

Stem cells rise in the East

As China pours research funds into regenerative medicine, its scientists are starting to explore the field's technical and ethical frontiers. Carina Dennis visits the labs that are creating an international stir.

*"When joy is at its highest
Sad thoughts run rife
Youth and strength, how short they last
How hopelessly we age!"*

Emperor Han Wudi, Western Han Dynasty¹

More than two millennia ago, China's emperors searched in vain for the elixir of youth. Today, facing the demographic consequence of its one-child policy — a steadily ageing population — the country as a whole is grappling with the same challenge.

Rather than turning to wistful poetry, China's current leaders see a solution in the field of regenerative medicine. They have started to spend lavishly on labs working on stem-cell research and therapeutic cloning, hoping to develop the means to grow cells and tissues to replace those lost to the ravages of age and degenerative disease.

With this generous support, and in a cultural environment in which there are fewer of the moral objections to the use of embryonic stem cells that have hampered the field's development in the United States, Germany and elsewhere, expatriate Chinese biologists have rushed back home. "There has been a real boom in stem-cell research in China in the past two years," says Lingsong Li of Peking University in Beijing, who returned in 2000 from a postdoctoral position at Stanford University in California.

Questions remain about China's ability to attain a world-class presence in the field. But as news about the projects under way in China circulates through the scientific community, and reports of the most eye-catching work emerge in the international press,

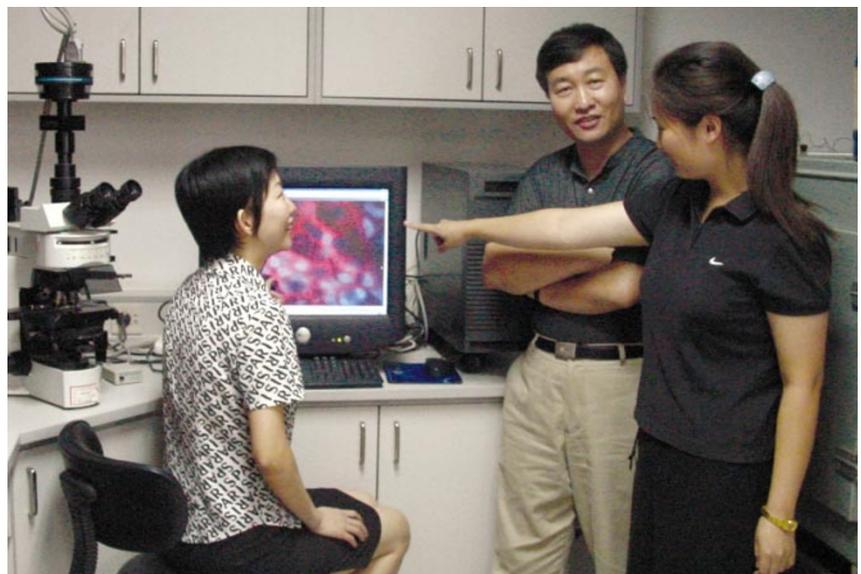
Western researchers are taking notice. "It is clear that there is a group of scientists doing good work," says Peter Donovan, a stem-cell biologist at Thomas Jefferson University in Philadelphia, who was a keynote speaker at the 2002 International Symposium on Stem Cell Research, held in Beijing in May. And *Nature* recently had a rare opportunity to visit some of their labs.

A few hours spent with Li provide some intriguing insights into China's current stem-cell push. He has the confident air of a Californian biotech entrepreneur — and the research facilities to match. Li heads the Peking University Stem Cell Research

Eyes on the prize: will stem cells help maintain the health of China's greying population?

Center, which boasts a staff of some 50 people. He has received more than US\$4 million — from the university, the central government, and Chinese venture capitalists — to set up the centre and to cover its running costs for three years.

As he shows visitors around the gleaming new labs, Li fields calls on his mobile phone from his scientific, political and business contacts. Energetic and ambitious, he is attracted to the fast pace of stem-cell research — and to China as the right place to pursue it. His rise



Booming business: Lingsong Li (centre) enjoys the fast pace of emerging stem-cell research in China.

to prominence has certainly been meteoric. Li does not have an established track record in the field, but says that his training at several US universities, mostly in immunology, gave him the confidence to seize his current opportunity. "I am motivated by the challenge of growing within the field, as well as growing the field within China," says Li.

His centre will focus on how the differentiation of embryonic stem cells is regulated, and will try to apply various types of stem cells to the treatment of cardiovascular disease, neurological disorders and diabetes. Li's group has developed a method of genetically altering neural stem cells so that they can multiply indefinitely in culture but retain their ability to differentiate into neurons. His team has also created animal models of human neurological diseases to study the signals that tell stem cells how to develop and direct them to sites of injury where they are most needed.

