

# THE RETURNING TIDE

How China, the world's most populous country, is building a competitive research base

BY WILLIAM A. WELLS

When China turned its back on the Cultural Revolution, it aimed to build a thriving capitalist sector. It got one. Now, it wants a world-class research enterprise. How far has it progressed in the biosciences, how did it get there, and how far does it have to go?

**T**he meteoric rise of China and its 1.3 billion people is the story of the century. Change comes so fast that visitors looking for smoke-belching factories—the first chapter in this tale—now have to look west. China's prosperous east coast, meanwhile, is dominated by a less visible world of big business and high tech.

Biology research is one part of this second chapter of

knowledge-based innovation. It is being driven by a change in migration patterns. For 20 years, the educated elite of China have fled to the West (predominantly to the United States), becoming a significant part of the workforce in US research laboratories. Finally, this flood is yielding a trickle of returnees. They are staffing new and rejuvenated institutions—just a handful, to be sure. But in hindsight, establishing those first



**KEEPING THEM OUT NO MORE**

China's opening to the outside marked the country's scientific rebirth.

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beachheads may have been the hard part. "As long as the politics are stable," says Yixian Zheng (Carnegie Institution, Washington, DC), "I think China will become a very good place for science."

**THE POTENTIAL**

Beyond the neon-covered high rises of Shanghai and the bustling boulevards of Beijing, China remains a developing country.

Half of its people still make their living from the land, and only 2.4% own a car.

But in this case, "developing" is a fact rather than a hopeful moniker. The Chinese economy has grown by 9.4% on average for each of the last 26 years. China is responsible for half of the world's concrete use, and is now the world's second largest energy producer and consumer. It does not, however, register on



an innovation index of 24 countries devised by the *Economist*.

Changing that situation is a priority. “The government has a lot of money to spend on innovation,” says Shao Feng at Beijing’s National Institute of Biological Sciences (NIBS). “You have to be capable in that respect, otherwise you are just a big manufacturer. They have the money, and they want to spend it.”

It helps that many of China’s leaders were educated as engineers at the prestigious Tsinghua University in Beijing. In 2003, notes Bruce Alberts (former head of the US National Academy of Sciences), the Chinese President Hu Jintao talked at a meeting of scientists and then stayed for 1.5 hours. Similar attention to science from a US president is “hard to imagine,” said Alberts recently. “China is run by scientists and engineers, and they get it.”

China currently spends 1.23% of its gross domestic product (GDP) on research and development—a high proportion for a developing country, but about half that of many developed countries. The target announced in August 2006 by the government was 2.5% by 2020. “If you think about the growth in GDP,” says Chinese Academy of Sciences (CAS) Vice President Chen Zhu, “that amount is huge.”

Individual researchers are feeling the effects directly. “Each year the government increases the money in research,” says Wang Shengdian of the Institute of Biophysics in Beijing. One academic reports a 24-fold salary increase since 1998; others a nearly 100-fold increase in the size of start-up grants over the last 13 years. “These last five years, Chinese science developed the fastest maybe in the world,” says Wang Shiqiang of Beijing University. “A new system was built up.”

The basis for these increases is twofold: the expansion of the economy; and the priority that China gives to scientists. In China, “people still respect scientists as a pillar of society,” says Mu-ming Poo (University of California, Berkeley, CA). As a result of this moral and financial support, Yigong Shi (Princeton University, Princeton, NJ) encourages Chinese nationals to go back. “I see China as the next major opportunity,” he says.

But Shi does not think all is perfect in the Chinese science expansion. “I don’t believe it is occurring as fast as possible,” he says. “If you look at the vast resources, China hasn’t exploited them much. If China only had 500 students in the US they would be doing very well. But looking at the base they have to draw on”—an estimated 8,000 Chinese graduate students and post-docs are working in US bioscience labs at any one time (1)—“they are not that successful.”

The scale of the potential returns is evident from the situation in the US. In 1996, says Shi, the US had less than 10 full professors who had arrived from mainland China after the Cultural Revolution, but today there are 500–1,000. “That is a 100-fold increase,” he says. “But China’s recruitment has not picked up 100-fold. It is in no way commensurate.”

China has many academics, but the number who are world-class is still low. By one estimate, there were only 500 “productive” biologists in China in 2004 (reference 2; a biologist was defined as “productive” if he or she published a certain number of medium-impact papers). This compares to an estimated 40,000 productive biologists in the US, including 3,000 of Chinese descent.

Shi draws a similar conclusion. “Princeton has maybe 1,000 faculty members,” he says. “How many at Tsinghua [University]

## Key figures in this article

Opinions from the following people appear in multiple places in this article.

### CHINA-BASED

**CHEN Zhu** is the only biologist who is also a vice president at the Chinese Academy of Sciences (CAS). He supports a balance between competitive NSFC-funded projects and MOST-funded infrastructure projects.

**LU Yongxiang** is a former engineer who was elected as the president of the Chinese Academy of Science in 1997. The following year he initiated the Knowledge Innovation Program (KIP), which revolutionized CAS operations.

**RAO Zihé** was until recently the director of the CAS Institute of Biophysics in Beijing, which he revitalized during his three-year tenure. He is now the president of Nankai University in Tianjing. He is supportive of the large group projects funded by MOST.

### UNITED STATES-BASED

**Bai LU** (NIH, Bethesda, MD) is a neuroscientist who from the mid-1990s has advised on science policies and CAS reforms; more recently he helped establish better peer review at the NSFC.

**Mu-ming POO** (University of California, Berkeley, CA) was a past chair of the Department of Biological Sciences and Biotechnology at Tsinghua, and founded and now directs ION in Shanghai.

**Yi RAO** (Northwestern University, Chicago, IL) was involved in the creation of ION, initiated a major graduate course in Shanghai and Beijing, and now has a lab at NIBS. With Bai Lu, he coauthored the banned *Nature* article that advocated for more merit-based science funding in China.

**Yigong SHI** (Princeton University, Princeton, NJ) is a structural biologist who is also an adjunct professor at his alma mater, Tsinghua. Several of his former postdocs have faculty positions in China. Shi stresses the importance of better teaching in China.

**Xiaodong WANG** (University of Texas Southwestern Medical Center, Dallas, TX) is a founding codirector of NIBS in Beijing. The other codirector is Xingwang Deng of Yale University, New Haven, CT.

would qualify for full professorship at Princeton? I doubt the number is over 10.” By general agreement, the roster of good researchers falls off even more sharply outside of major centers such as Beijing and Shanghai.

But the numbers build daily. Many of the researchers profiled here are such recent arrivals that they have not yet had time to publish from China. Even many in China are unaware of these recent arrivals’ presence and past publication records.



**TOWERING FUTURE** Shanghai's Jin Mao Tower, the fourth highest building in the world, is a symbol of China's ambitions.

Imperfections notwithstanding, mainland China remains a stunning example of how to kick-start a research enterprise (progress in Hong Kong and Taiwan will not be covered in this article). Development is a difficult, messy business littered with far more failures than successes. To see any measure of progress in an area as challenging as high-level biology research is astonishing and deserves a close inspection to see what went right.

### THE FLOWS THAT DRIVE CHANGE

So many things in China—the size of the population, the pace of change and economic growth, even the scale of the scenery—seem more dramatic than in any other country. The generational differences driving changes in Chinese science are no exception.

“There is a lot of energy in China—everyone wants to move ahead,” says Junying Yuan (Harvard University, Cambridge, MA). “The biggest limitation is still the brain drain during the Cultural Revolution. They are missing one generation.”

During China's Cultural Revolution (1966–76), universities were emptied and professors and students sent to the countryside for “re-education.” Research and economic conditions remained hostile enough to force most researchers overseas for a long time afterwards.

Thirty years later, human resources come in the form of a distorted pyramid, with a very wide base but very narrow top. At the peak of this pyramid is a tiny group of leaders. These are the few people who managed to do three things: first, clamber back

## Science in mainland China: a primer

*Descriptions of modern China are usually out of date by the time they are printed. With this caveat in mind, the following is a broad brush outline of some key characteristics of the Chinese scientific system.*

**GEOGRAPHY** The best biology research is heavily concentrated in Beijing, the source of most funding, and Shanghai, arguably the most cosmopolitan mainland city. Exceptions include a primate research center in Kunming in the south. New developments are being promoted in areas that have a lot of economic activity but little or no science. These include a proteomics center in the Pudong area of Shanghai and a new biomedicine institute in Guangzhou, near Hong Kong.

**THE ACADEMY** Traditionally, the focus of Chinese universities has been on teaching. The best research has been concentrated instead in the institutes of the Chinese Academy of Sciences (CAS), which tend to be more flexible in adjusting to new priorities. CAS also operates as an exclusive club of respected scientists. Election to the position of CAS

academician brings with it an extraordinary level of deference that far exceeds the respect shown in the West to a member of the US National Academy of Sciences or the UK Royal Society. One of the CAS vice presidents, Chen Zhu, is a biologist himself and thus the voice for other CAS biologists.

**INSTITUTIONS** Shanghai has a cluster of CAS institutes including the Institute of Neuroscience (ION), Institute of Biochemistry and Cell Biology (IBCB), and the new Institute of Health Sciences (IHS). Shanghai's most famous university is Fudan University. In northwestern Beijing are the Harvard and MIT of China: Beijing University (also known as Peking University or, colloquially, as Beida) and Tsinghua University (pronounced, and sometimes spelled, as Qinghua University). The CAS Institute of Biophysics (IBP) is also nearby, and further north is the recently formed National Institute of Biological Sciences (NIBS), which is independent of both the CAS and university systems.

**THE EXPATRIATES** Chinese-born but US-resident academics have been

significant in the development of biology research in China. See the “Key Figures” box for some examples.

**MONEY** CAS institutes have some stable funding of their own, but even CAS researchers require additional funding sources. The dominant presence is the Ministry of Science and Technology (MOST), which has a penchant for big projects. It has been widely criticized for basing grants on politics rather than merit. The National Natural Science Foundation of China (NSFC) has a proper grant review system, but a US\$425 million budget compared with the US\$1.7 billion disbursed by MOST. Additional money comes from a patchwork of provincial, city, and local government initiatives.

**THE WORKFORCE** Ph.D. students are the main workforce in the labs. The best undergraduates from the best universities often do their Ph.D.s overseas (most in the US), but there are plenty of students from more distant universities to take their place. Large numbers of technicians and Master's students also contribute; postdocs are almost all done overseas.



**CULTURAL REVOLUTIONARY** Mao emptied the universities 40 years ago, but the effects are still being felt today.

## Key Laboratories, Normal Universities, and other translation idiosyncrasies

Fluid Chinese-to-English translation is always a challenge, and China has its fair share of exciting attempts at English (e.g., a “Fall down carefully” caution sign, and an “escaped” (i.e., wild) mushroom restaurant). But translation is particularly difficult when dealing with the collectivist-style government language that still litters China. The meaning of “State Key Laboratory” is somewhat clear—it is an important, state-sanctioned lab—even though somehow it doesn’t sound quite right.

The early Chinese communist governments used such language in subdividing the education sector. According to Soviet principles, each university was restricted to a single task, and there was one such university in each region. Thus, each major city had a “Normal University” to educate teachers, a “Jiaotong University” to study transportation and communication, and a “Military Medical University” for medicine. In general, these universities have now broadened their faculty to cover all disciplines, but the original, slightly odd names remain.

into the educational system immediately after the Cultural Revolution; then, finagle their way into some overseas experience; and finally, take the gamble to return to a very immature Chinese research system.

Next come the more recent returnees. The first of these returnees were still taking a very big risk, and the emphasis in this early period was more on short-term visits, with researchers retaining their primary faculty appointments in the US or Europe. Some of those part-timers have operated as a kind of Greek chorus during China’s scientific development, prodding the Chinese government to commit to basic science and to allow scientists to determine the agenda.

