



# Monkey business

China is preparing to become the world's supplier of research primates. But are Western scientists ready to buy? Apoorva Mandavilli reports.

The weather in Kunming is pleasant year-round. The city, located in the southwest of China, has a backdrop of mountains, wide boulevards and lovely parks and is famous for its flowers. Where Beijing is noisy and polluted, Kunming, dubbed the 'City of Spring', is quiet and beautiful.

Kunming has lately seen more than its usual share of visitors. In the past months, representatives of several large pharmaceutical companies, including AstraZeneca and Wyeth, research institutes and individual scientists from the US and Europe have all visited the city—in their quest for monkeys.

In the forests on the outskirts of the city is the Kunming Primate Research Center, which houses about 1,800 monkeys. Because the climate is warm all year, the monkeys are kept outside with enough space to run and play. A short drive away is the respected Kunming Institute of Zoology, a division of the Chinese Academy of Sciences.

There are several primate centers in China—although Kunming is the best-known—and they all offer immediate benefits. At approximately \$800, buying a monkey in China is roughly one-tenth as expensive as it is the US. Maintaining monkeys is similarly cheaper. Add trained scientific staff and an environment largely free of animal activism, and doing primate research in China seems to make good sense.

Little surprise, then, that monkey facilities are mushrooming in China. Bridge Pharmaceuticals, a California-based contract research organization, in November 2005 launched an animal center in Beijing, the first in China to be built to US specifications. Anthony Chan of the Atlanta-based Yerkes National Primate Research Center is teaming up with a new institute in Beijing to create monkey models for heart disease and diabetes. And Bruce Lahn, who in 2003 launched a stem cell research center at Sun Yat-sen University in Guangzhou, got so many requests for collaborations that he teamed up with his brother to launch a company called Cyagen.

"Ten years ago, the infrastructure wasn't there. Ten years from now, it might be too late," says Lahn, a geneticist at the University of Chicago in Illinois. "You don't want to come too early and be a guinea pig. But you don't want to be too late either."

By all accounts, it's not too early for an

individual researcher to collaborate with one of these centers. But China may still have some work to do before companies seeking monkeys for large-scale projects are ready to sign on.

"It will take a while before Chinese facilities and the situation in China improve to a point where people feel comfortable with it," says John Reid, director of Global Discovery Alliances for AstraZeneca. "I doubt that it fits everything that needs to fit in order to make it happen right now."

## Close to man

Nonhuman primates are the models of choice in several disciplines, including for the study of the brain and behavior, HIV/AIDS and other infectious diseases and for testing vaccines and drugs. In the US, a majority of academic research in monkeys is done at one of eight centers funded by the US National Institutes of Health (NIH). The centers together are home to more than 20,000 monkeys of more than of 20 different species, including rhesus and crab-eating macaques, spider and squirrel monkeys, tamarins and marmosets.

In 2004, scientists in the US used an estimated

54,998 monkeys. That number is expected to rise sharply in the next few years. Companies are increasingly turning to protein-based therapies, which are likely to elicit an immune response. By size, physiology and complexity, the mouse, most scientists' first choice in research, is a poor predictor of human's immune responses—a monkey delivers a much closer picture.

But with the prohibitive costs of maintaining monkeys, studies can quickly run up big bills. In China, however, toxicity tests in monkeys of new drugs average from \$2,000 to \$5,000 per monkey per trial. "That's definitely a role for China in cutting costs while maintaining quality," says Glenn Rice, president and chief executive officer of Bridge Pharmaceuticals.

Cost is definitely a big driver for drug makers seeking monkeys in China. But company officials are quick to point out that that benefit cannot come at the expense of the highest standards. They are also concerned that they may be seen as going to China because regulations there are lax.

"The issue is the global concern over animal rights," says AstraZeneca's Reid. "I think it's a big enough issue that if it's not handled carefully, it could negatively impact sales of pharmaceuticals globally."

AstraZeneca has for years had a conservative policy that excludes primate research, but has recently begun to reconsider that policy. For the company to partner with a Chinese center, Reid says, it would need to find a center that



**Tricky questions:** Primate research centers in China, like this one in Guangdong, are built to high standards. But are they good enough?

David Cyranoski



**Animal house:** There are several facilities in China with a few hundred monkeys or more. Some are just breeding facilities, but a few also have a research mission.

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meets and exceeds international standards for animal care.