Creating a buzz

Li may be one of the main movers and shakers on China's stem-cell scene, but the most intense international interest has so far focused on the leaders of two other labs. In March, with rumours about the work already buzzing around the stem-cell research community, *The Wall Street Journal* reported that a team led by Guangxiu Lu of the Xiangya Medical College in Changsha in central China had since 1999 been creating cloned human embryos with the goal of extracting stem cells. The same article claimed that researchers led by Huizhen Sheng of Shanghai Second Medical University had extracted stem cells from embryos created by fusing adult human skin cells with rabbit eggs that had been stripped of their own chromosomes.

Sheng's work is based on the now-familiar concept of therapeutic cloning — cloning an embryo from the patient's own cells to harvest stem cells that could be used to grow tissues genetically matched to the patient, so eliminating problems with immune rejection. Sheng turned to rabbit eggs because the human variety is in short supply. Human eggs would be used if therapeutic cloning ever becomes a clinical reality, but the idea is to develop the techniques involved without exploiting this precious resource.

Other researchers are working along similar lines — the biotech firm Advanced Cell Technology (ACT) of Worcester, Massachusetts, revealed in 1998 that it had experimented with cloning using human cells and cow eggs. But ACT is not thought to have extracted stem cells from the resulting embryos. The report of Sheng's research also came at the height of the US political debate over cloning, and was seized on by lobbyists on both sides. Those in favour of therapeutic cloning argued that the United States risked losing the lead in an important field, whereas anti-cloning activists sought



Huizhen Sheng (left) has trained a large team of young researchers to work on embryonic stem cells.



to portray China as a morally bankrupt 'Wild East' of biology.

Unlike ACT, which has been widely criticized for making media announcements about unpublished work of uncertain scientific merit, Sheng did not court publicity. *The Wall Street Journal* picked up the story from someone who had heard Sheng present her data at the University of Texas Southwestern Medical Center in Dallas. Disturbed by the attention focused on work that has not been peer-reviewed, she has no intention of discussing its details until it appears in the scientific literature. "We receive hundreds of calls from journalists," says Sheng. "I don't blame the media — they are doing their job. But if data are reported too early, it can interrupt the normal process of scientific review."

Sheng's lab is an oasis of calm in the hub-bub of central Shanghai — mirroring her circumspection amid the media scrum that has surrounded her work. Situated on the top floor of a building in the Xinhua Hospital, her lab overlooks the city's rooftops. In her bright, airy office, our conversation is punctuated by the faint sounds of sirens as ambulances pull up to the emergency department downstairs.

Along the corridor, students are peering down microscopes at tiny balls of embryonic cells dividing in culture. Sheng heads a team of over 40 people, more than half of them students, and she thrives in her role as teacher and mentor. But it was tough to get the lab started, because so many of China's top young scientists go abroad. "I had to

Searching for an ethical consensus

Mention the phrase 'embryonic stem cells' in many Western countries, and you're thrown headlong into arguments over the morality of extracting cells from human embryos just a few days old. But in China, the potential medical benefits are seen as justifying the practice. "The population more readily accepts this research," says Renbiao Chen, a member of the Chinese National Human Genome Center at Shanghai's bioethics committee.

Cynics might argue that China lacks the democratic traditions likely to foster a public debate on the issue. But Chinese researchers and officials are anxious to dispel the notion that the country is an unregulated frontier for stem-cell science — not least because they want to attract investment and scientific collaborators from the West. "We need to set up guidelines that follow international standards," says Lingsong Li, who heads the Peking University Stem Cell Research Center in Beijing.

Draft national regulations on stem-cell research are due later this year, and are expected to borrow from Britain's liberal legislation. If so, Chinese researchers would be able to extract new human embryonic stem-cell lines. Harvesting stem cells from embryos created by cloning may also be allowed.

While officials in Beijing wrestle with the details, scientists in China's second city have drawn up their own rules. Stem-cell researchers in Shanghai already have to comply with guidelines drafted by the bioethics committee at the city's genome centre, which were published in October last year in China's leading medical ethics journal⁵. The Shanghai guidelines are also based on Britain's regulations, with one significant difference — they allow experiments that aim to harvest stem cells from embryos created by fusing human cells with eggs from other mammalian species that have been stripped of their own genetic material.

This is only allowed for basic research — clinical therapeutic cloning would have to use human eggs. But it is unclear whether the national regulations will follow Shanghai's permissive lead. "People in the scientific community and government agencies have different opinions," says Li.

recruit fresh students and train them for a couple of years," she says.

