



MONKEY KINGDOM

China is positioning itself as a world leader in primate research.

BY DAVID CYRANOSKI

An hour's drive from Kunming in southwestern China, past red clay embankments and sprawling forests, lies an unusual zoo. Inside the gated compound is a quiet, idyllic campus; a series of grey, cement animal houses stack up on the lush hillside, each with a clear plastic roof to let in the light. This is the Yunnan Key Laboratory of Primate Biomedical Research, and its inhabitants are some 1,500 monkeys, all bred for research.

The serenity of the facility belies the bustle of activity within. Since it opened in 2011, this place has quickly become a Mecca for cutting-edge primate research, producing valuable disease models and

seminal publications that have made its director, Ji Weizhi, a sought-after collaborator. Its campus houses a collection of gene-edited monkeys that serve as models of Duchenne muscular dystrophy, autism and Parkinson's disease. Ji plans to double the number of group leaders working there from 10 to 20 in the next 3 years, and to seek more international collaborations — he already works with scientists in Europe and the United States. “In terms of a technology platform, Ji is just way ahead,” says one collaborator, cardiologist Kenneth Chien at the Karolinska Institute in Stockholm.

Ji is not alone in his ambitions for monkey research. With support from central and local governments, high-tech primate facilities have sprung up in Shenzhen, Hangzhou, Suzhou and Guangzhou over the past decade. Last month, the science ministry approved the launch of a facility at the Kunming Institute of Zoology that is expected to cost millions of dollars to build. These centres can provide scientists with monkeys in large numbers, and offer high-quality animal care and cutting-edge equipment with little red tape. A major brain project, expected to be announced in China soon, will focus much of its efforts on using monkeys to study disease.

The enthusiasm stands in stark contrast to the climate in the West, where non-human-primate research is increasingly stymied by a tangle of regulatory hurdles, financial constraints and bioethical opposition. Between 2008 and 2011, the number of monkeys used in research in Europe declined by 28%, and some researchers have stopped trying to do such work in the West.

Many have since sought refuge for their experiments in China by securing collaborators or setting up their own laboratories there. Some of the Chinese centres are even advertising themselves as primate-research hubs where scientists can fly in to take advantage of the latest tools, such as gene editing and advanced imaging. “It could be like CERN in Switzerland, where they set up a large facility and then people come from all over the world to get data,” says Stefan Treue, a neuroscientist who heads the German Primate Center in Göttingen, Germany.

With China fast becoming a global centre for primate research, some scientists fear that it could hasten the atrophy of such science in the West and lead to a near monopoly, in which researchers become over-reliant on one country for essential disease research and drug testing. “Governments and politicians don't see this, but we face a huge risk,” says Erwan Bezdard, who researches Parkinson's disease at the French national biomedical research institute INSERM in Bordeaux, and has set up his own primate-research company, Motac, in Beijing. Europe and the United States still have the lead in primate research, he says, but this could change as expertise migrates eastwards. “China will become the place where all therapeutic strategies will have to be validated. Do we want that? Or do we want to stay in control?”

SIMIAN SIMILARITIES

For decades, researchers have relied on monkeys to shed light on brain function and brain disease because of their similarity to humans. Growth in neuroscience research has increased demand, and although high costs and long reproductive cycles have limited the use of these animals in the past, new reproductive technologies and genetic-engineering techniques such as CRISPR–Cas9 are helping researchers to overcome these drawbacks, making monkeys a more efficient experimental tool.

China has an abundance of macaques — the mainstay of non-human-primate scientific research. Although the population of wild rhesus macaques (*Macaca mulatta*) has declined, the number of farmed animals has risen. According to data from the Chinese State Forestry Administration, the number of businesses breeding macaques for laboratory use rose from 10 to 34 between 2004 and 2013, and the quota of

animals that those companies could sell in China or overseas jumped from 9,868 to 35,385 over that time. Farm populations of marmosets, another popular research animal, are also on the rise.

Most monkeys are shipped to pharmaceutical companies or researchers elsewhere in the world, but the growing appreciation among scientists of monkey models has prompted investment by local governments and private companies in dedicated research colonies. The country's 2011 five-year plan singled out primate disease models as a national goal; the science ministry followed up by pumping 25 million yuan (US\$3.9 million) into the endeavour in 2014.

Scientists visiting China are generally pleased with the care given to animals in these facilities, most of which have, or are trying to get, the gold-standard recognition of animal care — accreditation by AAALAC International.