Those who actually made the jump to full-time residence in China were often rewarded, despite their young age, with significant leadership positions, including directorships of new institutes (3). “People in their early thirties are too young to be controlling major scientific decisions,” says Yuan, “but there is nothing [else] you can do.”

With every year that goes by, the size of the gamble involved in returning to China lessens. More and more Chinese citizens are embarking on postdocs in the US or Europe with no intention of staying overseas.

Their return is fuelled by the wide base of the pyramid: a vast supply of eager students. The offspring of 1979’s one-child policy have streamed into universities. University and college enrollment tripled in China between 1995 and 2003 to reach 11 million. Of these students, “the brightest young people still go into science and technology rather than business and law school,” says Poo.

The results for returning PIs are striking. Four months after arriving at the Institute of Biochemistry and Cell Biology (IBCB) in Shanghai, Chen Degui already has four students and three technicians. It took Gao Shaorong of NIBS only one year to accumulate his eight graduate students and five technicians. His story is not unusual.

As for the students, their motivations vary. Some talk about scientific curiosity but others are more matter-of-fact. “It’s a job,” said two students, asked independently. Still others see it as a career that might allow them to experience life overseas.

Finally, there is the Chinese belief in the transformative power of learning, especially for the many students who grew up in the countryside. Lan Rongfeng is now a graduate student at Beijing University, but he grew up in a village of 70 farmers in Zhejiang province. “For people in the villages,” he says, “education can change their life.”

### ADVICE, BOTH WANTED AND UNWANTED

After the Cultural Revolution, Chinese science needed an update from outside. The government had to send people out of the country, trusting that some would return. “I remember what [Chinese leader] Deng [Xiaoping] said at the beginning of the reform,” says Chen of CAS. “If just one-tenth come back it should be considered a success.”

**Every year the size of the gamble involved in returning to China lessens.**



## What's in a name?

Beijing taxi drivers who are fluent in English still seem to be the stuff of legend, but within Chinese research institutions English is widespread. At the better universities a proportion of the technical classes are taught in English, and a majority of the more accomplished professors have spent significant time in English-speaking countries.

The Chinese language remains, however, an immeasurably rich cultural resource. One area where English is a particularly poor substitute is with names. The English transliterations of Chinese names not only lack the poetic meanings of the written originals, but also obliterate any clues as to what tones (e.g., rising or falling) should be used in pronouncing the name. This leaves session chairs at conferences struggling to pronounce correctly the names of less-familiar Chinese scientists.

Mutual confusion also surrounds the identification of family names. Many Chinese, such as the CAS President Lu Yongxiang, have three-syllable names. In these cases, the isolated syllable (Lu) is easily identifiable as the family name and the remainder (Yongxiang) as the personal name. The same trick fails with names such as that of CAS Vice President Chen Zhu. Here both names are single syllables, and sometimes both are potential surnames. Email addresses are often not standardized and so yield no clue.

Of course there would be no problem if Chinese names were always ordered, as they have been historically, with the family name first. But many scientists based in China switched that order when they did Ph.D.s or postdocs in the West, or do so now when publishing or to ease other interactions with Western scientists.



**DISAPPEARING TRADITION** The embrace of English leaves the richness of written Chinese behind.

For the purposes of this article, we will use the traditional Chinese ordering for any scientist currently based primarily in China, but the Western order for those working in the West.

But first they had to find a way to leave. A critical step for biologists was the establishment of the China–US Biochemistry and Molecular Biology Examination and Administration (CUSBEA) by Ray Wu of Cornell University (Ithaca, NY). The outside world did not know what to make of a flood of unsolicited applications from mainland China, but from 1982 to 1989 CUSBEA's standardized test helped smooth the path to US universities for 425 mainland Chinese students.

CUSBEA students made it easier for those who later applied independently. Based on the CUSBEA precedent, the main flow of graduate students continued to go to the US rather than Europe.

Most graduates from the CUSBEA program (such as Xiaodong Wang and Chen Ling; see below) did not immediately return to China. "Then, if you went back to China you pretty much didn't do science effectively," says Carnegie's Zheng.

The expatriates did, however, mature into a kind of external independent advisory board for Chinese bioscience. Official government language evolved in recognition of realities: "return and serve the country" (*hui guo fuwu*) became simply "serve the country" (*weiguo fuwu*), while the government would "only seek to utilize, not possess" (*danqiu suoyong, buqui suoyou*) the expatriates (4).

The expatriates have the security and prestige of tenured employment, mostly in the US, and thus an extraordinary level of political independence even when acting within China. They "have become a new political constituency for whom special policies have been designated, institutes set up, resources provided, and for which government departments

compete with each other for resources and demonstration of achievement," said one recent report (4).

They remain, however, a select few. "We're the first group that came to the US and got Ph.D.s from reasonably good institutions," says Bai Lu (NIH, Bethesda, MD), who arrived in the US in 1985. "And the more you do, the more people ask you to do. I hope more people will get involved."

The Chinese government alternately seeks this group out as valuable advisers and avoids them as irritants. The *China Voices* incident was clearly an example of the latter. It started with good intentions: *Nature* had published a supplement about China and wanted to publish a follow-up called *China Voices II*, initially in Chinese and later in English. In 2004, Yi Rao (then at Washington University, St Louis, MO), Lu, and Tsou Chen-Lu (then at the CAS Institute of Biophysics [IBP;



**SILENCED VOICES** An article coauthored by Yi Rao stirred controversy in China.

Beijing], and recently deceased) wrote an article for the supplement that was "a little bruising," says Princeton's Shi. It cited ineffective and political decision making at the Science Ministry and called for its effective gutting (5). A week after publication, the article and entire supplement was banned in China.

Banning stopped nothing. "It was all over the place—from very high up to graduate students," says Lu. The posted article attracted



**LOOK AWAY** Chinese politicians find it hard to ignore suggestions from overseas.

2,000 online comments in one day and, says Lu, “the vast majority were supportive of our views.”

Poo agrees that often the expatriates are speaking for the majority. “The polarity of opinions,” he says, “is not between scientists inside and outside but between the majority of scientists and a few administrators and scientists in power who benefited from the present system.”

The burden of criticism often falls on the expatriates because those based in China, especially the young returnees, are not willing to speak up. For this article, there was an unusually high level of concern among many of the China-based interviewees who were asked to talk publicly about policy issues. Their concern appeared to be far more about how their colleagues would react than about any possible official rebuke.

Generally such matters are felt to be handled much better in private. “Chinese don’t like confrontation,” says Shi. “When things turn confrontational they get worse.”

But some issues such as funding (see below) affect far more than the private group that may be able to debate them. How to deal with these issues once they reach the press is an evolving challenge in Chinese science. Leaving the role of public critic in the hands of expatriates is problematic: such outsiders may be resented by those who have worked in China for many years, including the days when funding was far more scarce, and who now deal with the realities of Chinese bureaucracy every day.

Despite the public spat, Lu continues to be an often-consulted adviser on science and technology policy. “I’ve made my voice

heard,” he says. “I wouldn’t say it’s been completely effective. ... Some of the ideas have been taken, but I don’t think they like [to see] these ideas on paper, especially in foreign journals.”

### PRACTICAL HELP

Far less controversial, and increasingly common, have been the research collaborations between US- and China-based Chinese biologists. Asked if she has such a collaboration, Harvard’s Yuan asks, “who doesn’t?”

These activities are the flip side to the expatriates’ role as commentator; they get experience within the Chinese system as research advisers, teachers, and even institute directors.

Zheng, for example, visits Zhu Xueliang’s lab at the IBCB in Shanghai for two one-week trips each year. For 16 hours a day she discusses projects and the drafts of papers with students.

Yuan has more regular contact with her four students at the CAS Institute of Organic Chemistry in Shanghai. In a “mutually beneficial” collaboration with CAS principal investigator (PI) Ma Dawei, the students provide Yuan with compounds to test in her assays, and she introduces them to cell biology. “The screening is just as advanced as in the US but often they don’t have the [sufficiently interesting] projects,” says Yuan. She conducts group meetings using Skype and data sent by ftp, but regrets she cannot “see the primary data through the microscope” as she is used to doing in her US lab.

Rao, who is now based at Northwestern University (Chicago, IL), has no such misgivings about his outpost of 20 people at Beijing’s NIBS. He visits the lab 10 times a year, and communicates with lab members via Skype and Googletalk every day. “I’m a hands-off person,” he says. “I run the lab here [in the US] hands-off. Sometimes, I find I run the lab in China more than the lab here.” He stresses that expatriates like him have not just been commenting, but doing.

### BREAKING WITH TRADITION

The NIBS lab is not Rao’s first lab in China. In 1996, he, Lu, and Lin Mei of the University of Virginia, Charlottesville, set up a joint lab in the CAS Brain Institute in Shanghai. The lab’s success inspired them in 1998 to propose a new Institute of Neuroscience (ION), with Lu’s former mentor Mu-ming Poo (then at the University of California, San Diego) as part-time director.

“Because the economy was doing well, they were ready to do basic science,” says Poo. By contrast, “20 years ago at Tsinghua I knew they were not ready.”



Harvard’s Junying Yuan collaborates with a chemistry institute in Shanghai.

Poo had definite ground rules. “I decided it would be difficult to promote [neuroscience in China] without a new structure,” he says. “The old institutes have old traditions that are hard to get rid of.”

Many of those traditions centered on hiring and firing. Poo’s involvement was contingent on him being given broad powers to hire who he wanted and to institute a uniform evaluation system. “Our review is rigorous, and that is how





## A second guidance

For Duan Shumin, a Ph.D. (in Kyushu, Japan) and two postdocs (at the University of Hawaii and University of California, San Francisco) were not the end of his training. That came only once he became a co-PI with Mu-ming Poo at Shanghai's ION.

"When I came back to China, I had a good training in techniques," he says. "But when I worked with Mu-ming I learned to think more critically and found important things to do. Then I learned my own way, my own direction. If you can say I succeeded, that is the most important thing."

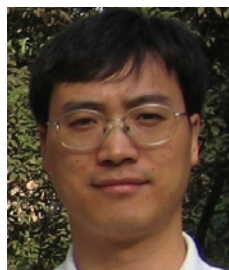
In collaboration with Poo, Duan revealed that chemokines (1) and Rho family proteins (2) help guide neural growth cones. (Yuan Xiao-bing, the first author of the latter paper, is now also a PI at ION. He recently reported that TRPC channels help guide growth cones [3].)

Duan then turned to glia, which he found make D-serine to support neuronal synapse strengthening (4) and ATP to suppress neuronal synapse transmission (5). Direct synapses between neurons and certain glia were, Duan found, subject to a unique form of activity-dependent modification (6).

Now, Duan is interested in how glia package and release their messengers. He also hopes to selectively knock



DUAN SHUMIN



SHU YOUSHENG

out glial subtypes and functions. Many previous investigators have assumed that the nervous system phenotypes of their knockouts arose from neuron defects, but Duan is not so sure.

Duan's colleague, Shu Yousheng, is also taking a new look at a well-studied problem by investigating chronic pain not in the spinal cord but the cortex. Two other projects focus on how neural networks with stable, balanced activity (7) might be turned on and off, and how sub-threshold signals that modify action potentials (8) might be changed in disease states. Finally, he is testing how pyramidal neurons integrate two very different types of information: memory-related inputs from their apical dendrites; and visual and auditory updates that arrive via their basal dendrites.

1. Xiang, Y., et al. 2002. *Nat. Neurosci.* 5:843–848.
2. Yuan, X.B., et al. 2003. *Nat. Cell Biol.* 5:38–45.
3. Li, Y., et al. 2005. *Nature.* 434:894–898.
4. Yang, Y., et al. 2003. *Proc. Natl. Acad. Sci. USA.* 100:15194–15199.
5. Zhang, J.M., et al. 2003. *Neuron.* 40:971–982.
6. Ge, W.P., et al. 2006. *Science.* 312:1533–1537.
7. Shu, Y., et al. 2003. *Nature.* 423:288–293.
8. Shu, Y., et al. 2006. *Nature.* 441:761–765.

we are doing so well," he says. "We fired people who refused to be reviewed, including an academy member." This is in a country where, Rao says, "members of CAS are held to be gods."

