

# Health biotechnology in China—reawakening of a giant

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**U**NDER the Communist regime of the 1950s, Chinese achievements in science suggested that the country would soon join the elite group of countries spearheading innovative scientific research. After the 'Cultural Revolution' that began in 1966, however, and its devastating impact on Chinese science for the next 10 years, China's scientific capacities quickly fell behind those of developed nations and vital scientific personnel were lost. By the late 1970s and early 1980s, extensive government reforms—including policies that began to shift the nation from a centralized, planned economy toward a market-based one—identified the science system as central for the country's modernization and economic development. Although these reforms have set China's health biotechnology innovation system on a solid footing, the reorganization of R&D organizations and activities, the promotion of linkages between various actors and even the political and legal environment remain in flux. Nevertheless, spurred by the goal of 'catching up' with the advanced, industrialized nations, the past two decades have seen China work hard to move products from the laboratory to the market.

## The success of China's health biotechnology sector

China's participation as the only developing country in the Human Genome Project

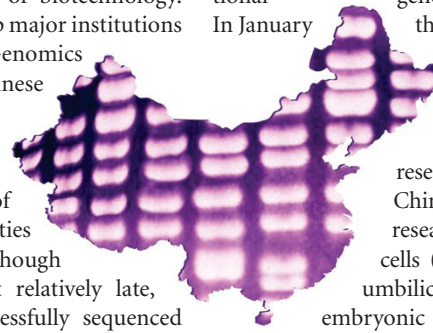
showcased its capability in genomics and its intent to become one of the world's leading contributors to the field of biotechnology. The country quickly set up major institutions in genomics, the Beijing Genomics Institute and the Chinese National Human Genome Center (with branches in Beijing and Shanghai), equipped with state of the art sequencing facilities and computers. Even though they entered the project relatively late, Chinese researchers successfully sequenced 1% of the human genome with an accuracy rate of 99%. They have continued to demonstrate their strength in the field, and in 2002 sequenced the rice genome of the most widely cultivated subspecies in China<sup>1</sup>.

The country's participation in the Human Genome Project is indicative of how rapidly China has reached world standards in sequencing, and this in turn reflects its general advanced state of development in health biotechnology. Since China initiated research in the field in the late 1980s, it has approved several vaccines and diagnostics and therapeutics for the market (see **Table 1**). Many of these are based on technologies developed abroad, but Chinese innovation in this field is increasing and resulting in new products.

China is focusing on several subfields of health biotechnology, including therapeutic

antibodies, severe acquired respiratory syndrome (SARS) research, gene therapy, functional genomics and stem cells. In January the world's first commercial gene therapy was announced in China (see **Box 1**). In addition, several research institutions in China are pioneering research on adult stem cells (e.g., from blood and umbilical cord) and on embryonic stem (ES) cells; a Chinese research group recently reported the capacity of nonhuman oocytes to reprogram human adult somatic cells into bona fide ES cell lines<sup>2</sup>. There are stem cell banks and related services in several centers, including Beijing, Shanghai, Sichuan, Guangdong and Zhejiang. With a comparatively liberal environment and access to important materials for this type of research, China has the potential to become a leader in human embryo biotechnologies<sup>3</sup>.

In addition, China is continuing to work in the field of genome sequencing. It is using its large population and the availability of several homogeneous subpopulations to move more into functional genomics and the identification of disease genes. It now has more than 150 health biotechnology products in clinical trials<sup>4</sup> and is increasing the number



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**Table 1 Selected examples of Chinese health biotechnology products**