**Natural advantage**

China is not the only country with monkeys. India has an overabundance of rhesus macaques, but has laws banning their export. Vietnam, Cambodia and Thailand harbor many monkeys, but don't offer a strong scientific base. China has several large and well-established primate centers that are affiliated with a research institute (see map), but are they up to snuff?

"I think that most facilities [in] China are not good enough as the visitors said," says Weizhi Ji, director of the Kunming institute. "However, I think in general my institute is ready in terms of cleanliness, safety and care of the monkeys."

Kunming, because of the linked Institute of Zoology, is undoubtedly the top contender for foreign collaborations. The center has a stem cell bank, rooms equipped to handle dangerous pathogens, and modern facilities. The center's officials have also invited several experts and freely solicited advice on how best the center can meet Western scientists' expectations.

"They know that if they want to be taken seriously, they have to work to the very highest standard," says one UK-based researcher who serves on the Kunming advisory board, and who wished to remain anonymous out of fear of animal rights activists. "In no way is this a cheap third-world kind of facility," the researcher says.

In the US, primate research is regulated by the Animal Welfare Act, which is enforced by the US Department of Agriculture. The law requires that every research institution have a committee to consider other alternatives, minimize pain and

distress, and oversee standards for research. The NIH also has a set of guidelines, to which institutions receiving federal funds must adhere. In addition to all this, an independent organization, dubbed the Association for Assessment and Accreditation of Laboratory Animal Care International or AAALAC, conducts thorough inspections and certifies the facilities.

If US scientists who receive NIH funds wanted to work in China, their institutional committees would still be required to ensure that the work met certain standards. Some Chinese centers, including Kunming, have negotiated with the NIH to sign a statement of compliance that says they meet the international guidelines. These guidelines, however, are broad, and don't cater to specific requirements.

No one disputes that overall, the centers in China get most things right. The cages are big enough and are kept in clean rooms with dim lighting, and the monkeys appear happy. But the devil is in the details. Most Chinese cages have bars made of plastic, for instance, but AAALAC prefers steel. How many times the air in the rooms is changed and what kind of air filters are used is another issue.

"What China probably needs to do is build new facilities from the ground up," says Rice, whose facility in Beijing was built to meet AAALAC standards. These small details, Rice says, are difficult to clone onto an existing facility. "You really have to start over."

For companies, Rice says, the fact that some of the centers are affiliated with the Chinese government may strike another note of caution. "If there's intellectual property leakage, who're you going to sue?" he asks. "How many people have successfully sued the Chinese government?"

**Strange encounters**

The worst-case scenario for any scientist who collaborates with a Chinese primate center is discovering that the monkeys are being mistreated. Visitors to these centers say they've never seen any signs of abuse, but a few recount having seen unusual incidents.

In one instance, a US-based neuroscientist visited Kunming in 2002. In one office, he says, he saw a monkey sitting next to an oscilloscope, a machine routinely used take physiological readings of brain cells. The monkey, which had implanted electrodes, was connected to the oscilloscope by a wire, but was not contained in any other way and its head was not held in place as would normally be expected.

The researcher, who did not wish to be identified, says the electrodes seemed to be positioned by a makeshift device made from a syringe, but the oscilloscope was nevertheless recording electrical discharges from single nerve cells. This was in a sense evidence that although these centers may need to straighten out their policies, he says, they are reasonably skilled scientifically.

The incident is bizarre, but not entirely without precedent, say others.

It's not unusual for researchers to get attached to animals and treat them as pets, notes Robert Desimone, director of the McGovern Institute for Brain Research at the Massachusetts Institute of Technology. Even in the US and Europe, Desimone says, the rules have only recently become as strict as they are now. He recalls that about 15 years ago, one researcher at a major American university used to have a monkey in a cage next to his desk.

Desimone has also visited Kunming and says everything he saw was modern and impressive. "I wouldn't have any hesitation based on the individual labs I've seen," he says.

Still, for pharmaceutical companies wary of any adverse publicity, there may be too many unresolved questions.

"Overall, none of them currently meet the international standards and that's going to be a big issue in getting them up to quality. I think it's too difficult, too risky right now," says Reid. AstraZeneca may collaborate with Chinese centers on small-scale research, Reid says, but larger projects will probably be shunted to existing facilities in the US and Europe.

In the meantime, the primate centers in China continue to welcome visitors and are trying to adapt to Western needs, says Kunming's Ji. "We still work hard to match the international standards, such as AAALAC standards, in details."

*Apoorva Mandavilli is Nature Medicine's senior news editor.*

*With additional reporting by David Cyranoski.*