China's leap forward in biotechnology

An interview with Zhu Chen, Director of the Chinese National Human Genome Centre of Shanghai and Vice President of the Chinese Academy of Sciences

EMBO reports: After China joined the Human Genome Project, it contributed around 1% of the whole sequence. That is quite a major achievement for an emerging economy. Why did the Chinese government decide to contribute such a considerable effort to this international project?

Zhen Chu: There are two reasons. China is the most populated country in the world. We have 56 ethnic groups and we think that these represent an important genetic resource that can be used to study the history of the population and many important biological traits, including human diseases. We also need to increase our capacity for building a knowledge base for the further development of biomedicine in China. We think that the Human Genome Project gives us a good opportunity to make a leap forward in the biological sciences and in technology development. We have lost opportunities in the past. There was no research during the so-called cultural revolution, and Lysenkoism in the former Soviet Union had an influence on China as well. So genetics and molecular biology were missing during that period. If we take this opportunity now, then we may promote the development of biotechnology in China and catch up to the advanced world's level.

ER: But to turn knowledge into new products, you need support and interest from industry. As China is still a developing country regarding biotechnology, how does the government plan to make sure that new products are developed?

ZC: Our policy is that we have to set limited but achievable objectives in the area of basic research. Much attention has been paid to technology transfer and

industrialization of research results. To promote this, the Chinese Academy of Sciences encourages scientists from research universities and research institutions to use their intellectual property. But the big problem for industry in China, particularly high-tech industry, is innovation. Therefore, the Chinese government decided about four years ago to establish a national innovation system and the Chinese Academy of Sciences was the first to propose a pilot project for the knowledge innovation programme. As a result, the funding for the Chinese Academy of Sciences has now almost doubled and we are setting up new mechanisms to make better use of the resources. For example, we have introduced systems to encourage competition and objective evaluation.

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ER: How does this work? By classical peer review?

ZC: Peer review and review from international experts. And we are trying to establish evaluation systems using both quantitative and qualitative criteria, such as the number of publications, the impact factor of the journals and the number of patents. But the most important thing is what kind of scientific achievements are obtained by our institutes. And recently, there has been another initiative from the Ministry of Public Health to initiate a National Institutes of Health China project. All these reflect a strong commitment by China to enhance the knowledge base and the capacity for innovation. Furthermore, we have introduced policies to stimulate technology transfer. Scientists are encouraged to establish their own companies, and they can be shareholders while keeping their academic positions for a limited time. Another good thing is the public-private partnerships to boost biotechnology in China.

ER: Do these start-up companies get financial support from the government? What role does venture capital have in China?

ZC: In China, we have different kinds of venture capital. Some are set up by the government, and there are venture capitals set up jointly by government agencies and industry. The private investment into R&D (research and development) is still relatively low, but I think in the future this will increase. I have to say that the private sector in China is taking a more and more important role in our economic growth. But I also have to point out that the funding situation is far from satisfactory, because most Chinese companies are not strong enough and want quick returns.

They invest their money today and they want to see returns tomorrow, so scientists doing both science and business are under high pressure.

ER: So there needs to be more awareness that biomedical research takes time to be turned into products?

ZC: Yes, when we meet with entrepreneurs in China we often point out that for information technology there could be a relatively rapid recovery of investment. But if you look at the lifetimes of these products, they are very short. For biomedical products you need more time for research and clinical studies, but if it is a good product it will have a long lifetime. I always take the example of aspirin, which has been used for over 100 years and is still a very good drug. So we need more education. We need more interaction between research, industry and the public to increase social awareness.

ER: You mentioned earlier the goal of finding therapies against diseases, so what are the special medical problems in China that you need to address?

ZC: China almost has a dual society structure. In the eastern part, particularly in the big cities such as Beijing and Shanghai, disease profiles are now very similar to those of developed countries. But if you look at the western part of China, there are still many poor regions that have diseases of developing countries. In general, we have to deal with diseases of developing countries and we also have to cope with diseases related to modern society—obesity, diabetes, hypertension, cardiovascular disorders and certain types of cancer. In addition, we have new diseases, most notably AIDS, which is not trivial. According to the Chinese government, there are about a million people in China infected with HIV while experts from the WHO (World Health Organization) estimate it could be 2 million. But the problem is the growth rate of 40% a year. If we cannot stop this dangerous trend, then by 2010, China will have 10 million HIV-positive carriers and will be the country most affected by AIDS.