Not surprisingly, "the initial establishment was problematic," says Rao. ION's inauguration date coincided with the closing of the moribund, but heavily populated, Institute of Physiology, and there was general discontent that ION would divert funds away from other neuroscientists. A huge meeting was organized to protest against ION, students threatened to demonstrate, and the central government got nervous. Others voiced their discontent at a meeting in Hebei. "There were several movements to get rid of me," says Poo. "I didn't think I could last so long."

At times, the founders found safety in numbers. "There were different times when one or two of us wanted to pack up but the others said no," says Rao. But any doubts that Poo might have had are long gone. "Those hard feelings are forgotten now, I hope," he says. "The institute was the right thing to do."

"After three or four years," says Rao, "it was uniformly respected, and it has never really diverted funds from anyone." (See below



Mu-ming Poo met resistance when forming ION.

for more on funding.) Poo claims modestly that for recruitment "we are competing with second-tier universities in the US." For China in 1999, or even in 2007, this is no mean feat.

Poo "has put in an enormous amount of energy," says Yuan at Harvard. More is to come. ION now has 15 labs and is aiming for 30 within the next few years, with Poo hoping to fill in deficits in cognitive and systems neuroscience. Poo is based at the University of California, Berkeley, but still works in Shanghai, for free, one week a month. "I will continue," he says, "until they fire me."

### THE GOLD RUSH

ION was not on its own in trying to recruit foreign-based talent. Government-backed programs provided significant incentives. The CAS "hundred talents" program began in 1994 and the Ministry of Education's Changjiang Scholars program in 1999. The incentive programs have, ironically, strengthened the motivation for young Chinese researchers to leave the country initially so that they can subsequently return and receive the incentives.

Recipients in both programs mostly come from overseas and receive salaries 2–10-fold higher than standard Chinese professorial salaries; an ION starting salary is now ~US\$20,000 per year plus an initial US\$65,000 to help with housing. Even with Shanghai's booming real estate market, this puts ION PIs in a better position than many PIs in expensive foreign cities. The



## Shaping up

According to the rules of the Institute of Neuroscience (ION) in Shanghai, Yu Xiang has four years to prove herself as a first-rate principal investigator. That is okay by her. "If I can't do it," she says, "I'd rather leave as soon as possible."

Yu's four-year contract, and the one-year contracts of those working under her, are a huge change. Every worker in the Chinese education and academic system, from technician to professor, used to be guaranteed lifetime employment from the first day onwards. This cultural change is one of many that the ION has helped bring to China.

Yu has already proven herself at Cambridge University in the UK and at Stanford University in California. This is, however, her first stint as an independent lab head. It is not without its challenges. With few postdocs in sight in China, "it means I have to work a little harder," she says. "It means I



YU XIANG

am the lab head and senior postdoc."

Her focus is on the intersection of neural morphology and activity. In her previous work, Yu showed that activated nerves grew more complex and longer dendrites, and that this operated via  $\beta$ -catenin (1). Now, she has found that the cell compensates for the enlarged dendritic tree by making smaller synapses. She is

keen to test whether these pathways also apply in vivo and how they translate into altered connections between neurons during development and disease.

1. Yu, X., and R.C. Malenka. 2003. *Nat. Neurosci.* 6:1169–1177.

incentive awards include start-up packages of US\$242,000 over three years—half or less of what might be expected in the US, but in China the labor costs are far lower.

Returnees must often create a scientific culture almost from scratch. Many Chinese institutions lack practices usually taken for granted: regular group meetings; journal clubs; visiting speakers; seminar courses and lab rotations for students; and collegial interactions between research groups. ION pioneered a number of these practices in China and has encouraged their spread to other locations.

## In China, opportunities for personal reinvention are significant.

But the opportunities for personal reinvention are also significant. Pei Duanqing (Guangzhou Institute of Biomedicine and Health) previously had a faculty position in the US but wanted to switch to stem cell work. "I realized it's very difficult to switch careers in the States," he says. "Coming back to China allows you to do new things." Other returnees were driven from the US by the tight NIH funding, or because they could not recruit enough students.

Although the number of returnees is still small for such a large country, the number of world-class institutions for returnees to join is even smaller. These institutions have been filling their vacancies at breakneck speed, leaving fewer opportunities for late-comers. Now, "a lot of postdocs in the US want to come back but cannot get a good opportunity," says Wang Shengdian of Beijing's IBP. "Now, the opportunities will be less and less, and the standard will become higher and higher."

There is, however, a vast potential outlet for returnees. "There are very few [successful] institutes like IBP in China," says Wang. "But there are a lot of universities that need good people." At Beijing Normal University (BNU), Cong Yusheng is "trying to recruit people now," he says. "I got a lot of applications. There are a lot of successful people in the US trying to return."

BNU is better off than most universities: it is surrounded by some of the best research institutions in China, and it is in Beijing, a well-funded city on the well-funded east coast. It will take more economic development in China, however, before the myriad universities outside of Beijing and Shanghai get more funds and become attractive to returnees.

Even once the money arrives, there would be another problem. "Institutes like IBP focus on research and give PIs a lot of support," says Wang. "But, in the universities, the administration is not very good. Even if they have money, they don't use it for research. Instead, they build a very good building." To change such a culture, he says, there is one crucial ingredient: "The leader is very important."

### BRING IN THE LEADER

Wang's focus on leadership is no coincidence. IBP, where Wang works now, was revived by the strong leadership of structural biologist Rao Ziheng, building on the work of his predecessor Wang Zhixin.

Rao was 16 when the Cultural Revolution began. "It was a very difficult period but probably the most important period for me in my life," he says. "I suffered. I never had experience working in the countryside, and the field work was so hard—you cannot imagine how hard." After all this time, he says, "I still know how to farm." But, more importantly, he says, "it made me physically strong and mentally very strong so I can face any challenge."

As the Cultural Revolution waned, Rao was one of 200 students chosen, mostly from the countryside, to have their university attendance sponsored by CAS. After graduation, he did a Master's at IBP, a Ph.D. at Melbourne University in Australia, and a postdoc



Rao Ziheng has helped build protein structure and function studies at IBP.



at Oxford University in the UK. His first project at Oxford was a struggle with an influenza protein whose structure has still not been solved, but he was also “lucky” to be working on the structure of EGF. This factor was thought to be unstructured, but Rao showed otherwise (6). Soon afterwards came a structure of an HIV matrix antigen (7).

“I always wanted to come back,” says Rao. “I think I prepared my mind to come back and do something even better than [what I did] outside.”

But the timing had to be right. “I always tell my students: if you don’t get any good results, don’t come back—no one will pay attention to you,” he says. “I was so excited when I got my result and got my *Cell* paper” but he was not yet ready to return. “But when I got my *Nature* paper I made an immediate decision to come back.”

Rao initially avoided IBP, as it lacked any molecular biology or work on protein function, and his influence there would have been complicated by the presence of his former supervisor. In 1996, he set up a lab at nearby Tsinghua University. Finally, in 2002, CAS President Lu Yongxiang asked Rao to be the director of IBP.

CAS initially gave Rao 20 million RMB (~US\$5 million) to set up a core research unit devoted to protein structure and function. IBP’s proteomics center has robots for spot picking, and fancy mass spectrometers; the institute’s shared lab space has a sea of shakers, two protein crystallization machines, and a room packed with 10 HPLC machines.

Along with the equipment came people: 13 new faculty hires in Rao’s first year alone. (Some came in the wake of recruiting efforts by Rao’s predecessor, Wang Zhixin.) Liu Yingfang, for example, arrived after determining structures of TNF family ligands and receptors (8, 9). Xu Tao, by contrast,

is using his previous work on exocytosis (10, 11) to focus on the regulation of insulin release. Meanwhile, Rao had his own triumph with a publication in *Cell* (12). This and another paper, authored earlier in 2005 by students under the supervision of Yi Rao (13), represented the first two *Cell* papers from teams based in mainland China.

The 36-year-old Xu has now replaced Rao at the helm of IBP. After just three years of leading IBP, Rao “was ordered” to take on the presidency of Nankai University. The university is southeast of Beijing in the economic powerhouse city of Tianjing. Rao explains that “[Former President] Jiang Zemin made Shanghai Pudong”—a booming techno-financial area. “The current government wants Tianjing to become like this.”

Rao Zihe, it seems, is their man for the job.



IBP’s new director, Xu Tao.

## THE EVOLUTION OF AN INSTITUTE

ION was created as a new institute, and the reincarnated IBP looks almost new. Poo at ION and Rao at IBP took advantage of that newness: they had the freedom to institute revolutionary new policies and to hire a handpicked new faculty roster.

But many universities and institutes must undertake a task that is perhaps even more challenging: evolution from an existing structure and faculty base. The two current deputy directors at Shanghai’s Institute of Biochemistry and Cell Biology (IBCB), Zhu Xueliang and Jing Naihe, have seen that process in action.

IBCB was born in the 1950s as two separate biochemistry and cell biology institutes. The changes that transformed these institutes and the rest of CAS began in earnest with the election of CAS President Lu Yongxiang in 1997 and the start of his Knowledge Innovation Program (KIP) in 1998. “That was the most difficult and exciting time,” says Zhu.

Lu was faced with an institution in crisis. Soviet-style, institute-based research at CAS was clearly being outperformed by university-based research in the US and Europe. As a result, “people were arguing about whether CAS needed to exist,” says Zhu. “From 1999, we reprogrammed the whole system.”

SHANGHAI’S WONDER The Pudong area is part of China’s shiny new future.





Wang Shengdian at IBP; the cranes behind are building the 2008 Olympic village.

### Opportunity, but with a price

Switching from Johns Hopkins University (Baltimore, MD) to the IBP in Beijing has broadened Wang Shengdian's options. His past work was restricted to basic research on lymphocyte costimulatory molecules (1, 2), but now he is branching out into both lab and clinical work on HBV and tumor immunotolerance. "In the US, you cannot do something that is not related to your lab's major interest," he says. "But here I can do anything. Here, you have a lot of students who can try out your ideas."

Nothing comes for free, however. His students, though plentiful and hardworking, need a lot of supervision. "In China, most students only know how to get data," he says. This is a task well suited to postdocs, he says, but for students "the major task is to learn how to study." Unfortunately, says Wang, "most Chinese professors don't get students to read papers, and are too busy to have a journal club or even lab meetings. But, in our lab, we have journal club every week."

Wang's colleague at IBP, Tang Jie, puts a similar emphasis on student-driven design of experiments, even if the students prove only a minor hypothesis. "After this cycle, they are ready to do science," he says. "Although the paper may not be a high-impact paper, the training is more important."

China has other advantages for a clinician like Wang. "In China, there are a lot of patients as a resource," says Wang, who has contacts at Beijing Union Medical College, his Ph.D. alma mater. "Here, I can have a lot of collaborations with doctors and other researchers." Tang has also escaped restricted choices in the US, where he had to alternate between jobs in either basic research or industry. "Here," he says, "I can do both. I have more freedom."

1. Wang, S., et al. 2002. *J. Exp. Med.* 195:1033-1041.
2. Wang, S., et al. 2003. *J. Exp. Med.* 197:1083-1091.

Under the KIP proposal, the 123 CAS institutes were to be reduced to 80 (the final number reached in 2005 was 89) by spinning off commercial enterprises and amalgamating redundant institutions. Furthermore, the 59,000-strong workforce would be halved even as graduate student numbers and the overall CAS budget both doubled.

The merger that created IBCB occurred in 2000. Within two years, the 700 employees, including more than 60 administrators, had been cut to fewer than 200 employees and 12 administrators. PIs were not fired, but retirement at 65 was enforced (allowing the recruitment of 16 new, young PIs since 2000), and commercial and administrative positions were spun off.

