A great leap forward

After helping to sequence the human genome, Chinese scientists are debating how best to continue the push towards becoming a world power in biology. David Cyranoski reports.

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China wears its participation in the international Human Genome Project (HGP) like a badge of honour. Last month, when the HGP published its sequence of the human genome in *Nature*[1], Chinese institutes were among those sharing the spotlight.

"Now everyone in China knows what the human genome is," says Huanming Yang, director of the Beijing Genomics Institute (BGI). "Chinese people are so proud to be part of this international effort."

In 1998, China's scientific leaders overcame scepticism from some members of the HGP — and from many of their own researchers — to become the only developing country to take a role in sequencing the human genome. The Ministry of Science and Technology launched its Chinese National Human Genome Center (CHGC), with branches in Beijing and Shanghai. A year later the Chinese Academy of Sciences opened the BGI. These institutes contributed 1% of the published sequence — an achievement that is of huge symbolic importance.

Having now proven its mettle in sequencing, and following earlier successes in plant transgenics, China is now taking a leap towards assembling all the elements needed to become a major force in biology and biotechnology. With strong government support, researchers are setting up programmes in everything from stem-cell research, through large-scale efforts to determine protein structures, to population studies to hunt for human disease genes. There is even talk of trying to clone the endangered giant panda.

For researchers returning from positions abroad, the pace of change is striking. Although most of China's biologists still work in run-down buildings, these labs are starting to bulge with gleaming new equipment. And many institutes are planning to expand their facilities — just part of the construction upheaval that is currently transforming China's cityscapes. Returning after three years at the Memorial Sloan-Kettering Cancer Center in New York to Shanghai, a city he "no longer recognized", molecular geneticist Zhu-Gang Wang of Shanghai Second Medical University was startled to find that reagents could now be acquired overnight, rather than in the months that he remembered.

But amid this rapid growth, some researchers are warning that there is more to be done than simply matching the spending of the established powers. As Chinese biologists debate the optimal balance between building more capacity for DNA sequencing against investing in areas such as functional genomics and medical genetics, there are calls for more coordination, and better peer review to judge the relative merits of the various programmes being considered. Other researchers are concerned that, despite moves towards a market economy, China still lacks the genuinely competitive environment needed to nurture a vibrant biotechnology industry.

A valuable lesson

Although many Chinese researchers originally questioned the value of a Chinese contribution to the HGP, there is now little doubt that the work has provided a springboard for the development of Chinese biology. "We learned large-scale sequencing, how to coordinate many centres, and how to do bioinformatics," says Zhu Chen, director of the Shanghai CHGC and vice-president of the Chinese Academy of Sciences.

Now, those who led China's contribution to the HGP are debating how to strike a balance between building on these strengths and exploring other frontiers. At the BGI, Yang is pressing on with sequencing. In late January, he opened a new sequencing facility in Hangzhou, south of Shanghai. This will work on two main complete genome sequencing projects: the pig — a collaboration with Danish scientists — and the parent strains of China's 'superhybrid' rice, a productive variety that accounts for 60% of the country's rice harvest.

"Some people say, 'sequencing is not everything'," says Yang, "but I believe that it is the best place to start." However, Yang feels he is losing a tug-of-war over central government funding to those who are switching to functional genomics, research that aims to


BGI

The Beijing Genomics Institute made an important contribution to the human genome sequence.

GREG BAKER/AP

Food for thought: Chinese researchers are turning their attention to the genome of 'superhybrid' rice.

identify the biological role played by the newly sequenced genes. To open the Hangzhou facility, Yang had to borrow US$6 million from the city government.

Although Chen's Shanghai CHGC was responsible for about a quarter of China's HGP contribution, he is now more excited by the possibilities offered by the hundreds of full-length complementary DNAs sequenced as part of China's involvement in the project. These represent the sequences of expressed genes, and can be engineered into cells which are then cultured to mass-produce proteins so that their structures can be determined.

