending $50 million over 5 years to set up the Bio-MAX Institute; its goal is to foster interdisciplinary research in the life sciences, with a major focus on stem cells. Hwang will be moving his lab to Bio-MAX. Meanwhile, Moon continues to direct activities at the Korean Stem Cell Research Center. Established in 2002, the center has an annual budget of $7.5 million to support 30 researchers. And last year, the government put $5 million into a new competitive grant scheme for research related to therapeutic cloning, stem cells, and xenotransplantation. Funding could rise to $25 million per year by 2008.

In Taiwan, the government-affiliated Industrial Technology Research Institute (ITRI) is trying to nurture the island's biotechnology industry by developing stem cell expertise. ITRI researchers were the first in Taiwan to start working with human ES cells, in 2001. They have an 18-person group working to derive their own mouse-feeder-free cell lines and to learn to control differentiation. Their first target, too, is insulin-producing cells. While ITRI focuses downstream, Academia Sinica, Taiwan's premier collection of publicly funded science labs, is now ramping up a stem cell program focusing on understanding basic stem cell biology.

Challenges

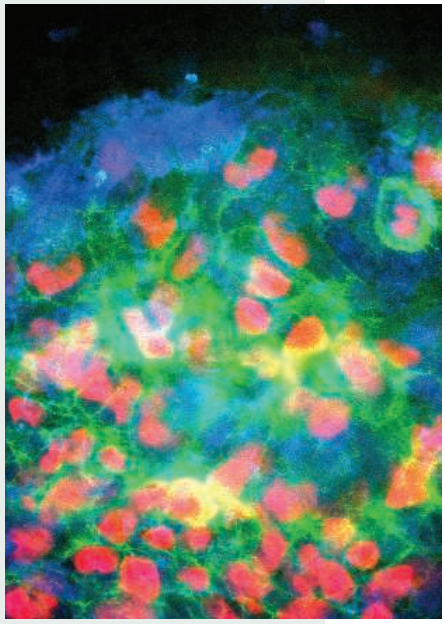
Although Asia's stem cell efforts are coming into their own, the region faces a number of challenges. Some worry that important stem cell research is going unpublished because of the intense interest in commercialization by Asian governments, companies, and researchers. Unlike Western biotech companies, which often seek the limelight, representatives of private companies in both Tai-

Asian Countries Permit Research, With Safeguards

Government officials, researchers, and ethicists in Asia readily link the region's general acceptance of research using human embryonic stem (ES) cells to its dominant Buddhist and Confucian religious-ethical traditions. But the countries of East Asia have also put a lot of thought, effort, and public debate into formulating policies that define researchers' responsibilities, as well as oversight mechanisms to ensure that guidelines are followed.

Although broadly similar, the policies adopted throughout the region differ in details. China, South Korea, Taiwan, and Singapore have all banned reproductive cloning with the intent of creating a child. All four regions also allow the derivation of ES cells from surplus in vitro fertilization (IVF) embryos obtained with informed consent; China, in addition, allows researchers to use embryos from aborted fetuses or miscarriages. South Korea's law stipulates that only embryos preserved for at least 5 years can be used. In each country except China, bioethics advisory committees have proposed national review boards to approve and oversee the derivation of new stem cell lines and each specific research project using them.

Singapore and China allow the creation of embryos through IVF for research purposes; South Korea and Taiwan forbid this. Countries are split on therapeutic cloning, or the use of adult somatic cells to create stem cells genetically matched to the donor. Singapore and China will allow it with the same oversight as for ES cells. South Korea has decided to restrict therapeutic cloning to a limited number of groups and solely for work that can't be done using typical ES cells. The country's national review board will decide which groups and projects qualify. Taiwan's advisory committee "split 50-50" on therapeutic cloning, says committee member Daniel Tsai, a physician on the faculty of National Taiwan University. It put off a decision pending further study.



Socially acceptable. Asian countries are less encumbered by the ethical dilemmas that have hamstrung research in the West.