PIs now had to pass two evaluations given every four years before their positions were secure, and the institute's own money was divided up based on performance. (Before, each lab got roughly an equal share.) Other staff were put on 2-year contracts, and PIs were given the power to hire and fire their own staff. "This may not sound surprising, but in China we are supposed to be socialist, so it was quite hard," says Zhu. It is also, he says, one of the reasons why CAS has flourished in the 21st century relative to the universities.



ZHU XUELIANG

CAS also emphasized bringing in younger directors. From 1991 to 2003, the average age of directors and their deputies fell from 56 to 47. The newcomers, with better publication histories, were not afraid to introduce evaluations based on publishing papers in internationally recognized journals.

**NEW DIGS** The IBCB, like many Chinese institutions, has a new building.





## From isolation to leadership

When Jing Naihe arrived in 1982 to do his Ph.D. at the CAS Institute of Biochemistry in Shanghai, it had a history of huge teams where “two or three were the brains, and the rest were the hands. But when you [eventually] had to do individual research you didn’t know how to do it.” Although group size had shrunk by the time he joined, Jing was still isolated from international science. “I never read *Nature*, never read *Science*, never read *Cell*,” he says. “It was not my business.”

Jing had no money to buy imported chemicals, so he spent three years making them. Only then could he get started on peptide synthesis.

In 1989, he had a chance for his first overseas stint—a neuroscience postdoc in Japan—via an exchange program. “Neuropeptides seemed very interesting,” he says. “But what is neuroscience—I didn’t know. The first year was very hard.”



JING NAIHE

His two-year stay in Japan coincided with the 1989 Tiananmen Square protests and crackdown. In response to Tiananmen, the US eased visa and permanent residence restrictions for Chinese nationals. Jing had a US visa offer, but for reasons that “would take an hour to explain” decided instead to return to China. Of the three others in his exchange group, two are now in US biotech companies, and the other has a position at Harvard Medical School.

Jing has no regrets. At first, his return to Shanghai was marred by impure water that ruined cell cultures and sick rabbits that couldn’t make good antibodies. But his lab budget has increased 10-fold since 1991, and his salary has allowed him to buy a house and afford a car. “In 1991,” he says, “I never dreamt of that.”

The results were striking. In 1999, researchers at IBCB’s two predecessors published 284 papers, but only 85 in journals listed on the Science Citation Index (SCI)—the rest were in Chinese language journals. In 2001, IBCB researchers published 258 papers, but now 197 were in SCI-listed journals. As Zhu says, “That’s quite a big change.” The average impact factor (IF) of IBCB publications continues to rise, from 1.8 in 2001 to over 5 in 2006.

Zhu’s students, who share an open office space with him, choose other high-profile papers for a weekly journal club. The students also research the background and find pictures of the overseas PI. “When we read papers we only read names,” says Zhu, “but at least this way we have some visual knowledge.”

Zhu himself published the first paper in the *Journal of Cell Biology* by a team based in mainland China (14); the second was from Wang Yizheng at neighboring ION (15). The first *Journal of Experimental Medicine* paper from mainland China also came from IBCB (16); the senior author was Pei Gang, who is now the director of IBCB’s parent organization.



Pei Gang oversees Shanghai’s CAS biology institutes.

But more important than any individual paper, says Zhu, is that he, Jing, and others are working for their country’s development. “We are making a group effort to do good research, and I am only one of them,” says Zhu. “The most important thing is [that] each of us becomes stronger so all of CAS and all of China becomes stronger.”

## BUILDING THE ROAD

The success of ION has led to the founding of several other institutes. Like ION, they have directors with extensive hiring and firing power, but unlike ION they are focused on translational or medical research.

The Institute of Health Sciences (IHS) in Shanghai, for example, opened in 2002 as a joint venture between CAS and Shanghai Jiaotong University School of Medicine. It covers a wide range of basic, clinical, and translational research, and is run by Zang Jingwu, who left his professorship at Baylor College of Medicine (Houston, TX) to become IHS director.

A newer venture is the Institute of Molecular Medicine (IMM; at Beijing University), which is focused on cardiovascular research. It was founded in 2004, with Xiao Rui-Ping as the director.

For many years, Xiao and her husband Cheng Heping shuttled between Beijing and their full-time, tenured jobs at the National Institutes of Health (NIH; Bethesda, MD). Finally, says Cheng, it was time to commit. “There is opportunity here,” he says. “I needed to come back and push with both hands, not with one hand.” He resigned from the NIH in early 2006.

His gradual commitment is part of a common pattern. Many overseas Chinese academics initially commit only to part-time involvement in China. But, says Cheng, “that phase is almost over. In that transition period, even if you came for a seminar it helped, then if you came for a while it helped.” Now, although Cheng says the visitors are still useful “for connections,” their involvement has become increasingly controversial (17), and the real demand is for full-time staff. “For our recruitment, we usually give a couple of years for the transition,” he says.

Once in China, says Cheng, “you do the same work, but you make a greater difference here. Through me, the students can get closer to the frontier.” There is also the challenge of creation—whether it is the hiring of faculty or the building of animal facilities. “At the NIH, everything is predictable,” he says. “Here, you have to build the road when you move forward. It’s exciting, but you need to work twice as hard.”

IMM currently has six faculty. “With Mu-ming [Poo at ION],



he had to recruit who he could, but now it's a little better," says Cheng. "We had the luxury of predesigning the institute" by hiring only those faculty with specific subspecialties. One of those recruits to IMM was Zhou Zhuan, whose previous lab at ION studied calcium-evoked secretion (18, 19). "He is the one successful transfer within China," says Cheng. "Mu-ming should be proud."

### GUANGZHOU SPEED

Like IHS and IMM, the Guangzhou Institute of Biomedicine and Health (GIBH) is new and is aimed at translational research. But it stands out for another reason. Within one year of its founding, GIBH had its first 15 PIs. "This is what we call Guangzhou speed," says GIBH deputy director Pei Duanqing.

That speed makes Guangzhou, which is just northwest of Hong Kong, part of one of the most extraordinary areas in an extraordinary country. Neighboring Shenzhen has grown an average of 28% annually in the last 25 years, in the process expanding from a fishing village to a city of 12 million.

The growth also explains the presence of GIBH. "Scientific development lags behind economic development," says Pei. "[Closing] this gap requires investment and also a lot of people."

The Chinese government is now trying to connect researchers, thematically and geographically, with the frantically expanding economy of the new China. GIBH and a planned proteomics institute in Pudong (an area of Shanghai recently transformed from farmland to international finance hub) are two signs of this effort.

Bridging the gap between academia and commerce requires a different kind of research institute, says GIBH Director General Chen Ling. "We want to combine the best of both worlds in this institute," he says. Academic freedom will be backed by the clear goals and timelines more characteristic of industry. "If [a PI] has something promising, the institute will coordinate moving it forwards" into development or clinical trials, says Chen.

Chen got his Ph.D. from Indiana University; he had been admitted as part of the fourth class of CUSBEA students. Later, at Merck, he helped develop an HIV vaccine that is currently the most advanced in clinical trials; he then moved on to the mouse knockout company Lexicon Genetics.

He arrived at GIBH in 2004 and by the end of April had only 3 colleagues, including a driver and an accountant. Two years later, there are 18 PIs, 220 staff, and 100 graduate students. The aim by 2009 is to have 30 PIs, with a final count of 400–500 staff and 500 students. Most of the PIs have significant experience in industry, including large companies such as Bristol-Myers Squibb, Amgen, and Wyeth, giving GIBH a more explicitly commercial emphasis than IMM and IHS.

Next comes the real challenge of producing results. "There is no single criterion" for success, says Chen, although it will include a mix of successful recruitment of PIs, education of

## GIBH brings science to a booming economy.

### Moving ahead

Once Zhang Yonglian entered her sixties, her career really got going. She had been based at the Shanghai Institute of Biochemistry (the precursor to the Institute of Biochemistry and Cell Biology [IBCB]) since 1957. But it was not until 2001, ten days after her 66th birthday, that she published three very significant pages. Those pages were the first *Science* paper from her institute and only the third *Science* paper in biology for all of mainland China.



ZHANG YONGLIAN

Zhang had not been idle before 2001. After the Cultural Revolution she got her Ph.D., a degree that was not offered under the previous Soviet-style system. Then, in 1983, she began two years of work at the Imperial Cancer Research Fund in London, UK. Subsequent work in Shanghai was punctuated

by research stints back in the UK and in the US and Australia.

Chinese awards came for her work on androgen regulation of gene transcription, but it was a switch to a study of the epididymis that was crucial. She chose the subject matter for reasons of national need: population control was the topic of the day, and the epididymis is the conduit that directs sperm maturation. As the maturing sperm travel, they encounter first proteins that stimulate motility, and later proteins that boost their survival and resistance.

The result, says Zhang, is "beginning and end regions that are more different from each other than heart compared with eye." Subtractive hybridization has given her a host of differentially expressed genes whose products are expressed on or bind to different parts of maturing sperm cells. Following up on those proteins continues to keep her busy. Zhang got the "model worker of China" award in 2003 and shows no signs of slowing down.

The *Science* paper was based on

Bin1b, one of the differentially expressed proteins. Zhang found that this epididymal protein not only looks like but also acts as an antimicrobial  $\beta$ -defensin peptide (1). Leukocytes can't get into the epididymis, and Bin1b was the first clue about how the male reproductive tract protected itself from the outside world. Zhang later helped show that Bin1b also turns on sperm motility (2).

Submitting to *Science* seemed reasonable, said Zhang, because a paper about an epithelial defensin had been in the journal in 1995. "And our paper," says Zhang with a cheeky smile, "was more interesting." It went through the review process at *Science* quickly. With eyes moistening, she explains how she was "deeply moved" by the editing help that the staff at *Science* gave her. And the acceptance, says Zhang, "was like a dream."

1. Li, P., et al. 2001. *Science*. 291:1783–1785.
2. Zhou, C.X., et al. 2004. *Nat. Cell Biol.* 6:458–464.



## The general

One fringe benefit of employment at the Second Military Medical University (SMMU) in Shanghai is a military rank. For Cao Xuetao, that makes him not only a professor, director of the Institute of Immunology, and vice president of the university, but also a general. It is a rank that carries over, in a less official capacity, to the world of Chinese immunology.



Cao Xuetao used his own funds to build his immunology institute in Shanghai.

Cao is a member of a key MOST committee and thus has intimate knowledge of, and involvement in, funding decisions. Only a select number of other bioscientists have his kind of broad political influence.

In part, this influence stems from his remarkable, made-only-in-China story. Born in 1964 to two professor parents, his entire education and career has been based at SMMU. He had an M.D. by age 22, a Ph.D. by 26, and a full professorship by 28, and then was appointed chairman of the Department of Immunology by 31, and director of the Institute of Immunology by 35. He is now president of the Chinese Society for Immunology.

His ailing supervisor retired in the second year of Cao's Ph.D., but he asked Cao to turn down a postdoc offer from Charles Janeway in 1991 so that Cao could keep the lab open in China. Since then, Cao has made short visits to labs in many countries. But his lack of long-term overseas experience, he says, "is very unique in the current [Chinese] system."

It has also been an opportunity. "Although I'm young, I've had the chance to attend the important national meetings and be part of national bodies to develop science, to evaluate grants, and to determine the funding," he says.

Cao's methods for building a local power base have been entrepreneurial and far from conventional. It started with Cao signing over rights for the production of various recombinant cytokines to a company in Shanghai. "I used the money I earned to establish this building," he says. "This whole building"—a five-story institute within SMMU—"is my lab, designed by me,

together with my colleagues and the architects."

He moved into the building in 1999. The current staff includes 12 Ph.D. students, 6 Master's students, 2 postdocs, and 14 technicians, but also 18 other staff (lecturers, associate professors, and research assistants). The Institute therefore resembles a multitiered German lab more than the independent labs being set up by young PIs returning to China from the US.