Sector	Type	Application	Producer <sup>a</sup>
<b>Vaccines</b>	Recombinant hepatitis B surface antigen	Hepatitis B	Shenzhen Kangtai Biological Products (Shenzhen, China)
	Recombinant live oral vaccine, which expresses protective antigens of both <i>Shigella flexneri</i> 2a and <i>Shigella sonnei</i>	Shigella dysentery	Lanzhou Institute of Vaccines and Biological Products (Lanzhou, China)
<b>Therapeutics</b>	Recombinant interferon $\alpha$ 1b	Ulcerative keratitis/ Hepatitis B and C	Changchun Research Institute of Biotechnology (Changchun, China) Shanghai Research Institute of Biotechnology
	Recombinant epidermal growth factor	Skin injuries	Shanghai Dajiang (Group) (Shanghai, China)
	Recombinant human interleukin-2	Many uses, including for cancer (e.g., renal cell carcinoma)	Shenzhen Neptunus Interlong Biology Technique Holdings (Shenzhen, China)
	Recombinant granulocyte colony-stimulating factor	Neutropenia	Amoytop Biotechnology (Fujian, China)
	Recombinant erythropoietin- $\alpha$	Anemia	Shenyang Sunshine Pharmaceutical (Beijing)
	Recombinant human somatotropin	Dwarfism	Changchun Jinsai Pharmaceutical (Changchun, China)
	Recombinant streptokinase	Cardiovascular	China Tonghua Herbal Link
	Recombinant Ad-p53 gene therapy	Head and neck squamous cell carcinoma	Shenzhen SiBono GenTech (Shenzhen, China)
<b>Diagnostics</b>	Enzyme-linked immunosorbent assays	Hepatitis C virus and human immunodeficiency virus	Shanghai Huaguan Biochip (Shanghai, China)

<sup>a</sup>Some of these products have more than one producer in China.

of health biotechnology patents by around 30% per year<sup>5</sup>.

A comparison of China's health biotechnology publications in international peer-reviewed journals with its patents granted in the United States Patent and Trademark Office (USPTO, Washington, DC, USA) between 1991 and 2002 provides another indicator of the country's innovation level in terms of scientific output and commercial potential (Fig. 1). Data derived from Science-Metrix show that China's scientific publications have been increasing, particularly in the late 1990s in the area of health biotechnology<sup>6</sup>. The country's patent activity is still modest but is increasing (based on a search of inventors' addresses in USPTO granted patents in health biotechnology carried out in July 2004, <http://www.uspto.gov/>).

### Main features of the Chinese health biotechnology sector

Bureaucracy at the central and local level in China has hampered implementation to promote biotechnology; nevertheless, initiatives to foster an innovation system that promotes private sector development have provided a solid basis for encouraging biotech venture creation. China's strong public education and research programs are driving innovation in both state-owned enterprises and the

burgeoning number of private enterprises. Although public discussion of health biotechnology issues has been limited, several initiatives are in place to inform the population more effectively about these technologies and their societal impact.

**Government.** The Chinese government has played a central role in promoting capacity building and innovation in the health biotechnology sector. However, with the 'nationalization' of science and technology in the 1950s, China's science and technology system experienced heavy top-down government intervention. This led to inflexible management structures, rigid hierarchies and inefficient allocation of resources that hindered both innovation and the industrialization of scientific achievements.

The origins of modern biotechnology research in the country can be traced to the late 1950s. In 1958, the policy of the 'Great Leap Forward' was launched in an effort to catch up with, and try to surpass, the technological development of industrially advanced countries. One part of the policy was an initiative to develop synthetic bovine insulin, which succeeded in 1965 when Chinese scientists successfully developed the first synthetic protein in the world.

After 10 years of hiatus following the Cultural Revolution, the 1978 State Reform

was passed to once again encourage Chinese science. In 1986, the government launched 'The National High Technology Research and Development Program of China,' also known as the '863' Program to promote development in six priority fields, including health (medical) biotechnology. Under the 'Ninth Five Year Plan' in 1997, the health biotechnology research system received increased financing and support to build up institutions and research capacity. As part of its program to establish a national system of innovation, the government now is promoting innovation and industrialization of the health biotechnology sector. This includes the Special Project on Biotechnology of 1999, which has promoted venture creation in this area<sup>7</sup>.

The government has also been active on the regulatory and legal front. In 1978, China began implementing a patent system, and a patent office was established in 1980. However, even with the 1985 Patent Law of the People's Republic of China, IP protection covered process, rather than product, innovations<sup>8</sup>. Since then, China has twice revised its patent system and now allows patenting of pharmaceutical products. With its accession to the World Trade Organisation (WTO, Geneva) in 2001, there is evidence China is moving quickly towards implementing the

## Box 1 China first to approve gene therapy

Late in 2003, the Chinese firm Shenzhen SiBono GenTech was the first firm in the world to obtain a drug license for a recombinant gene therapy<sup>26</sup>. China's State Food and Drug Administration approved the product, which is aimed at treating head and neck cancer. The product (Gendicine) comprises an adenovirus vector containing a *p53* gene. Clinical trials carried out to test the therapy over 5 years revealed an acceptable side effect profile.