Singapore, South Korea, and Taiwan incorporated societal views through high-level bioethics committees that held public hearings and made recommendations for the governments to codify into law. South Korea adopted a law governing ES cell derivation and research in December 2003. In September 2004, Singapore banned reproductive cloning but left pending the creation of a national review board. Under both laws, violators face prison sentences of up to 10 years or hefty fines or both. South Korea's review board is now being formed. Singapore's and Taiwan's need enabling legislation. For now, researchers using ES cells in Singapore must report their activities to the Ministry of Health. Until Taiwan passes legislation, says Tsai, institutions are trying to follow the recommendations of the bioethics committee; anyone violating the administrative ban on human cloning could lose a license to practice medicine or be forced out of an academic post.

Serious debate in China on stem cell research ethics began only in late 2001, after a team led by Chen Xigu of Zhongshan Medical University in Guangzhou claimed it had cloned embryos by inserting a child's DNA into an enucleated rabbit egg. Although the news was met with skepticism, and the team never published its results, the report set off a public storm. Galvanized by the furor, Chinese bioethicists held several meetings in 2002 and 2003, submitting the results to a newly formed interagency committee of the ministries of Health and Science and Technology. Issued in December 2003, the committee's "ethical guiding principles" are much less formal than other nations' regulations—they are fewer than 500 words long and specify no penalties for violation. Although the regulations are intended to "give researchers a lot of freedom," the bottom line is clear, says Deng Hongkui of Peking University: "There will be no reproductive cloning in China."

–D.N. AND C.C.M.

wan and South Korea were reluctant even to name their research topics to *Science*. Speaking under condition of anonymity, two Chinese researchers confessed they had not fully informed their granting agencies of what they were doing.

Deng Hongkui, a former New York University researcher known for his work on HIV, moved in 2001 to Peking University. Deng readily concedes that he has delayed submitting his research on the mechanisms of differentiation for publication for 2 years partly because his lab was preoccupied with the SARS emergency and partly, he says, because he wanted to secure worldwide intellectual property rights.

In China, researchers admit, the penchant for secrecy is heightened by rivalry and suspicion, which sometimes prevents groups from sharing data, expertise, and equipment as freely as their colleagues in the West. But they contend that this lack of communication is exacerbated by Asian researchers' continuing isolation from the scientific mainstream. Yang attributes some of this isolation to what he calls Western researchers' "inability to believe that top-rank research can come from developing nations in Asia." The biggest challenge facing the region "is not the lack of financial resources or good bench-level researchers but the lack of leaders," says Haifan Lin, a stem cell researcher at Duke University in Durham, North Carolina, who serves on a grant review committee at China's National Natural Science Foundation. All of these countries are trying to recruit researchers from outside their borders. Singapore has been the most aggressive, partly because it is so understaffed. Singapore also has advantages in recruiting nonnatives, as English is the language of commerce and government and the city is relatively cosmopolitan. "For me, it was Singapore or nothing," says ES Cell's Colman. Fifteen nations are represented on ES Cell's 25-person scientific team.

Some countries are already following China's lead and targeting expatriate sons and daughters. At Taiwan's Academia Sinica, most of the half-dozen Ph.D.-level researchers in the new stem cell group are Taiwanese or Chinese researchers returning from stints in the United States, the United Kingdom, or Australia. Group leader John Yu is a case in point. The former director of experimental hematology at Scripps Research Institute in La Jolla, California, Yu says he was lured back by the opportunity to get in on the ground floor of an exciting new effort and the chance to work in his native region.

Yu and other Asian scientists say they view these questions about leadership, openness, efficiency, and labor power as hurdles, not barriers, and are determined to overcome them. And they say their Western colleagues should expect to see more headline-grabbing research results come out of Asia in the next few years.

–DENNIS NORMILE AND CHARLES C. MANN

CREDIT: A. LASLETT, A. FILIPCZYK, AND M. PERA/MONASH INSTITUTE OF MEDICAL RESEARCH AND AUSTRALIAN STEM CELL CENTRE

Published by AAAS