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ER: You are the Director of the Chinese National Human Genome Centre in Shanghai. What is the focus of your centre in disease research?

ZC: Actually, I have been the Vice President of the Chinese Academy of Sciences for two years now, but I still keep the position of the Director of the Human Genome Centre of Shanghai. There are two other centres in Beijing; one is the Chinese Human Genome Centre in Beijing, and the other is the Beijing Genome Institute affiliated to the Chinese Academy of Sciences, and we all share tasks. For some of the big projects, for example the Human Genome Project, we work together; but the Beijing Genome Institute has strong sequencing facilities and bioinformatics tools, so in the future they will be more orientated towards large-scale operations, such as sequencing and annotation. The Shanghai centre is particularly orientated to medical genomics, with half of the scientists coming from basic research and half from medical research, and we have good links to the medical centres in Shanghai. We think in functional genomics the best model will be to use human diseases. Not only can we get a better understanding of the structure–function relationship and the genotype–phenotype relationship, but also it will allow us to study disease markers and drug targets. For example, my centre recently identified a gene responsible for atrial fibrillation (AF). AF is the most common chronic arrhythmia in humans. However, there was no molecular basis for this disorder. Through analysis of a large family with inherited AF, we now have the first molecular explanation. At the same time, we identified a gene coding for an ion channel as a potential drug target. In the future, we are going to tackle not only monogenic diseases, which are relatively rare, but also more polygenic diseases, such as hypertension, obesity, diabetes and cancer. In China, we have to take advantage of our huge population, particularly in the western part, where we still have many isolated populations, representing a precious genetic resource.

ER: Similar to the Icelandic population...

ZC: In China, we have dozens of such isolated populations and we have to make use of them. In general, we think genomic research in China should include sequencing, gene identification and functional

analysis, proteomics, structural genomics and, in particular, medical genomics.

ER: You mentioned discovery of disease markers and potential drug targets, but many of these are often protected by patents. Do you see this as a problem for the development of treatments for the diseases that you are interested in?

ZC: This is an important issue. I have to say that in China, patenting a gene is not easy. Basically, the Chinese Patent Office has adopted policies similar to the European Patent Office. In this sense, if you cannot tell us about function and utility, it is not a patentable discovery. Even for disease-related genes, you still have to point out the utility—whether you can use them for diagnostics or as a drug target. Therefore, first of all the international community needs an appropriate assessment of patent issues related to genes. And second, even if the sequences are patented, the function should be a different issue. I think the analysis of the involvement of genes in human diseases could be a new approach to demonstrate function. To do that in China, we established a nationwide sample collection network and we observe the international consensus on ethics, such as informed consent.

ER: Is there a public debate in China about such ethical issues in biomedical research?

ZC: This is something relatively new to China. That is not to say that we don't have the concept of ethics—if you look at the writings of Confucius, they are full of ethical concepts. In traditional Chinese medicine, there is a famous saying that to practise medicine is to do something of benefit, so I think China does consider ethics. Since Dolly was cloned five years ago, more concern has been paid to biotechnology, and the bioethics issue has become obvious in China. There have been many debates, but maybe not at such a deep level as in western countries. Also, concern has been drawn to the issue of genetically modified (GM) organisms. The Chinese government and the scientific community are now working very closely to draft guidelines, and the state council issued strict regulations for GM crops in 2001. Our policies encourage basic research, but the field trials are subject to strict regulations. So far, only transgenic cotton has been used in agriculture, and half of these plants are from the United States. It's like facing the challenge from outside.

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ER: What about stem-cell research? *Nature* recently published that a Chinese researcher had created a chimera by transferring a human nucleus into a rabbit egg.