The therapy cost the company more than \$9.6 million to develop, in addition to research grants from the government and over five years of clinical trials. In China, hundreds of thousands of patients die each year of cancer without having access to any kind of therapy. Gene therapy may be an attractive option although it has until now not lived up to its early promise. There are some recent promising signs, though, and currently, five gene therapies are being tested in China.

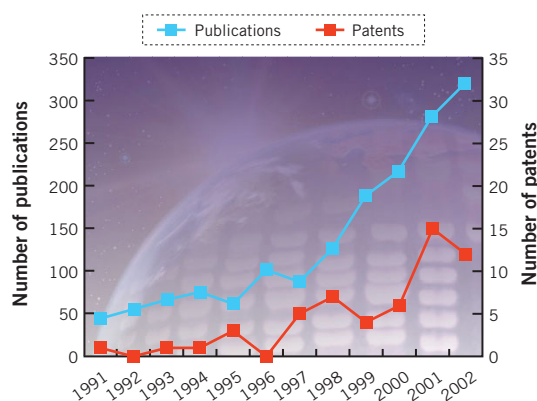
Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement for the 2005 deadline. For example, according to the 2003 annual report of the People's Supreme Court (Beijing), almost 24,000 IP cases were adjudicated between 1998 and 2002, signaling to biopharmaceutical firms China's seriousness in protecting IP<sup>9</sup>.

The government has also modified its safety regulations. In 2003, China reorganized its State Drug Administration (Beijing) into a new entity called the State Food and Drug Administration, which makes it possible to coordinate the regulations of new food and drug products.

**Research institutes and universities.** Under China's 'planned' economy, public research institutions played a central role in science innovation. There was a complex structure in which each institute had a relatively well-defined mission. The institutes fell under the control of various central and state governmental units, including The State Council (Beijing), Ministry of National Defense (Beijing), Ministry of Health (Beijing), Ministry of Education (Beijing) and Chinese Academy of Sciences (Beijing). Some of them, such as the institutions under the Chinese Academy of Sciences, were heavily involved in basic research. Others, connected with the different ministries or local governments, focused on applied research. Institutions within the Chinese Academy of Sciences (see Box 2) have played a major role in health biotechnology. From 1991 to 2002, they published about 20% of all the Chinese-authored papers in this field that appeared in the international peer-reviewed literature<sup>6</sup>.

In the 1950s, China adopted policies similar to those in the Soviet Union to encourage higher education development, creating both comprehensive and more

focused universities. However, the role of universities has changed extensively since the 1980s. Although they traditionally have concentrated on teaching and training human resources, universities are now moving into the research realm. According to data com-



**Figure 1** Chinese publications and USPTO patents in health biotechnology (1991–2002). Source: Publication data are from ref. 6. Patent data are from the USPTO.

piled by Science-Metrix, universities have been very successful in making this transition in health biotechnology, and they have become strong producers of new knowledge in this field<sup>6</sup>. In addition, they are expanding their teaching programs and setting up new educational options in biotechnology. An initiative that began in 2002 is aimed at training scientists and technologists for the life sciences industries. Thirty-six universities and colleges are participants in this special initiative. These programs combine teaching, research and industrialization<sup>10</sup>.

**Industry.** Health biotechnology industrialization was not initiated until after the mid-1980s but expanded rapidly when some of the public research institutes were transformed into enterprises for manufacturing medicines. During these first 10 years,

industry was mainly involved in copying products developed abroad, and government almost exclusively funded R&D activities. With the collaboration of Canada's International Development Research Centre (Ottawa) from 1996 onward, the Chinese government has increased its commitment to foster a national innovation system. Policy is focused on placing firms at the center of innovation in the country.