Like the Shanghai CHGC, the Beijing branch is turning increasingly to functional studies. The two centres have several joint projects, focusing on genes related to liver cancer, nasopharyngeal cancer, oesophageal cancer and leukaemia.

But there is one major point of convergence in the research strategies of the BGI and the CHGC: both are using their sequencing machines to identify single-nucleotide polymorphisms (SNPs) from Chinese populations. These markers of genetic variability should aid the search for the genes that predispose humans to complex diseases such as cancer and psychiatric disorders. Some critics argue that the Chinese SNP projects will largely duplicate the efforts of the international SNP Consortium, a collaborative effort uniting leading Western genome centres and drugs companies. But Chen argues that about 30% of the SNPs in Chinese populations will be different from those found elsewhere — twice as many as has previously been thought.

Whether or not a separate Chinese SNP effort is required, there is widespread agreement that China has a lot to offer geneticists. The country's array of isolated, relatively homogeneous sub-populations from 56 different ethnic groups represents a unique resource for disease gene searches. Inbreeding has produced a homogeneous genetic make-up within each population, and the lack of emigration or immigration means that it is easy to construct large family pedigrees. These features have made Iceland and Finland hotspots for mapping the chromosomal location of genes predisposing to disease. "We have several Icelands and several Finlands," says Lin He of Shanghai Jiao Tong University, who coordinates a bank for blood, tumour and cerebrospinal fluid samples collected from populations across China.

The search for genes that underlie diseases, and for ways to block their effects, is a national priority. "With an estimated population of 1.6 billion by 2030 and an ageing society brought on by the one-child policy, we will need medical breakthroughs," says Xu Zhi-Hong, president of Peking University. "This is our challenge."

It is a challenge that both the government and researchers are taking on. In 1998, the government set up a programme alongside the HGP sequencing effort, which has established banks of blood samples and associated information about family pedigrees in Hunan, Guanzhuo, Beijing and Shanghai. Independent scientists have been working in parallel. Yunnan University recently announced that it has assembled the largest biological sample collection in the world in terms of ethnic diversity. At Shanghai Jiao

Politics, ethics and collaborations

As China's medical geneticists move to exploit the unique resource offered by the country's isolated, genetically homogeneous populations (see main text), there should be opportunities for fruitful collaborations with researchers from abroad. But such collaborations are still difficult. On the Chinese side, geneticists are concerned at becoming little more than 'sample vendors' for their foreign partners. Many Western geneticists, meanwhile, remain uneasy about China's flirtation with eugenics.

In 1997, China's Premier, Jiang Zemin, threw medical genetics into the spotlight by commenting publicly on the country's genetic heritage. "One without foresight will encounter sudden doom," he said. "We must treasure our genetic resources." At the time, several projects had raised concerns about whether China's genetic resources were being plundered by visiting scientists. This led to formation of the Human Genetic Resources Administration of China, which must now approve any research using human samples for genetic studies.

The administration's guidelines state that, among other conditions, both sides of any international collaboration will share in resultant intellectual property. But opinions are divided on whether the potential for abuse has been removed. "The guidelines are clear, and 90% of international projects are approved," says Zhu Chen, director of the Chinese National Human Genome Center in Shanghai. But Huanming Yang, director of the Beijing Genomics Institute, is unconvinced. "Regulations are still too loose," he says.

Geneticists visiting China sometimes have doubts about the quality of their collaborators' family pedigrees and samples. "People will say they're related to anyone if they think they can get free medical treatment or some money by participating," says one Chinese biotechnology veteran. Some Western researchers also question the accuracy of clinical diagnoses. "I would guess schizophrenia diagnosis in a totalitarian country would be far from reliable," says one US-based geneticist.

The political climate in China also raises deeper ethical concerns. Many geneticists were appalled when, in 1995, the Chinese government introduced the 'Mother and Infant Health Care Law'. This required couples planning marriage to undergo genetic screening, and included provisions to encourage sterilization of those found to be carrying disease genes.