A large lab is necessary, Cao says, because the Institute is self-sufficient and does not draw upon central facilities elsewhere in SMMU. "If we have 50 people in my lab," he says, "it is equivalent to 20 people in the US."

The large-scale science extends outside of SMMU. Cao coordinates a national program in immunology research that covers almost 20 labs; its mandate starts again in 2007. This is the kind of structure favored by MOST. The NFSC, which is the funding body preferred by many individual PIs, "uses a very efficient and equal evaluation method," admits Cao. "But this is for individuals not teams. If we want to do teamwork, especially uniting several great labs, the NSFC has no ability to coordinate it. MOST has the ability to coordinate it."

Cao's own research is focused on dendritic cells (DCs) and various aspects of immune regulation. In the last three years, he has published 1 paper in *Immunity* (1), 10 papers in *Blood*, and he recently found that splenic stroma spurs mature DCs to differentiate into regulatory DCs (2). A DC-based vaccine that he helped develop is in a phase II trial for advanced cancer.

The next challenge is to build capacity in immunology outside of SMMU. China's "background is very weak in immunology," says Cao, although he says returnees such as Zang Jingwu at the CAS Institute of Health Sciences in Shanghai have helped improve the situation. In addition, he hopes his own domestic career can show others that "you have a chance," even without overseas experience. The opportunity is there, he says, "but you have to communicate with the officials of the government to get their funding, to get their support."

1. An, H., et al. 2006. *Immunity*. 25:919-928.
2. Zhang, M., et al. 2004. *Nat. Immunol.* 5:1124-1133.

## A painful funding increase

Two rather sad seedlings are perched on Bao Lan's filing cabinet. Her son is conducting an early science experiment. Plants, it turns out, do poorly if they have either only earth or only water.



BAO LAN

These days Bao's lab at the Institute of Biochemistry and Cell Biology (IBCB) is well equipped, but 10 years ago her department in Xi'An, in western China, looked more like her son's plant experiment. After getting an initial grant of only 30,000 RMB (less than US\$4,000), "I immediately spent 10,000 of that on a computer to write the next grant," she says. The money was so sparse that her husband, Zhang Xu (now at the CAS Institute of

Neuroscience [ION] in Shanghai), would go back to Sweden every year to do experiments at the Karolinska Institute.

As the funding picked up, Bao and Zhang discovered an unusual pathway: an opioid receptor that was sent to the plasma membrane not by constitutive but rather by a regulated, inducible pathway (1). They later found that the induction was via binding of pain neuropeptides to the receptor (2). Zhang continues to research pain conditions, but Bao is now focusing on Na<sup>+</sup> channel trafficking, which is modulated by nerve injury and inflammation.

1. Bao, L., et al. 2003. *Neuron*. 37:121-133.
2. Guan, J.S., et al. 2005. *Cell*. 122:619-631.



GIBH Deputy Director Pei Duanqing (left) and Director General Chen Ling (right).



GIBH is based in booming Guangdong province.



students, publishing of papers, and registering and licensing of intellectual property.

GIBH was funded by a start-up grant of US\$36 million, with equal shares coming from CAS, the province of Guangdong, and the city of Guangzhou. “The stakeholders put up this much money, so they have a right to demand an outcome,” says Pei.

But in an area accustomed to building factories and getting quick results, the slower speed of drug development will take some adjustment. Developing a drug in the US is estimated to take 10–15 years and cost US\$800 million; GIBH has far less money and time. “It has been my job to communicate the differences and the gap we perceive, and so far they have been very receptive,” says Pei. “They have become more realistic and have been very supportive of the direction and progress we are making.”

Chen is not without his doubts. “I don’t know if China is truly ready for this,” he says. “It still takes time and effort to optimize the research conditions. But if we don’t come to push it now it won’t get better.”

As they move into commercial research, Guangzhou and China may initially make use of their built-in advantages, such as cheap and plentiful sources of nonhuman primates and low labor costs for mouse facilities. But “over time,” says Chen, “China is so big that it can do everything.”

## Pluripotent energy

Some researchers take an hour to explain a single project. Jin Ying at Shanghai’s IHS gets through half a dozen, plus a few phone calls, within less than 20 minutes. With all the spinning toward her audience to address each new topic, an inevitable byproduct is some spectacular fly-away hair. Jin is a woman in a hurry.

Her projects are focused on understanding the pluripotency of embryonic stem (ES) cells and how self-renewal is regulated. Starting from the key transcription factor Oct4, she is purifying associated proteins and identifying target genes. One interacting factor ubiquitinates and inactivates Oct4 (1) and in turn binds proteins linked to chromatin remodeling and apoptosis. Jin also used chromatin immunoprecipitation to identify a factor that seems to drive endodermal differentiation. These functions can now be tested with the siRNA system that Jin has perfected for use in mouse ES cells.



JIN YING

Jin is also codirector of the Key Lab of Stem Cell Biology, a consortium made up of IHS and IBCB faculty. This is one of several groups that are making China a leading center for stem cell research (2).

1. Xu, H.M., et al. 2004. *J. Biol. Chem.* 279:23495–23503.
2. Normile, D., and C.C. Mann. 2005. *Science.* 307:660–664.

## UNCLE HOWARD GOES TO CHINA

If ION was a break from the old CAS culture, then Beijing’s National Institute of Biological Sciences (NIBS), led by Xiaodong Wang and Xingwang Deng, is a complete rupture. Wang is a long-time recipient of the Howard Hughes Medical Institute’s (HHMI) largesse. Now, he and Deng have brought that concept—of supporting individuals rather than specific projects—and convinced the Chinese government to bankroll an audacious center of excellence.

NIBS has its critics, who feel it is too elitist and soaks up too much money, and the resentment has led to difficulties in establishing collaborations with other Chinese scientists. But Wang is unapologetic about the money. “I think it’s the only way you get on the fast track: you create a place that will be competitive on an international level,” he says. “If you want a scientist that has international market value, you have to pay them accordingly. You can certainly justify these salaries by merit.”

Salaries at NIBS are US\$50–60,000 for an assistant investigator—10–15 times the income of an average Beijing resident, and almost three times what starting PIs at most other Chinese institutions get. Without having to write an external grant application, each NIBS junior PI also gets 3 million RMB for the first year and 2 million RMB for each of the subsequent four years, for a total of ~US\$1.4 million over five years.

For a normal lab in China, “this money is enough for at least 20 people,” says Shao Feng, a PI at NIBS. Typical costs in China are ~US\$5,000 for a technician, ~US\$6,000 for a postdoc, and ~US\$2,000 for a student, although NIBS tends to pay more.

Other costs are also lower. “I have close to 4,000 mice here,” says NIBS cloning researcher Gao Shaorong. “You can imagine in the US how much I would pay for that.”





## NIBS supports individuals rather than projects.

Any equipment costing more than US\$10,000 is paid for by NIBS, not out of the PI's general budget, and special requests for more funds can be made to Wang and Deng. Applications for outside funding are allowed but not encouraged; few have taken this route so far.

Wang is based at the University of Texas Southwestern Medical Center (Dallas, TX) and, like Poo at ION, does not draw a salary from China. "That makes my job a little easier," he says. As a volunteer, Wang is unlikely to be criticized for being part-time or for lobbying for high salaries for others.



Xiaodong Wang has brought the Howard Hughes model to NIBS in Beijing.

Deng (Yale University, New Haven, CT) was the first to contact his friend Wang about running NIBS. Wang considered quitting HHMI and Texas to move to NIBS, but decided that this would compromise his current research, which requires significant manpower in chemical synthesis. In April 2003 he did, however, sign up for the directorship. His involvement was a key factor for many subsequent hires. The Chinese government has been known to change its mind abruptly, but with Wang on board, said one PI, "I know he's really going to do it."

The NIH's Lu says that the Chinese government needs to do whatever is necessary to get more leaders like Wang. "First-class people recruit first-class people," he says, "but second-class people recruit third-class people," because they are insecure about competition.

NIBS was built in a new industrial park north of Beijing. Insects still invade the labs as a reminder of the area's swampy past, and the staff and students rely on shuttle buses for transport to the isolated site. A subway extension to the park has been promised, however, and a 3,000-bed hospital will be one of the park's new tenants and hopefully a source of collaborators with NIBS researchers.

The first PI to arrive at NIBS full-time was Guo Yan in January 2004. "It was really scary," he says. "The building was totally empty. I spent almost one year just ordering machines."

Three years later, it is a very different scene. In addition to the outpost labs of the three US-based PIs (Wang, Deng, and Yi Rao), there are now 15 full-time PIs at NIBS. Meals at the cafeteria must run in shifts.

The PIs are a very young group. "By default, most people are young, fresh out of postdocs," says Wang. For now, "it's impossible to get established people here. As time goes on, with turnover, it will become like other places."

Officially, recruitment has been competitive. Most of the PIs, however, have worked with a US-based Chinese PI, who either recommended them or twisted their arm to convince them of NIBS's potential. Whatever the method for recruitment, the results are impressive. The one senior and 14 junior PIs at NIBS had, for example, a total of 15 *Cell*, *Science*, and *Nature* first authorships upon their arrival; two had turned down offers from Duke and Harvard Universities. NIBS is currently limited to 25–30 PIs, and recruitment is only likely to get more selective.

### Inventive pathogens

For Shao Feng at NIBS, it's all about keeping things interesting. "For a biochemistry lab you need to be constantly creative to come up with new things," he says. "That's the way I like to do science."

Luckily for Shao, he studies pathogens, and pathogens do many bizarre things to their hosts. Shao found that a *Yersinia* protein cleaves the host cell's Rho to release it from the membrane (1). A similar *Pseudomonas* protein cleaves a kinase in plants, and it is the cleavage not the invading protein that is detected by a plant resistance protein (2).

Now, he is on the trail of proteins from two bacterial pathogens: one that uses "a completely new enzymatic reaction" to chop out a protein modification (3); and another that causes cells to halt at an unusual cell cycle arrest.



SHAO FENG

The projects have kept multiplying as he has expanded to a lab of 12 within 18 months. "For a lot of jobs you are constantly repeating," he says, "but here you are constantly reinventing."

1. Shao, F., et al. 2002. *Cell*. 109:575–588.
2. Shao, F., et al. 2003. *Science*. 301:1230–1233.
3. Li, H., et al. 2007. *Science*. In press.



**CHEAP LABOR** Plenty of willing workers translates into cheaper labor costs in Chinese laboratories.



**GROWING FAST** NIBS has rapidly built its staff into the hundreds.

The one complaint from the NIBS PIs is a lack of international visibility, leading to skepticism from reviewers of NIBS manuscripts. Not only is NIBS new, but so are the PIs. Many of them came directly to NIBS, thus missing out on the self-advertisement that goes along with being on the US or European job circuit.

NIBS is, above all, an experiment in funding. But will China rely elsewhere on the NIBS/HHMI-style funding of the individual rather than the project and build more NIBS-style institutes? “Yi Rao says we can have 10 of them,” says Poo. “I doubt it.” Even NIBS supporters talk of the institution as a “catalyst” for cultural change rather than a funding template for all of China. “China has a vast network [of research institutions] already,” says Princeton’s Shi. “How to make those institutes better is the primary challenge.”

Deputy Director Zhi Gang says NIBS will also be important in that process. “This institute is in China, so it is surrounded by traditional behavior,” he says. “You have to break up this environment for the new system to work.” The stakes are high. With possibilities for expanding or replicating NIBS, or exporting its faculty and the NIBS culture to other sites, success at NIBS could have far-reaching consequences for Chinese bioscience.

### TEACHING THE NEXT GENERATION

The future of Chinese science revolves around three main challenges: improving the education system for graduate students; forging a connection between scientists and the general public; and constructing a funding system suited to the country’s unique needs. If these three issues are solved, getting more returnees should not be a problem.

Although the research environment continues to improve, the fix is often slowest for students. “Teaching is a major problem facing Chinese graduate training,” says Shi. “If students don’t have good teaching, they won’t develop critical thinking.”