As a result of these initiatives, China's health biotechnology industry is rapidly expanding. Today, there are about 500 biotechnology firms in China, employing more than 50,000 people. Around 300 of those firms work in health biotechnology, and about half of them were established in the past 5 years<sup>5</sup>. In a recent Ernst & Young report, China/Hong Kong had the second largest biotech sector (behind Australia) in the Asian region<sup>11</sup>. With biotechnology identified as a strategic target by the government, this new approach is expected to develop and commercialize indigenous health biotechnology products that are internationally competitive.

There are two main types of health biotechnology firms in China. The first type consists of state-owned enterprises developed from the former public research institutions. They typically receive generous government support, are well equipped, operate in a policy environment that is favorable to them and have an advanced technological capacity. Many of them, however, suffer from inflexible management structures and have relatively limited innovation potential.

The second type of firm is the small private enterprise, often set up by former employees of public research institutes or by Chinese professionals who have returned from abroad. The latter group brings into the country technological and management knowledge from overseas and promises to become a new force in the sector. In addition, operations of certain foreign firms, including multinationals, are being established in China, including Pfizer Pharmaceuticals (Beijing), Glaxo SmithKline China (Beijing), Novartis Pharmaceutical (Beijing) and Merck China (Shanghai). Most of these firms collaborate with Chinese health care biotechnology enterprises, and several have established joint ventures with domestic companies.

**The general public.** It is a matter of contention whether the political environment in China allows an open and critical discussion of the impact of health care biotechnology on

## Box 2 The Chinese Academy of Sciences spearheads innovation

The Chinese Academy of Sciences (CAS)<sup>27</sup> was established in 1949 in an effort to manage the nation's science and technology. Since the 1970s, CAS has been a significant actor in promoting and developing a research base for China's economic and social needs through its numerous research bodies throughout the country. The academy's research, education and training activities are diverse and cover a broad spectrum of scientific fields. It has also been involved in policy innovation, including the restructuring of research institutions, restoring the graduate student system and reforming the 'closed' system of innovation. It provides support to other research institutes, including the Beijing Genomics Institute, which was founded by overseas Chinese scientists in 1999, and

was involved in the Human Genome Project. CAS is also involved in promoting scientific collaboration with developed and developing countries.

The Shanghai Institutes for Biological Sciences (SIBS) is a key actor in health biotechnology within CAS. This R&D organization consists of several research institutes, including the Institute of Biochemistry and Cell Biology, the Institute of Neuroscience, the Institute of Medica Materia, the Health Science Centre and the Institute for Nutritional Science. These institutes focus on eight key research fields, including functional genomics, proteomics, and bioinformatics; brain development and functions; and biotechnology development.

society. Yet, the Chinese government has made some efforts to encourage public engagement in science and technology. These include suggestions through the Internet on how the country should rebuild its science and technology by 2020 (ref. 12). China has also introduced tax measures to promote science communication. A new law will exempt any science museums, planetariums and laboratories in colleges and research institutions from import duties and value-added tax if they regularly engage in science communications aimed at the public<sup>13</sup>.

### Main challenges for development

Although there has been rapid growth in the Chinese health care biotechnology sector in recent years, the scientific excellence and expertise available in universities and public research institutions has not been exploited to its full potential. In addition, although an increasing number of expatriate scientists are returning to China to form startups, the proportion of Chinese scientists that work and study abroad may be limiting growth of the national health care biotechnology sector. The creation of new ventures in technology and health care is also limited by insufficient venture capital and a lack of exit options for investors. Health care biotechnology enterprises find it particularly difficult to attract investment because of the short-term expectations of the Chinese investor community.

**Limited domestic collaboration.** Experts in China have singled out the limited collaboration among different actors within the health biotechnology sector as the foremost challenge to its development (see Box 3). In particular, universities and public research institutions carry out world-class research, but their activities are not connected to the budding industrial sector. Patent statistics reveal that public research institutes and

universities own 80% of all biotechnology patents<sup>14</sup>. Only 6% of new biotechnology therapeutics and vaccines in China are the result of joint developments by universities and enterprises<sup>5</sup>.

In an effort to encourage domestic collaboration, the government has established programs and initiatives such as the National Engineering and Technique Research Centre (Beijing), the Research Center of Engineering & Technology for Medical Bioengineering (GuanZhong City, China) and several incubator institutions. There are signs of increasing collaboration. In 1991, only 13.6% of all the articles published by Chinese scientists in the international peer-reviewed literature included authors from more than one institution, but by 2002 the number had risen to 30% (ref. 6).