Sheng returned to China in June 1999 after spending seven years as a postdoc with Heiner Westphal, a developmental biologist at the National Institute of Child Health and Human Development in Bethesda, Maryland. There, she had become interested in the possibility of using nuclear-transfer cloning to reprogramme adult cells to an embryonic state. However, constraints on the use of US federal funds would have prevented her from pursuing the research in Bethesda. "At that time, the Shanghai municipal government offered me a large grant to set up a lab," says Sheng.

But this opportunity came at a personal price. "My husband loves his job in the United States and my son is now at college," says Sheng. Although she sees them several times a year, the separation is hard to bear. "I miss them very much, but it is such an exciting time in science and that keeps me going."

Ethical dilemma

Sheng remains troubled by criticisms of the ethics of her work. Far from operating in an ethical vacuum, she points out that all research on embryonic stem cells in Shanghai adheres to guidelines published last year (see 'Searching for an ethical consensus', previous page). "I think people have a tendency to think that scientists in China just push their research wherever they want it to go. But this is not the case," she says.

Although many Western experts have become sceptical about the prospects of therapeutic cloning ever being made efficient enough to become a routine clinical procedure, there is more enthusiasm in China. At least one other Chinese group in addition to those of Lu and Sheng — that of Xigu Chen of Sun Yat-Sen University of Medical Sciences in Guangzhou — has also experimented with the technique².

Whether China can make a clinical success of therapeutic cloning and other stem-cell therapies won't be clear for some years. The strategy has been to concentrate funding in about a dozen laboratories. "Research labs can find themselves better off than those in the West," says Robert Chunhua Zhao, executive director of the National Key Laboratory for Experimental Hematology in Tianjin, southeast of Beijing, and head of the National Center for Stem Cell Research, which opened in the same city this year.

China has tried the strategy of investing heavily in a select few centres in other areas of biology. Since 1998, it has launched a handful of DNA sequencing facilities, which participated in the international Human Genome Project³. Yet despite an increasing number of publications in top-tier journals, China's accomplishments in the wider field of genetics remain modest compared with those of leading scientific nations.



While cities such as Shanghai prosper, many Chinese are too poor to benefit from medical advances.

Opinion is divided on whether the prospects are brighter in regenerative medicine. "The gap between stem-cell research in China and other countries is not so great," says haematologist Xuetao Pei, director of the Beijing Institute of Transfusion Medicine and Stem Cell Center. But bringing stem-cell therapies to fruition will require expertise in a wide variety of disciplines, from molecular, cellular and developmental biology, through immunology and tissue culture, to clinical medicine. And in that regard, the relatively low level of China's research base could pose problems. Working in one of the country's new stem-cell labs is a little "like doing research on an island", concedes Pei.

Share the knowledge

Vigorous networking between Chinese stem-cell researchers and colleagues working in the West might help. "It is important that we share information to address the imbalance," says Linzhao Cheng, who works on stem-cell engineering at Johns Hopkins University in Baltimore, Maryland.

But even if such links succeed in providing China's stem-cell push with the necessary foundation in basic biology, findings must still be transferred from the lab to the clinic. "I'm not convinced that the interdisciplinary medical teams needed exist in China," says Edward Lin, a clinical oncologist at the M. D. Anderson Cancer Center in Houston, Texas, who regularly visits the country.

Zhao, who returned to China in 1999, disputes this. He spent several years in the lab of Catherine Verfaillie at the University of Minnesota in Minneapolis — who works on 'mesenchymal' stem cells in adult bone marrow that, under some conditions, can differentiate into a variety of tissues⁴. Now Zhao is trying to coax mesenchymal stem cells to differentiate into blood cells, and he points to

his own national haematology laboratory, which has 350 beds for patients with blood diseases and has already conducted clinical trials of bone-marrow transplants. He has applied to initiate clinical trials using stem cells in China next year, transplanting mesenchymal stem cells into patients with chronic myeloid leukaemia. Pei also hopes to begin trials with the same cells, to treat disorders including liver and nervous-system diseases.

Alex Zhang, who returned from Stanford last year to head the Cell Therapy Center at Xuan Wu Hospital in Beijing, is similarly enthused by the clinical opportunities in China. But he is concerned that things may proceed too quickly. "I worry that doctors in China are too eager to get into clinical trials," says Zhang. "I would like to see some guidelines for stem-cell trials in place to avoid rushing into the clinic before the basic science has been done." The government is now working on such guidelines, but they are not expected to be in place for a year or two.

Although Zhao and others are confident that China has the necessary clinical expertise, they become less assured when asked about who is likely to benefit from stem-cell therapies. "One obstacle is the expense of the treatment," says Zhao. China may have a large and ageing population, but most are poor. Even if China's stem-cell pioneers achieve their scientific goals, sheer cost could mean that the therapies they develop become primarily a commodity for export — and for the new elite who have inherited the mantle of China's ancient emperors. ■

Carina Dennis is Nature's Australasian correspondent.

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