In protest, many geneticists threatened to boycott the International Congress of Genetics, held in Beijing in 1998. Although the controversy was partly defused by a government promise to rewrite the law, the changes have yet to be made. Last December, the Ethical, Legal and Social Issues Committee of the Chinese Human Genome Project renewed its call for the promise to be acted upon.

Tong University, meanwhile, He claims to have compiled the world's largest sample bank related to neuropsychiatric disease, in a joint project with the Shanghai Institutes of Biological Sciences.

Rising stars

Studies of samples taken from Chinese populations are already yielding advances. The first success came in 1998, when a team led by Jia-hui Xia of the National Laboratory of Medical Genetics of China in Changsha, Hunan province, identified a gene for a form of neurological deafness[2]. Then, last year, researchers led by He mapped the gene for brachydactyly type A-1 — a disease in which joints of the figures are missing, misplaced or disfigured — to a small region of chromosome 2 (ref. 3). He and his colleagues say they have now isolated the gene, beating competition from several groups around the world, and have submitted the results for publication. "We just had good samples with good pedigrees," He says .

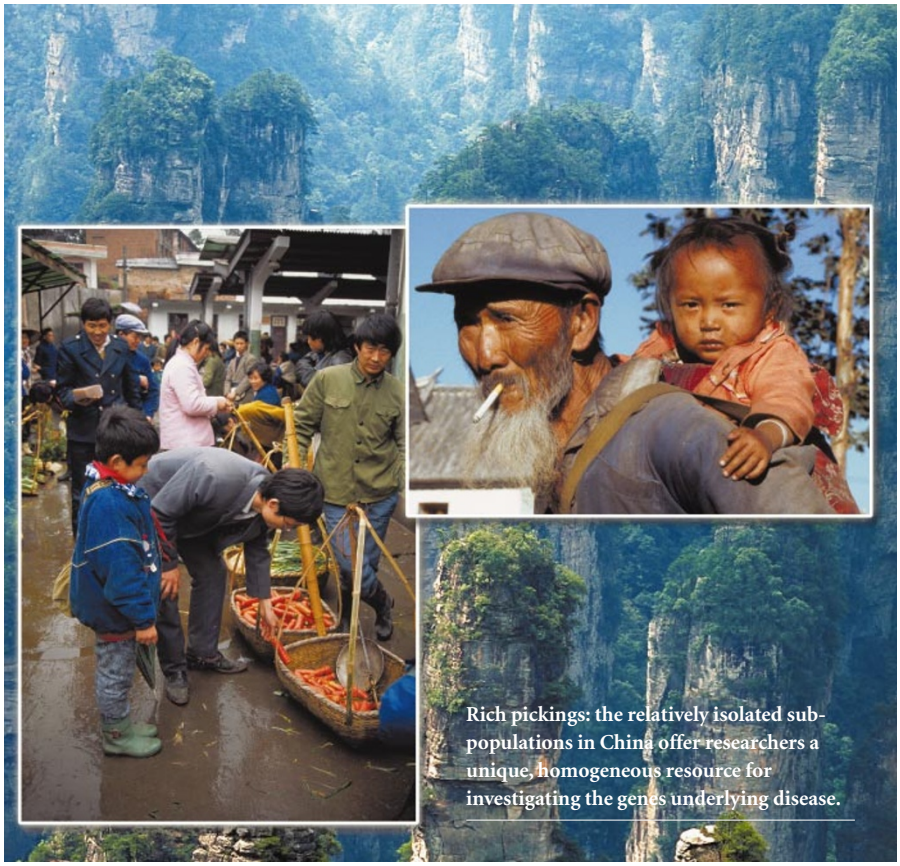
And the pace looks set to pick up. Last month, researchers led by Yan Shen of the Institute of Basic Medical Sciences in Beijing revealed the genetic basis of another disease, dentinogenesis imperfecta Shields type II, in which the teeth are discoloured and chip easily[4]. From their studies of large pedigrees in the Jiangsu province, north of Shanghai, the team showed that a mutation in a gene called *DSPP* is responsible. Alongside this paper, researchers led by Xiangyin Kong of the Shanghai Research Center of Biotechnology reported, from their studies of three extended families from the same region, that mutations in *DSPP* can also cause hearing loss[5].