**Limited funding.** The shortage of financing options creates another major bottleneck for the health biotechnology sector in China. The government remains the main source of funding for R&D and commercialization.

In terms of R&D, insufficient and short-term funding has been criticized as a major cause of China's low scientific impact<sup>15</sup>. Moreover, with direct government control over research, major funding is generally awarded to projects clearly defined by the government and scientific administrators wield enormous power over the allocation of resources<sup>16</sup>.

The government is slowly reducing its dominant presence and encouraging private sector investment in high-technology enterprises in the country. For example, in the early 1990s, the State Science and Technology Commission (Beijing), the Ministry of Finance (Beijing) and the Industrial and Commercial Bank of China (Beijing) set up the National Science and Technology Venture Capital Development Centre (Beijing) to promote industrialization of high tech in the country. In its early days, most funding originated from the government, but over time it also came from other channels, including national

## Box 3 SARS outbreak reveals collaborative flaws

During the SARS outbreak in China, the Beijing Genomics Institute (BGI) made a great effort to find cooperative partners to sequence the SARS virus. The institute is well positioned to work in this field in terms of qualified research personnel and research infrastructure. Early in the SARS outbreak, BGI staff members traveled to the epidemic center in Southern China to get virus samples, only to come back empty-handed. The official reason given was that the safety regulations banned the transfer of the virus, but suspicion was rampant that competition between research institutions and political influence hampered the collaboration. "It's like you have a lawnmower in your hand, but other people are trying to do the job with paper cutters," says Yu Jun from the BGI. The virus did not enter BGI until a group at the BCCA Genome Sciences Centre in Vancouver, Canada had posted the entire genome sequence of the virus on the Internet. With more cooperation, coordination and political will, the Chinese group would have had an opportunity to showcase Chinese science all over the world and help in an initiative to battle a disease that was most devastating to the Chinese population<sup>28</sup>.

enterprises, foreign-funded organizations and financial organizations<sup>17</sup>.

Nevertheless, Chinese firms still have very limited access to venture capital. Investors in China are focused on returns on investment that can be had more rapidly than typical for health biotechnology ventures, which are renowned for their risky nature and protracted development times<sup>18</sup>. Foreign investors have also been reluctant to enter the Chinese venture capital market. The lack of exit strategies that would allow investors to pull out with their capital gains discourages foreign venture capitalist funding. In addition, interactions between foreign investors and Chinese entrepreneurs are complicated by cultural differences in how business is conducted and remaining uncertainties in IP laws<sup>19</sup>. As a consequence of these conditions, Chinese companies have steered away from high-risk, capital-intensive R&D activity in health biotechnology and toward industrialization of more mature (less risky) technology (e.g., generic manufacture).

**Brain drain.** China has stressed higher education and has actively promoted foreign education for its citizens. In the early days following the Communist Revolution, Chinese students went mainly to the Soviet Union and Eastern European countries, but since the 1980s, students have been departing for the United States, Japan and Western European countries.

During the 1980s and 1990s, there was a massive increase in the number of Chinese students studying abroad, and many of these have not returned home. China's Ministry of Personnel estimates that about 580,000 Chinese students have gone overseas to study since the late 1970s, with only about 160,000 returning<sup>20</sup>. Of the nearly 300,000 Chinese students overseas at present, one-third of them are involved in the biotechnology field<sup>21</sup>.

### Conclusions

China is a populous country, with a population of more than 1.3 billion, highly developed public education and research institutions, and rapid economic growth (gross domestic product grew more than 7% from 1998 to 2002). The size and power of the Chinese economy may mean that many aspects important in encouraging growth of the health care biotechnology sector in China may be difficult to implement in less populous countries.

**Provide long-term government support.** The Chinese government has supported health biotechnology innovation in the public and private sectors from the mid-1980s,

and this has provided the necessary knowledge capacity to make a growth of enterprises in the health biotechnology sector possible. China has been willing to take risks and support uncertain research fields, and it has been willing to prioritize its support. By channeling resources, it has built up strong capacities in promising fields of health biotechnology (for example, stem cells or genomics). Many of these fields are still under development and have not yet produced an impressive list of health biotechnology products, but by continuing to support them, China is making bold efforts to invest in the future.