Teaching in China is complicated by a deeply ingrained respect for seniority in general and teachers in particular. Poo has blamed “the confucian tradition of respecting customs and hierarchy” and “deference to authority and to existing paradigms” (20) for stifling creativity and producing a stale teaching dynamic. According to Lu: “It’s not fostering creativity and innovation; it’s old-fashioned knowledge-based education.”

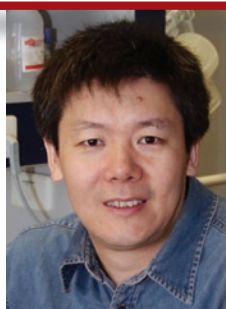
“In China, the professor talks and the students take notes,” says Jian Li of Harvard Medical School (Boston, MA), who teaches at the IMM at Beijing University. “I try to use

### Feeding the masses

“In China ‘food safety’ doesn’t mean what it means in the US,” says NIBS researcher Guo Yan. Rather than worries about transgenic food, “in China food safety is whether we have enough food to feed the Chinese people.”

Plant breeders and researchers did not go home when the Green Revolution was declared a success; they continued to get almost half of the money in Chinese biological research. Much of this money goes to traditional breeding efforts, but plant researchers such as Guo are a strong presence amongst the recent batch of basic science returnees.

Guo works on salt stress and drought response in *Arabidopsis*. “If I can really do something in [applied research] I would choose this first, but so far I have chosen to do basic research,” he says. “The more you work in this field, the more you think it is hard. If this is possible, God should have done it already. We need to understand it more before we can help.”



GUO YAN

the model of when I took classes in the US, and bring back discussion.” Without such discussion classes, says Carnegie’s Zheng, “I don’t think enough emphasis is being put on placing research in a bigger context. The later year students are still struggling with that.”

Yi Rao responded by creating Bio2000, a full-year course on molecular and cell biology originally given in Shanghai and now expanded to Tsinghua and Beijing Universities. Guest lecturers spend one week on a topic in both Beijing and Shanghai. But “we cannot take over the job of teaching,” says Shi. “It is up to the institutions.”

Some of those institutions currently struggle. Returnees who only did postdocs overseas were never exposed to the discussion-based courses common in US Ph.D. programs; they are also under immense pressure to publish as soon and as much as possible, so teaching is not high on their agenda.

CAS institutes have traditionally focused on research, not teaching, so some deputize universities to do the teaching for them. The resulting classes may be very disconnected from the students’ research. This kind of treatment of CAS students makes at least one Beijing University student happier to be in

## Not a candidate for engulfment



WANG XIAOCHEN

NIBS is competitive. Engulfment research is competitive. And Wang Xiaochen, despite her mild manner, is ready for both.

Wang studied general apoptotic mechanisms in worms (1) before moving on to her current interest: engulfment of dying cells. Mammalian studies had suggested that phosphatidylserine (PS) acted as an “eat-me” signal on dying cells; Wang identified the worm PS receptor and the pathway that it activated (2).

The weak phenotype from loss of the PS pathway in worms has inspired Wang to do an enhancer screen. She is also doing an RNAi screen for engulfment defects, as the existing engulfment mutants all come from cell death screens. Even the products of those earlier mutants pose plenty of questions: CED-1 is a receptor without a known ligand; and CED-7 is a transporter without a known cargo.

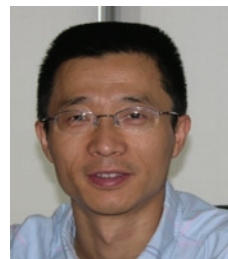
At NIBS, Wang has the ability to follow up all these ideas, and that made the decision to come an easy one. “The offer here was everything I was looking for,” she says. “The most important thing is there is enough funding so you don’t spend 80% of your time writing grants. And there are enough students. And a good research environment—a really good group of people. In the US there are a lot of good choices but the funding situation is very tough.”

The trade-off is the pressure. “The idea of this institute is to go to another level, to make the whole scientific work effort in China go to another level,” she says. “You need to be really good to survive here.”

1. Wang, X., et al. 2002. *Science*. 298:1587–1592.
2. Wang, X., et al. 2003. *Science*. 302:1563–1566.

## Structured energy

Chai Jijie has a whole lot of energy and is in a whole lot of hurry. In addition to reading papers, supervising his lab, and handling administration, “I spend a lot of time in the lab—at least 12 hours a day,” he says. “I’m kind of a crazy scientist.”



CHAI JIJIE

That energy yielded him six first (or cofirst) author papers—including two in *Cell* and two in *Nature* (1–4)—during his stay in Yigong Shi’s lab at Princeton. And yet he applied for only one US-based job (at the drug company Pharmacia). “I’m not good at looking for a job,” admits Chai.

Luckily, Shi is on the NIBS recruitment committee, so Chai ended up in Beijing. He couldn’t be happier. “With the money we get we can work on almost anything we want,” he says. “Especially for a new lab, that is really good—we can work in two or three fields and then end up focusing on the one that really works.”

Already Chai has branched out successfully from his postdoctoral work with Shi on the structure of apoptosis proteins (1–5). He has determined how a protein called WDR5 recognizes K4-methylated histone H3 (6), and how an auxiliary subunit of the voltage-gated potassium channel clamps the main channel together and modulates its gating (7). A submitted paper explains how a bacterial protein targets its plant host, and plenty of other projects are at earlier stages.

Driving it all is a simple enthusiasm. “Sometimes science is just like a game,” says Chai. At the end of the chase, “I can be the first one in the world to know something that other people don’t know.”

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1. Chai, J., et al. 2000. *Nature*. 406:855–862.
2. Wu, G., et al. 2000. *Nature*. 408:1008–1012.
3. Chai, J., et al. 2001. *Cell*. 104:769–780.
4. Chai, J., et al. 2001. *Cell*. 107:399–407.
5. Chai, J., et al. 2003. *Nat. Struct. Biol.* 10:892–898.
6. Han, Z., et al. 2006. *Mol. Cell*. 22:137–144.
7. Wang, H., et al. 2006. *Nat. Neurosci.* doi:10.1038/nn1822.



## Animal Farm

Liu Shusen was determined that banishment to a pig farm in 1969 was not going to be the end of his scientific career. Liu, like most Chinese academics during the Cultural Revolution, was sent from his research institute to pay his dues in the countryside. Initially, his research background counted for nothing.

But Liu's scientific mind was still at work. He figured out that the villagers' pigs were getting sick because they were eating cottonseed. Chemical analysis in a lab in Wuhan revealed that the toxic culprit might be a chemical called gossypol. Boiling the cottonseed destroyed its toxicity while preserving the cottonseed's nutritional value for the pigs. To Liu's relief, the villagers realized that a scientist could in fact be useful.

Once his reeducation year was up, but well before the end of the Cultural Revolution, Liu was put back into

research—his expertise in membrane biology fitted Mao's interest in the origin of life. (A sustained national interest in science did not reemerge, however, until Deng Xiaoping took over after Mao's death in 1976.) Since 1971, Liu has worked at the CAS Institute of Zoology in Beijing, focusing on the biochemistry of mitochondrial bioenergetics.

Liu's former student, Chen Quan, is at first glance a very different scientist. Chen has research experience in Europe and the US, and is a card-carrying cell biologist. He has recently found that a fusion protein works only when its motility domain can help to drive two mitochondrial membranes together.

But, in a strange twist of fate, Chen



Chen Quan (left) has inherited both scientific and historical lessons from his former supervisor Liu Shusen (right).

and Liu's careers recently circled back to meet one another. In the countryside, Liu had found that gossypol in cottonseed makes pigs sick. Now, Chen has reported that gossypol induces a conformational change in Bcl-2 to induce apoptotic cell death (1). Luckily for Liu, he didn't need to know that level of detail 35 years ago to save both the pigs and his career.

1. Lei, X., et al. 2006. *FASEB J.* 20:2147–2159.

a university setting. "Here, we are students," he said. "At the institutes, they are like workers."

But the institutes that have changed the most for PIs have also changed the most for students. "In my lab I encourage [students] to challenge me," says Shao at NIBS. "In this institute we are trying to change the culture."

Because NIBS is so young, most of its teaching is still done by universities. As more PIs arrive, however, in-house courses are being developed.

At ION, the process is further along. Compared with most other Chinese institutions, students are noticeably more willing to speak up and "much more active," says Rao. "They are leading the pack, and it affects the other institutes in China." ION achieved this, he says, "by having visitors and PIs encourage them and not treat them like slaves."

### SCIENCE IN SOCIETY

Perhaps the most nebulous challenge facing Chinese scientists is to build understanding and support for basic research amongst the general population. "Science as a discipline to seek knowledge for the sake of knowledge, I don't think that has roots in China," says Xiaodong Wang. "That's probably the basis for the problems [such as funding disputes]. I think if society treats that as a novel goal, things will be easier."

Unfortunately, as Poo has pointed out (21), science and technology are unified not only in the name of the Ministry of Science and Technology but also in the single word "*keji*." True innovation, a stated aim of the Chinese government, will be challenging if science is seen only as an engineering project (21).

Even some scientists have doubts about throwing so much money at science in what is still a developing country. Beijing University's Wang Shiqiang thinks basic education for the general population is more important. "For at least 20 years, I think the science should be secondary," he says. "China does not need such a large scientific team; they should shrink the team but make sure the ones in the team have sufficient support."

Rather than support science for science's sake, politicians have allotted money because science promises to contribute to national growth. That creates a dangerous situation for researchers. "The society is still young, and there is an inflated expectation that one day you discover and next day you have a cure," says the NIH's Lu. "You have to gradually educate the public that science takes time and needs support."

At least in some universities, the embrace of scientific advancement as a national goal is having positive effects, as support staff have fallen into step. "In the past, they didn't have much idea that the administration should service science; we had to fight for a lot of stuff," says Zhang Bo of Beijing University. "Now, it is much easier [for researchers] to concentrate on the science."

### FUNDING WARS

Money, or at least the total amount of money available, does not seem to be the limiting factor for Chinese bioscientists. The Chinese government has tripled the amount of its research and development funding in the last 10 years; it projects a further fourfold increase in the country's total research and development spending from now until 2020. By then, the share of the budget enjoyed by basic researchers is projected to triple to reach a



level comparable to that in the US.

The results so far are mixed. China had a 20-fold increase in publications in international scientific journals from 1981–2003. But the final total was just over 5% of the world's output, and much lower in the life sciences: only 2% for plant science and 0.8% for immunology. Even within that total, some of the publications come from overseas PIs with part-time appointments in China. The quality is also mixed. In 2001, China published only 1% of the world's top papers (classified in terms of number of citations [22]).

It is where the money goes that is the point of contention (23). CAS funds researchers at its institutes directly (covering approximately half of their needs), but most of the open applications from both CAS and university researchers go through two major channels: the National Natural Science Foundation of China (NSFC); and the Ministry of Science and Technology (MOST). MOST has more money but has not been winning the popularity contest.

NSFC “has been doing a fabulous job,” says Shi. “It has the most rigorous and fair system, and it is enormously popular among scientists in China. This already indicates a reform track. Agencies like NSFC should be strengthened and given more resources over time.”

To some extent this is already happening. The budget of NSFC has grown by an average of 23% a year since its founding in 1986, albeit from paltry beginnings. In 2006, NSFC had US\$425 million (still less than 5% of the government's research and development budget), and MOST had US\$1.7 billion. By comparison, the budget for the US National Institutes of Health is close to \$28 billion.

The NSFC, modeled on the US National Science Foundation, is a standard funding agency dedicated to the natural sciences. MOST is a stranger beast. Its critics say it favors large projects dictated by politicians rather than scientists (24). Most notable

## Results time



ZHANG CHUANMAO

Zhang Chuanmao is in a paper-writing and paper-revising frenzy. Four years after returning from a successful postdoc in Scotland, he has accumulated 15 students and 2 postdocs in his lab, which temporarily slowed his publishing record. The picture in one year's time should be very different.