Ji's Yunnan Key Laboratory is the most active primate facility, but others are giving it competition. The new monkey facility at the Kunming Institute of Zoology was funded as part of the national development scheme for big science equipment that includes telescopes and supercomputers. The money will help the institute to double its colony of 2,500 cynomolgus monkeys (*Macaca fascicularis*) and rhesus macaques.

Zhao Xudong, who runs the primate-research facility, says that the plan is to “set it up like a hospital, with separate departments for surgery, genetics and imaging”, and a conveyer

belt to move monkeys between departments. There will be systems for measuring body temperature, heart rate and other physiological data, all to analyse the characteristics, or ‘phenotypes’, of animals, many of which will have had genes altered. “We are calling it the ‘genotype versus phenotype analyser,’” says Zhao. It will take ten years to finish, but he hopes to begin building this year and to start research within three. Other facilities, although smaller, are also expanding and diversifying. The Institute of Neuroscience in Shanghai plans to increase its population of 600 Old World monkeys to 800 next year and expand its 300-strong marmoset colony.

A QUESTION OF COST

Outside China, the numbers are heading in the opposite direction. Harvard Medical School closed its affiliated primate facility in May 2015 for ‘strategic’ reasons. Last December, the US National Institutes of Health decided to phase out non-human-primate experiments at one of its labs and subsequently announced that it would review all non-human-primate research that it funds. In Europe, researchers say, the climate is also growing colder for such research.

Costs are a major disincentive. In 2008, Li Xiao-Jiang, a geneticist at Emory University in Atlanta, Georgia, helped to create the world's first transgenic monkey model of Huntington's disease¹ with colleagues at Yerkes National Primate Research Centre. But Li says that it costs \$6,000 to buy a monkey in the United States, and \$20 per day to keep it, whereas the corresponding figures in China are \$1,000 and \$5 per day. “Because the cost is higher, you have to write a bigger grant, and then the bar will be higher when they judge it,” says Li. Funding agencies “really do not encourage large-animal research”.

For Li, the solution was simple: go to China. He now has a joint position at the Institute of Genetics and Developmental Biology in Beijing, where he has access to around 3,000 cynomolgus monkeys at a farm in Guangzhou and some 400 rhesus monkeys at the Chinese Academy of Medical Sciences' monkey facility in Beijing. He has churned out a series of publications on monkeys with modified versions of the genes involved in Duchenne muscular dystrophy² and Parkinson's disease³.

Neuroscientist Anna Wang Roe says that red tape drove her to China. Roe's team at Vanderbilt University in Nashville, Tennessee, is

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attempting to work out how modules in the brain are connected, and she estimates that she and her colleagues have spent 25% of their time and a good deal of cash documenting the dosage and delivery-method for each drug they administered to their monkeys, as required by regulations. “We record something every 15 minutes,” she says. “It’s not that it’s wrong. It’s just enormously time-consuming.”

In 2013, impressed by the collaborative atmosphere at Zhejiang University in Hangzhou, she proposed that it build a neuroscience institute. The next day the university agreed, and she soon had a \$25-million, 5-year budget. “Once the decision is made, you can start writing cheques,” she says. She is now closing her US laboratory to be the director of the Zhejiang Interdisciplinary Institute of Neuroscience and Technology, where she hopes to open a suite of the latest brain-analysis tools, including a powerful new 7-tesla functional magnetic resonance imaging device that she says will give images of the primate brain at unprecedented resolution.

Bob Desimone was similarly impressed with the speed at which China moves. As a neuroscientist who heads the McGovern Institute for Brain Research at the Massachusetts Institute of Technology in Cambridge, in January 2014, he had a ‘meet and greet’ with the mayor of Shenzhen. In March, the mayor donated a building on the Shenzhen Institute of Advanced Technology campus for a monkey-research facility, and the centre’s soon-to-be director, Liping Zhang, promised that it would be ready by summer. Thinking that impossible, Desimone bet two bottles of China’s prized mind-numbing liquor, *maotai*, that it wouldn’t be done in time. He lost. The group raised most of the \$10 million needed from city development grants, along with a small input from McGovern, and soon the first animals were being installed in the Brain Cognition and Brain Disorder Research Institute. “This place just makes things happen quickly,” Desimone says.