In particular, China has kept a focus on stimulating the formation and innovation of high-tech enterprises. More recently, an increased emphasis in policies to foster venture creation and to transform research institutions into enterprises is helping a strong manufacturing base evolve into an

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Expatriates are likely to  
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innovation in the Chinese  
health biotechnology sector.

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engine of innovation. Past problems in knowledge sharing between the private and public sectors are being addressed by encouraging collaborations among universities, public research institutes and companies. There has been a substantial increase in such linkages since the country started to focus on more systemic innovation.

**Attract expatriate professionals.** From the late 1990s, the Chinese government has taken active steps to encourage expatriates to return home. This includes such incentives as government financing for scientists who wish to set up laboratories in China and support programs to facilitate entrepreneurs interested in setting up startup companies. There is evidence that expatriates are increasingly returning. For example, in 2002, 18,000 expatriates returned to China, twice the number that returned in 2000 (ref. 20). In Shanghai alone, more than 1,700 firms have been established by expatriates<sup>22</sup>. Returning professionals include a number with research and business experience in health biotechnology. For example, Jing Cheng, who pioneered the development of laboratory-on-a-chip systems when working for Nanogen (San Diego, CA)<sup>23</sup>, is currently the CEO and CTO of state-funded Capital Biochip (Beijing), and Huanming Yang, who returned to China after studying in

Denmark and working on pioneering research at prestigious institutes in France and the United States, is now the director of the Beijing Genomics Institute/Genomics and Bioinformatics Centre at the Chinese Academy of Sciences (Beijing)<sup>24</sup>.

It has been only a few years since this policy of actively encouraging expatriates to return to China has been in operation, and the expatriates are already making their mark. In years to come, these individuals are likely to be a strong driver for promoting innovation in the Chinese health biotechnology sector.

**Biotechnology development must go hand-in-hand with regulation.** Safety concerns play a central role in promoting successful new technologies like health biotechnology. It is always risky to be at the forefront of a new field and it is therefore important that as health biotechnology progresses appropriate policies and facilities are set up to ensure the safety of the new products. With new developments such as the introduction of gene therapy products, a strict and competent regulation regime is an essential prerequisite. China has been active in modifying its safety regulations and has set up a number of new regulations and laws to direct the development of the technologies. They include, for example, 'guidelines on the technological requirements of the clinical research on new preventative biological products,' 'essentials of the quality control on the recombinant DNA products in human therapy' and a new drug administrative law. In 2003, China also reorganized its State Drug Administration into a new entity called the State Food and Drug Administration (Beijing), which makes it possible to coordinate the regulations of new food and drug products.

**Leverage China's population base.** Having the world's largest population has been an asset to China in developing its health biotechnology sector. Local companies have a large domestic market for their products; in fact, most Chinese companies in health biotechnology focus entirely on the local market. Many of the new health biotechnology products in China have such a large market potential that several domestic firms produce them. For example, 16 firms are involved in producing recombinant human granulocyte colony-stimulating factors that stimulate the generation of white blood cells. The large population in China has also attracted many foreign firms, including large pharmaceutical firms that have established joint ventures with Chinese companies. This has given China access to new technology and management expertise.

Not only is the large population an asset in marketing products, but also it is an asset in developing and testing them. The country has more than 50 different ethnic groups and a number of homogeneous populations that can make it easier to identify disease genes. This is a great resource to develop therapeutics and diagnostics based on genomics. The large population also makes it easier to arrange clinical trials, and in the age of genomics, targeted clinical trials based on the genomics characteristics of the population will play a key role in health biotechnology. Attracting international linkages in terms of researchers and firms based on this advantage is also promising in that, as the Chinese population shows an increasing incidence of diseases of relevance to Western companies and their markets (e.g., there is a growing rate of cardiovascular disorders in China<sup>25</sup>), foreign researchers and companies are also to be more likely to form linkages with Chinese companies and institutions. The population advantage of China in health biotechnology is therefore likely to increase in the years to come.

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