In Scotland, Zhang found that nuclear envelopes would assemble around beads coated with Ran (1) or its effector importin- $\beta$  (2), and that Ran-GTP promoted vesicle recruitment whereas the Ran-GTPase cycle promoted vesicle fusion (3).

Once he returned to a professorship at Beijing University, Zhang uncovered a series of binding relationships leading all the way from the nuclear envelope, via importins, to DNA-binding proteins. He also has manuscripts detailing how Polo kinase regulates microtubule dynamics, and how an unusual pole reduplication can cause aneuploidy.

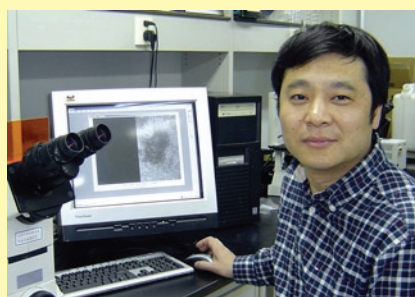
Zhang is extremely sociable, and finds phone and email communication with his colleagues outside of China frustratingly inadequate. Luckily, he says, the number of collaborators in mainland China is building steadily.

1. Zhang, C., and P.R. Clarke. 2000. *Science*. 288:1429–1432.
2. Zhang, C., et al. 2002. *Curr. Biol.* 12:498–502.
3. Zhang, C., and P.R. Clarke. 2001. *Curr. Biol.* 11:208–212.

## Extreme evaluation

During China's economic rise, millions have plunged from safe but meager livelihoods into a far more unstable existence where both the risks and potential rewards are high. Ding Mingxiao, dean of the College of Life Sciences at Beijing University, says the Chinese government has asked universities to go “step by step,” in contrast to the rapid changes at CAS (see main text). But with Deng Hongkui, his younger co-PI, Ding has found himself very much in risky territory.

Deng was awarded one of 43 Grand Challenge grants from the Gates Foundation. The grant requires regular reporting and yearly milestone achievements—a far cry from the university's usual, more leisurely tempo. For the university, says Ding, “this is a large grant from outside.” With the accompanying trainings on reporting, patenting, and collaboration, “the school can learn a lot.”



DENG HONGKUI

The Beijing team is attempting to differentiate human embryonic stem (ES) cells into liver or blast stem cells and then transfer them to mice. If the resultant mice have humanized livers or immune systems, it should be possible to infect them with either hepatitis C virus (HCV) or HIV, and then use the mice to test HCV and HIV vaccines.

Deng is not new to high risk, high reward science. Along with several other teams, he helped discover that CCR5 was a vital HIV coreceptor (1); this followed a multiyear hunt in which researchers hit many dead ends. Since his return to China in 2001, Deng's focus has been on ES cell differentiation, which Chinese researchers have identified as a key area for basic discoveries and commercial exploitation.

1. Deng, H., et al. 1996. *Nature*. 381:661–666.



are the group grants given in priority areas identified by the 863 applied science program and the 973 basic science program. Both programs are named after the year (1986 and 1997) and month when they started.

Agitation from Chinese PIs based overseas was aimed at heading off more of these megaprograms, but this appears to have been unsuccessful. “The major resources will go to big science—it is already decided,” says Poo. “The proteome project will take hundreds of millions of dollars. My advice, which wasn’t taken, was don’t put money in before recruiting.”

The proteome project is one of the megaprojects announced last year in the “National Medium- and Long-Term Programme for Scientific and Technological Development (2006-20),” or MLP (25). Part economic planning document and part funding manifesto, the MLP list of megaprojects was a disappointment to those who had been cheered by NSFC’s recent gains.

### THE PROBLEMS WITH BIG SCIENCE

The debate between MOST and its critics centers around two themes: a familiar big science versus small science debate; and a distinctly Chinese dialogue about how best to promote the country’s development. The merits of the anti-MOST arguments from those based outside China are generally accepted based on the first discussion, but then dismissed based on the second.

Poo authored an article in the banned *China Voices* series that was a critique of big science in China (21). “The drive for big science in China is really dangerous and unhealthy,” he says. “This is the Chinese way of operation—an extension of the planned economy.”

China has a history of central organization and control, but observers cite additional reasons for the persistence of megaprojects in the country. According to Yi Rao (and many others who are less willing to go on the record), “ministries argue for self-interest, not for what is best for the country.” MOST resists peer review, he says, because it takes away from its power. “The prime minister [Wen Jiabao] really wants to do something,” says Rao, “but he doesn’t know who to talk to.”

The large projects promote leadership by the few, and a top-down approach. Rao and colleagues described this as “Rule-by-Man” rather than “Rule-by-Merit” in their banned *Nature* article (5). In project selection, they wrote, there are “funds leading projects, not projects leading funds.” For refereeing, “one megaproject can include most, if not all, active researchers in that area, thereby leaving few or no experts who can provide objective and critical evaluation.” Finally, the authors dismissed any possible argument for big science: “At the present, as in most peace time, there are few well-defined goals that can be solved by a few simple megaprojects.”

Applications for project funds suffer from a lack of scientific scrutiny. “People overemphasize political significance,” says Shi. “Those applications tend to fly better with those who don’t have a

**Big science is “an extension of the planned economy,” says Mu-ming Poo.**



**FEEDING THE BEAST** Demands of growth cast science in a technological light.

background in science, because that is the part they understand.”

Other funders are looking for something tangible: buildings and big equipment. As a result, says one researcher, “for the big machinery, I would say we have too much money.” In several institutes, says Poo, proteomics facilities are already much better than those at the University of California, Berkeley (Poo’s home base), but lack sound projects that can make full use of them. Wastage of these large facilities is a particular risk in a country acknowledged to have a shortage of senior scientific leaders.

The first barrier faced by returnees trying to access the money is the politics of large group projects. MOST money “is only if you are famous,” says one researcher. “No one knows the rules about who gets what money.” Other researchers say that “we need to do the social work” to get MOST funding, and “the joke is that if you want a few million RMB you have dinner with someone.”

Evaluation has been another problem, initially for all grants. “Grants were reviewed by your friends,” says Lu at NIH. “It is diffi-



The NIH’s Bai Lu has helped improve grant review.



cult for very good science to emerge under those conditions.”

Five years ago, Lu initiated a program for reviewing bigger NSFC grants. Leading by example, he and other overseas colleagues encouraged critical discussion and confidentiality, both of which were previously lacking. Reviewing at MOST, however, has not seen similar improvements.

Publications are a major criterion for success. This was initially welcomed in China as a sign that merit-based evaluation had arrived, but some now feel the emphasis is suffocating. “The evaluation committee is generalist, so they just look where you published your paper,” says one researcher. “If you do science [just] for publications,” he says, “you are not a scientist.” According to Carnegie’s Zheng: “The biggest thing that is absent [in China] is evaluating progress rather than just the impact factors of papers published.”

Some of the problems with limited reviewing panels may decrease over time. “The Chinese scientific community is small,” says Xiaodong Wang. “They are the ones that get called for everything, and that generates the political problems. With the number of good scientists expanding, this problem will become less and less.” Similar issues are arising with regulatory bodies, where currently the regulators and the regulated sometimes overlap (26).

### IS IT BIG OR NOT?

The arguments countering the expatriates are based on two grounds: that most of the science isn’t really big; and that, when it is, it is needed to build the country.

“I don’t think that big science dominates in China,” says CAS’s Chen Zhu. “If you do a more careful analysis of the funding of biological science in China, then the funding for proteomics and genomics is just 15-20%. The small projects are still the mainstream in China.”

Chen, like many other academics high up in the decision-making tree, actually professes support for unplanned, basic science. “It is difficult to plan real science,” he acknowledges. “You can plan some engineering projects; you can plan some infrastructure projects; you

can even plan some areas of priority in science. But you cannot plan where the breakthroughs will come in science.” As a result, he says, the MLP strategy “will be evolving over time.”

Chen does, however, see the need for projects such as the proteomics center. “These are not research projects but infrastructure,” he says.

Part of the argument centers on a willingness to play the game. Politicians, says Poo, “think [that] in a socialist country you can

## Big science methods; small science thinking

Finding nuggets of information in huge piles of data is He Dacheng’s specialty. It starts in his office—with its cascading mountains of newspapers, reprints, and the odd dissecting scope and can of dried milk—and extends to his work as one of the pioneers of proteomics in China.

The heavy emphasis on proteomics in China was a question of timing. The Chinese government was very attracted to the orderly achievability of the Human Genome Project, but the country’s development came too late for it to make any more than a minor contribution to that project. That left a gap that, partly at He’s suggestion, was filled by proteomics. He helped form the Universities’ Confederated Institute for Proteomics (UCIP) in 2001 and became its chief scientist.

Proteomics in China has been criticized because of the tendency to focus on big science projects such as the identification of all proteins in the liver. He says that proteomics must initially focus on big science projects that identify many proteins. Some of these projects are receiving tens or hundreds of millions of dollars, under the leadership of people such as Rao Zihé (see main text) and He Fuchu (Institute of Radiation Medicine, Beijing).

But as it matures, says He Dacheng, proteomics “can and ought to be under the guidance of real biological questions,” he says. The focus on data and instrumentation is just a stage, he says; then, “you will necessarily go back to the hypothesis. The technique cannot replace and lead the human mind.” Getting more support for a small-science version of proteomics has been a primary goal for He.

Changing a system with such entrenched interests will be difficult, but change is one thing in which He has faith. After an undergraduate degree at Beijing University, He was diverted by the Cultural Revolution to work as a porter in an agricultural chemical factory. His subsequent Ph.D. at Beijing Normal University (BNU) was followed by 12 years in the US. For the last three years of that stay he bounced between BNU and his assistant professorship at the University of Texas. Finally, in 2000, he committed full time to BNU, where he became director of the Institute of Cell Biology.

Now part of the system, He has a chance to effect changes for his students. Currently, most students must do a short Master’s degree before moving to a different laboratory to extend this to a Ph.D. The jump between two short lab stints makes it almost impossible to complete a project of any significance. He is on the central government committee that oversees such policies and is confident that change will come in 2007. Next on the to-change list will be the two-year restriction on postdocs and rules preventing the youngest PIs from having their own Ph.D. students. Administration may not be glamorous, but the efforts of the genial He may be as important as any in bringing the Chinese university research scene to life.



HE DACHENG



organize science.” Therefore, “if you don’t have clear goals 5 or 10 years off, you don’t get the money.” So far, he has resisted window-dressing ION’s efforts or forcing his PIs to work only on diseases; this may explain the recent failure of his relatively modest funding request to support new hires. “CAS should do some applied research,” he admits. “It is the relative weight that is the problem.”

For those who can organize a group, however, the final result may not be too different from an individual grant. Chen Ye-Guang at Tsinghua says the emphasis on large groups doesn’t always translate into big science because “the most important discoveries are made by PIs not by groups.” A 973 grant on membrane trafficking in which he participates includes eight PIs, who work on a variety of loosely connected topics including nuclear dynamics, exocytosis, endocytosis, signaling, and proteomics.

Group funding can even benefit young PIs, says Fudan University’s Wu Chaoqun. A group grant enabled Wu’s colleague Huang Qiang, a young PI, to get computers for molecular simulations—equipment that he could never afford from his individual grant.



Chen Zhu sees the need for a balance of large and small projects.

Other large projects have actually been initiated by expatriates, including two based at Yale University (New Haven, CT). Tian Xu’s knockout mice at Fudan University are reportedly being made at 4–5 times less cost than would be incurred in the US (reference 27, and see sidebar), and Xingwang Deng has run a huge plant mutant project at Beijing University (17).

### BUILDING A NATION

But the main argument for big science in China comes down to the obsession with engineering China’s continued expansion. Development requires new infrastructure and new coordination mechanisms between newly developing sectors of the economy. Because this is deemed to be the government’s job, “in the US the scientists control the money, but in China it is the government,” says one researcher.