But there are obstacles to progress. Some Chinese people are unwilling to take part in studies for fear that discovery of a genetic disease could lead to discrimination. And in the longer term, China's one-child policy, and the increasing population mobility being promoted by the country's economic development, will pare down the number of large pedigrees and lead to genetic mixing between populations.

Commercial breaks?

To capitalize on the discovery of disease genes, biotechnology and pharmaceutical companies will have to take the lead. This is the weakest link in the chain, although with generous government support, universities are launching large numbers of spin-off companies. Peking University is the leader, boasting a portfolio of eight biotech firms.

"China's system for allowing professors to engage in industry is much more flexible than most others," says Jing Cheng, one of China's best-known biotech entrepreneurs, who runs a DNA microarray company spun off from Tsinghua University in Beijing. Indeed, compared with Pacific Rim neighbours such as Japan, there seems to be little or no restriction on university researchers trying their hand at business.



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Rich pickings: the relatively isolated subpopulations in China offer researchers a unique, homogeneous resource for investigating the genes underlying disease.

But unlike the situation in its capitalist neighbours, China's government retains a large chunk of any company, and may even fund its research. Some researchers argue that this is holding the sector back. "With generous government grants, people do not worry about making profits. Even if something is developed, it will sit on the shelf because no one will make the effort to commercialize," says one researcher working at an institute of the Chinese Academy of Sciences. "Many researchers seem just to use public funds freely to do research while claiming to set up their own company," says a senior executive of a Hong Kong-based biotech company.

Reliance on the government is "the greatest problem for biotech in China", agrees Yu-Min Mao, a geneticist at Fudan University in Shanghai. Venture capital is not well established, so would-be entrepreneurs have few other places to turn. But Mao is showing that it is possible to break the mould. In three short years, his United Gene Holdings has become China's biggest biotechnology company. It now covers a wide range of genomic science services such as gene cloning and sequencing, and claims to have identified 5,000 novel complementary DNAs.

Mao and his business partner, Yi Xie, invented their own venture capital format to encourage investment: they stipulate that, with any investment, one-third goes towards buying stock and two-thirds go towards a low-interest, long-term loan to the company. "There are few investment banks in China, but the principle is the same," says Mao. "We just borrow from individual investors instead of investment banks." For the investors, this lowers the financial risk, should the company fail. "Normally they would lose their entire investment, and we would only lose our technology. Now, they would only lose one-third of their investment, and we would still owe them the rest," says Mao. "It shows that we are confident in our products."

Apart from the struggle to generate a favourable climate for biotech investment, the other main obstacle to China's development in biology is the eccentricity of funding decisions, which are often based on political leverage rather than peer review. The result, critics claim, is a proliferation of uncoordinated projects. "Everybody is just trying to jump on the genomics bandwagon, but very few know where they are going," says Ming-Wei Wang, formerly chief executive officer of a Shanghai-based biotech company. "In China, everything is decided in backrooms, and then just announced," says one researcher with the Chinese Academy of Sciences. Genomics research in China is an uncoordinated "bunch of loose ends", complains another.

But others are optimistic that China will begin to apply more rigorous, open and accountable methods of decision-making. If so, its future as a leading international player in biology should be secure. Li Jin, formerly of Fudan University's Institute of Genetics, and now based at the University of Texas at Houston, is one of those predicting a bright future. "With increasing funding and by taking advantage of its unique resources, China will soon become a serious contender on the world stage," he says. ■

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