ZC: Stem-cell research is a big and complicated issue. In China, generally speaking, there hasn't been strong opposition to the use of stem cells for research, which is why some scientists practised nuclear transfer from human to animal cells. But we need formal regulations for that kind of research. Immediately after Dolly, the Chinese government made a statement that reproductive cloning is not supported, is not advocated, is not favoured. Early in 2002, the Chinese representative at UNESCO (the United Nations Educational, Scientific and Cultural Organization) reiterated this position. But regarding stem-cell research or nuclear transfer, the government has not yet issued guidelines. However, there have been some efforts by the scientists themselves. These guidelines were prepared by the Department of Ethical, Legal and Social Issues of the Chinese Human Genome Centre in Shanghai after I proposed to set up this department. It's maybe the first one in China as an integral part of a research institution, because I thought that this issue was so important. I was happy to see that report in *Nature* because it mentioned the Shanghai guidelines.

ER: Are you adopting some of the guidelines on stem cells and cloning that other countries have set?

ZC: Basically, we agree with the UK guidelines. You can manipulate the embryo for no more than 14 days—before 14 days there are no neuronal cells, so it is not considered to be a human being. Also, the guidelines state that nuclear transfer across species can only be used for basic research, not for any medical practice. Personally, I am not in favour of that kind of manipulation. That's why I suggested that we establish cell lines so that we can use nuclear transfer in human systems, and I am happy to learn that some new cell lines have been established in Shanghai. The message I would like to send out is that China should be and is a responsible country. On the other hand, we have to push our government. My basic attitude is

that freedom of research should be protected. However, research should be balanced with social acceptance, and science and technology should be used for the benefit of the community.

ER: One problem for China is the enormous brain drain of young scientists. The US National Science Foundation published data in 1999 that 33,000 scientists and students moved from China to the USA. How do you want to tackle this problem? How do you propose to keep these people in your country or attract them back?

ZC: We have to view these things comprehensively. On the one hand, it is true that many scientists go abroad. On the other hand, the resources for training and research in China, as a developing country, are quite limited. This means that sending scholars abroad is a good way to use global resources. Now the Chinese overseas scholars are considered to be a talented reservoir.

ER: But you have to lure them back.

ZC: Yes, the important thing is how to get these well-trained people to come back to the motherland. Over the past ten years, China has made major efforts in attracting these talents. In 1993, the Chinese National Science Foundation first launched a talent programme with an award for outstanding young scientists, and many institutions followed that model. In 1994, the Chinese Academy of Sciences launched the Hundred Scholars Project to support outstanding young scientists coming back to China. The budget package is quite good, about €250,000 for three years for their salaries and part of the housing and running costs of the lab, with additional support for equipment. They can also apply for grants through competitive channels. Actually, this policy has worked very well and we now have more than 700 talented researchers in the Chinese Academy of Sciences. Now each university, each research institution, has its own talent programme. As a result, many good scientists have been attracted back to the country, not just to rejoin academia, but also to set up start-up companies. We think in the future things will be more balanced. I particularly appreciate the scientific community and the governments of European countries, because their policy is to encourage foreign scholars to go back to their homeland after

their training to contribute to global collaboration. Several years ago, statistics from the Chinese embassy in France said that in that year, the number of scholars coming from China to France and returning to China was equal. I also heard of a similar situation in Germany.

ER: But you also have to give young scientists sufficient career options for them to come back.

ZC: These talent programmes have not only money, but more significantly, important positions. In the high-tech programme, many of the scientists who returned are now CEOs of companies. So they are considered a major driving force for the modernization of China and they enjoy very good social recognition.

ER: The Chinese Academy of Science restructured a few years ago and, at 42, you have been elected as the youngest member ever. Is this another way to make China more attractive for young scientists?

ZC: It is a good signal to rejuvenate our community, to give young people more opportunities. The good thing is that, after four years into the knowledge innovation project, the average age of our institute directors has been significantly reduced. I think the average age is now below 50. Nowadays, I think we have to pay attention to another tendency, which is when a young scientist returns to China or a young scientist makes achievements in China, immediately they are promoted to an administrative position. That's good for science but there should be a balance. Sometimes the scientists of the older generation complain that there isn't an outstanding old scientist award! Anyway, the investment for R&D is increasing. Two years ago, investment in R&D was 1%, whereas six years ago it was only 0.6%. The promise is that in the year 2005 it will be 1.5%. Hopefully, the 3% policy of the European Union will stimulate the Chinese government to invest even more. So it is possible with more funding, not only from the government but also from industry, that we will make China a great country for R&D in the future.

ER: Professor Chen, thank you for the interview.

The interview was conducted by Holger Breithaupt

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