The government “emphasizes that scientific research must benefit the country’s economic growth,” says Rao Zihé, who has been a strong proponent of some of the larger projects. “Chinese science has only grown in the last 10 years, and this is mainly because of the 973 and 863 contributions,” he says. “If you ignore this, it is a big mistake.” MOST, he says, “want[s] to do big things that are good for China’s construction.”

“China does have its own strategic concerns, for example for economic development, employment, and national security,” agrees Shi. “A government has to inject its own modifications into the research track. But it is really a mistake in the name of government regulation to invest the bulk of the money in megaprojects.”

In part, China’s current approach may be a transitional one. Until Chinese companies start doing more of their own research, the kind of applied, target-oriented research that in a developed

## A step forward for mouse genetics

Imagine if the power of genetic screens—especially screens for suppressors and modifiers of diseases—was available in mammals. This is the future that Tian Xu (Yale University School of Medicine, New Haven, CT) is trying to bring about.

Xu has his eye on forward genetics, in which random mutation is used to generate or modify a phenotype of interest. It has been a bonanza for yeast, worm, and fly researchers. Now, Xu plans to bring it to mice, and thus to the world of mammalian biology. He hopes that mutations that block obesity despite a high fat diet, or that block neurodegeneration despite a predisposing mutation, might break open new approaches for medical researchers.

“The methodology to produce the mutants is solid,” he says. “All we need to do is to crank up the space.” At the moment that space consists mainly of a new building with 10,000 cages at Fudan University, Xu’s alma mater in Shanghai. Another building, big enough to hold 25,000 cages, should be completed this year. “The speed things go in Shanghai, they can do this pretty rapidly,” says Xu.

Basing the project in China has worked well, says Xu. “For Yale, it allows us to carry out some experiments that are difficult to carry out here because of limits on space and personnel,” he says. “For Fudan, this is a great way to train their people, and bring exciting scientific projects there. And it put Fudan on the map.”

Xu’s quest began with an observation about the shortcoming of traditional reverse genetics in mice. Knockouts targeted to a specific gene are “very powerful,” he says, but “we are guessing what genes are involved, and more than 50% of knockouts don’t produce the expected phenotype.” The result is frustrated postdocs and wasted effort.



Mice with the RFP-marked *PB* transposon glow pink under UV light.





Xu's project uses tens (and soon hundreds) of thousands of mice.

This inspired Xu to bring in forward genetics, where you “let the genetics tell you what is interesting.” But first he needed the perfect mutagen. A chemical mutagenesis project run by NIH had been abandoned because it was too hard to find which mutations were causing a phenotype.

Xu was more interested in transposons. P elements had been very effective in flies, Xu's previous organism of interest, but did not work in mammals. Transposons found naturally in mammals, however, were subject to vigorous silencing by mammalian cells intent on preserving their genomic integrity.

Xu concluded that “maybe we need to try something strange—something that mammals have never seen before.” After eight years of trial and error, he hit upon *piggyBac* (*PB*), a transposon originally found in a moth. Signs of *PB* had been found in all sorts of genomes, and it turned out to transpose efficiently in mouse and human cells (1). “Luck shined on us,” says Xu.

At Fudan, a team led by Xu's former student Wu Xiaohui started hopping *PB* around the mice genome. Putting the *PB* transposase under the control of a germline promoter gave them one hop per generation at ~70% efficiency. So far, the team has 565 unique insertions, 50% of them in genes, with no evident insertion hotspots.

The first aim is to generate simple gene insertions in a wild-type background. A total of 100,000 mutants should ensure coverage of the ~20,000 mouse genes. “If we have another \$30 million we can produce and cryopreserve mutations of 70% of [mouse] genes,” says Xu. “It's not much money.”

In the first batch of mutant mice, some have autoimmune syndromes, neurodegeneration, hair loss, premature aging, or eye defects. Others keep eating but fail to grow, have social problems, circle counterclockwise, or grow tusks. His technicians, says Xu, “are all competing to find the first mutation that will be a *New York Times* cover [story].”

“The students are really in heaven,” he continues. “The first student has 75 knockouts and can choose the most interesting to work on.”

But that choice—what to work on first—is Xu's “headache right now,” he says. “We haven't made

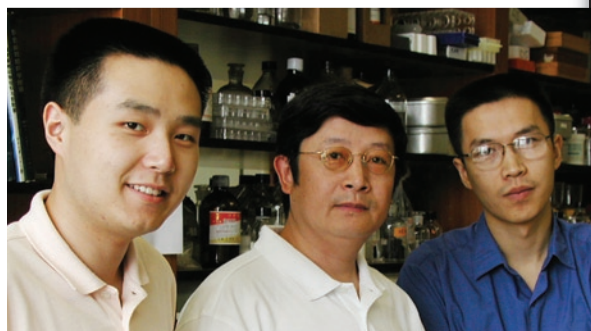
up our mind yet.” He also has to restrain his large workforce. “When the students see an interesting phenotype they want to work on it,” he says. “But in flies we [always] finish[ed] a screen before deciding what to work on. Otherwise we will get swamped.”

That prioritizing decision may have to come before Xu is ready to release mice to others, however. For now he says only that release “is going to be a huge operation.” In terms of dates, mechanism, and fees, he says, “we don't have a clear answer yet.”

Some of the other genome-wide mutagenesis projects, by contrast, are already making mutants available, but notably these are in the form of mouse ES cells, not live mice. These other efforts in Europe, Canada, and the NIH in the US combine with Xu's Chinese endeavor in a crazy patchwork of mutually overlapping projects (2). Xu has the benefit, however, of producing live mice from day one, rather than being held up by the expensive conversion of ES cells to live mouse.

His project also starts to sound very different when he brings in the idea of specific screens. Any suppressor or modifier screen would impose another huge burden on Xu's already expansive project, but “I'm gearing up to do both at the same time,” he says. He does not have a timeline for starting particular screens, but says he imagines splitting his work equally on the whole genome knockout and disease-suppressor screens. “It's all resources,” he says. “The rest is solved.”

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Xu with his former student Wu Xiaohui (right) and current student Ding Sheng (left).



## The signaling duo

The path leading to Tsinghua University's first biology paper in *Science* involves a lost letter, swans, and two stories of persistence.

The senior authors of that paper, Meng Anming and Chen Ye-Guang, both got their undergraduate degrees in 1983. Chen took the academic route,



MENG ANMING

CHEN YEGUANG

but had to battle through two Master's degrees (one in China and another at Fordham University in New York City) before he was accepted to a Ph.D. program at Albert Einstein College of Medicine (New York, NY).

Meng, however, worked initially as a research assistant at China's National Rice Research Institute. Under an exchange program, he got offers from at least five overseas universities and declined all except Wye College of London University (now Imperial College of Wye). But the leader of Meng's institute said the subject at Wye—soybean breeding—was too distant from his current expertise in rice breeding, and that Meng should wait for help in finding a rice place. "I had a visa and flight ticket, but gave them up," says Meng. "If I insisted, I could have gone, but that wasn't my way."

Help from the director was not forthcoming, and Meng's life was at a standstill. Then, two years later, he found a letter jammed in his desk drawer. It was his refusal letter to David Parkin at Nottingham University, which he thought he had sent two years earlier. "So I sent another letter asking again," says Meng, "and he said okay you can come."

Meng was plunged into the world of molecular biology. "The first time I used a pipette there I had never seen such tools before," he says. For his Ph.D., he did DNA fingerprinting on, of all things, swan

and sparrow DNA.

Back in China, there were no swans, so Meng focused on genetic variation in pigs, cattle, and chickens. "The first time I came back it was so difficult to do any work," he says.

"Some of the big equipment you could find, but small stuff you could not find." Lacking any absorbent tissue for Southern blots, he eventually resorted to the homemade paper used in local temples.

Next came a two-year stint in Georgia, which introduced him to zebrafish. When Meng returned to China he was the first in the country to use zebrafish for developmental studies.

Chen, meanwhile, had done a postdoc in Joan Massagué's lab at Memorial Sloan-Kettering Cancer Center (New York, NY); it yielded cofirst authorships on two-high profile papers on TGF $\beta$  signaling (1, 2). After a couple of years in a tenure-track job at the University of California, Riverside, however, he was restless. "I was projecting my life forwards," he says. "If I stayed at Riverside for 5 or 10 years, a secure job would be no problem. But if I can accomplish the same thing if I go back to China, then I should go back to China."

In 2002, Meng's zebrafish experience and Chen's TGF $\beta$  signaling background were united at Tsinghua. Meng had found zebrafish Dapper2 (Dpr2); a related protein, Dapper1, was known to block Wnt signaling. But Chen and Meng found that Dpr2 instead blocked TGF $\beta$  signaling. Dpr2 binds TGF $\beta$  receptors in late endosomes, thus accelerating their degradation and suppressing mesoderm induction by the TGF $\beta$  protein Nodal (3). It is still not clear exactly how Dpr2 directs traffic in this way.

Since that *Science* paper, Chen has found out how TGF $\beta$  recruits muscle and mesenchymal cells that build blood vessels (4), and Meng led a joint effort to work out how a protein called Tob1 limits dorsal development by binding  $\beta$ -catenin (5). In addition to Dpr2 and Tob1 two-hybrids, Meng is now doing large-scale



The fish that made a *Science* paper.

transposon trapping of maternally expressed genes to generate new research directions.

In the meantime, the pair have been joined by an increasingly stellar cast of colleagues in an increasingly competi-

tive faculty search process. Tsinghua, like other universities in China, had its job description narrowed during the rule of Mao Tse-Tung. Engineering became the sole focus, and the Department of Biology was closed from 1952 to 1983. Mu-ming Poo, acting on a part-time basis, helped get the department going again in 1984.

More recent full-time arrivals include Wu Wei, who works on Wnt signaling (6–8), Wu Jia-Wei, who solved Smad- and apoptosis-related structures with Yigong Shi at Princeton (9–11), and Li Peng, whose work has ranged from neuroblast asymmetry (12) to apoptosis (13, 14), and now to diabetes. According to one PI who was appointed in 2002, "This is all happening very fast. If I applied for [a job in] this department, now I'm not sure I could get it."

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country would be done by companies is instead the responsibility of the government. “In the future,” says CAS’s Chen, “more emphasis should be put on enhancing the research and development by enterprises.” This may in turn lead to greater freedom for academics.

The final argument is based on the politics of funding. At budget time, says Rao Zihé, everyone tries to get money independently: “MOST tries hard; the Ministry of Education tries hard; NSFC tries hard.” But protests from abroad have the potential to “stop MOST from getting money from the budget.”

Lu has a different opinion. “They think overseas scientists may not understand the politics, the societal needs—if you don’t get it this way the money will never come.” But, he says, “there is a principle: you have to do it by fair, competitive review. We can debate the details, but the principle is the principle.”

MOST has been responsive to some of the expatriates’ complaints on individual cases, says Lu, “but in the end you need to institutionalize, not rely on someone’s goodwill.” He thinks that MOST supports peer review, but “if you have a commitment of 10 or 20 years, you need an interim review to correct mistakes. It’s that kind of mechanism that is still lacking.”



Princeton’s Yigong Shi says government control should not overwhelm scientific diversity.

Shi and Lu stress that they are not trying to impose the US system on China. “No one knows the best funding system for China,” says Shi. “The current funding system has its reasons, but we must constantly think about how to improve it.”

Shi sees China’s problem as somewhat circular: recruitment at the top level is needed to improve the scientific consensus on funding; and a scientific consensus on funding is needed to improve the research environment and thus recruitment.

“If they can solve both of these problems, scientific development could be tenfold faster,” he says. “If someone thinks China’s research is really going well and cannot maintain this rate, this is absurd. China’s research can only be better, and it will be better. I cannot predict what China will be in 20 years.”

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PLAYING THE GAME Cooperation is key in Chinese science.

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