But money and monkeys alone are not enough to lead to discovery. Researchers say that China is short on talented scientists to take advantage of the opportunities provided by animal research. That’s why the organizers of the country’s new primate centres hope to attract an influx of foreigners to permanent posts or as collaborators. So far, many of those moving to China have been Chinese or foreigners with a previous connection to the country, but others are expressing interest, says neuroscientist Guoping Feng, also at the McGovern Institute. Already, the Shenzhen primate centre has recruited from Europe and the United States, and Desimone says that it will be “an open technology base. Anyone who wants to work with monkeys can come.”

EDITED MONKEYS

The rapid spread of CRISPR–Cas9 and TALEN gene-editing tools is likely to accelerate demand for monkey research: they are turning the genetic modification of monkeys from a laborious and expensive task into a relatively quick, straightforward one. Unlike engineered mice, which can be bred and sent around the world, “monkeys are difficult to send, so it will be easier for the PI or postdoc to go there”, says Treue.

Already, competition is fierce as researchers are racing for the low-hanging fruit — engineering genes with established roles in human disease or development. Almost all reports of gene-edited monkeys produced with these techniques have come from China. Desimone predicts that the pursuit of monkey disease models “could give China a unique niche to occupy in neuroscience”.

The cages of Ji’s facility are already full of the products of gene editing. One troop of animals has had a mutation genetically engineered into the *MECP2* gene, which has been identified as the culprit in humans with Rett’s syndrome, an autism spectrum disorder. An animal sits listless and unresponsive, holding tight to the bars of the cage as her normal twin sister crawls all over her. In another cage, a monkey with the mutation pumps its arm, reminiscent of repetitive behaviour seen in the

human disorder. Some incessantly suck their thumbs. “I’ve never seen that in a monkey before — never so constant,” says Ji.

Among the range of other disease models in Ji’s menagerie are monkey versions of cardiovascular disease, which he is working on in collaboration with the Karolinska Institute. And last year, Ji made the world’s first chimeric monkeys using embryonic stem cells⁴, an advance that could make the production of genetically modified animals even easier. The question now is whether these genetically modified monkeys will propel understanding of human brain function and dysfunction to a higher level. “You can’t just knock out one gene and be sure you’ll have human-like disease phenotype,” says Ji.

Researchers see an opportunity to understand human evolution as well as disease. Su Bing, a geneticist at the Kunming Institute of Zoology, is working with Ji to engineer monkeys that carry the human version of a gene called *SRGAP2*, which is thought to endow the human brain with processing power by allowing the growth of connections between neurons. Su also plans to use CRISPR–Cas9 to introduce human versions of *MCPH1*, a gene related to brain size, and the human *FOXP2* gene, which is thought to give humans unique language ability. “I don’t think the monkey will all of a sudden start speaking, but will have some behavioural change,” predicts Su.

INTERNATIONAL DIVIDE

Although the opportunities are great, there are still obstacles for scientists who choose to locate their animal research in China. Trying to keep a foot in two places can be challenging, says Grégoire Courtine, a spinal-cord-injury researcher based at the Swiss Federal Institute of Technology in Lausanne, who travels almost monthly to China to pursue his monkey research at Motac. He has even flown to Beijing, done a couple of operations on his experimental monkeys, then returned that night. “I’m 40 years old, I have energy in my body. But you need to really will it,” he says.

Another downside, says Li, is that policies can change suddenly in China. “There is uncertainty. That makes us hesitate to commit,” says Li, who has retained his post at Emory University. And the immunity that China’s primate researchers have had to animal-rights activism could start to erode, warns Deborah Cao, who researches law at Griffith University in Brisbane, Australia, and last year published a book on the use of animals in China⁵. People are starting to use Chinese social-media sites to voice outrage at the abuse of animals, Cao says.

China has competition in its bid to dominate primate research, too. Japan has launched its own brain project focused on the marmoset as a model: the animal reaches sexual maturity in a year and a half, less than half the time it takes a macaque. Some research facilities in China are now building marmoset research colonies — but Japan is considered to be several years ahead.

And some researchers want to ensure that such work continues outside Asia. Courtine says that he’s “fighting to keep alive” a monkey-research programme he has in Fribourg, Switzerland, because he thinks it’s important to have a division of labour. “Research that requires quantity, I’ll do in China. I would like to do sophisticated work in Fribourg,” he says.

Back at his primate centre in Yunnan, Ji is sure that such work is already taking place. His dream, he says is “to have an animal like a tool” for biomedical discovery. He knows there is a lot of competition in this field, especially in China. But he feels confident: “The field is wide, and there are many, many projects we can do.” ■

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