

Vaccine Development With a Distinctly Chinese Flavor

Shao Yiming is heading efforts to develop HIV vaccines, and he's considering one approach that the West has all but abandoned

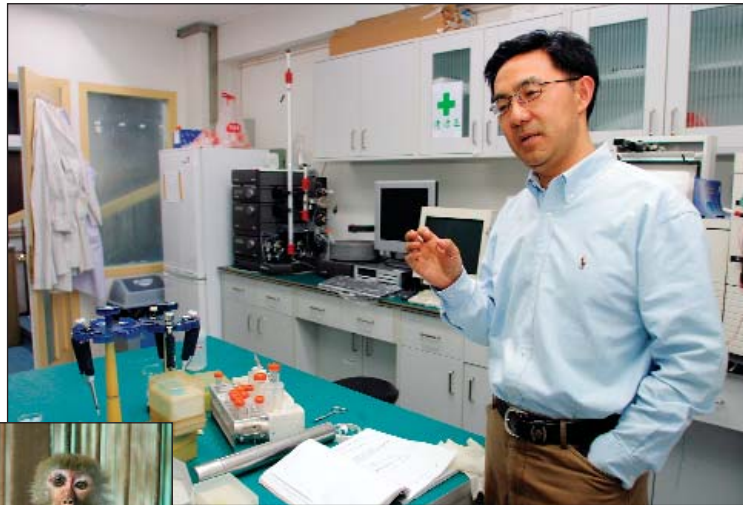
KUNMING—An unusual gray stone on the front lawn of the primate research center here is the first hint that the facility is not simply a clone of its Western counterparts. Carved with Chinese characters, the stone is a memorial to the center's monkeys, which serve as surrogate humans in biomedical research. Other centers may respect their experimental animals, but rarely with a memorial. And the difference is more than superficial: Even the AIDS vaccine work taking place in the center's laboratories has a uniquely Chinese cast.

For more than 2 decades, AIDS researchers have tested candidate vaccines on Indian rhesus macaques. But India, for political and religious reasons, banned their export in 1978, and many AIDS investigators today delay experiments because of acute shortages of the species. Researchers at the Chinese Academy of Medical Sciences' primate center here, however, face no such roadblock because they work with Chinese macaques, which they think may even prove a better model. And among the vaccine strategies they are pursuing is one that Western researchers have all but written off as too risky.

Like Indian rhesus macaques, Chinese macaques succumb to SIV, a simian cousin of HIV, but the human AIDS virus cannot copy itself inside their cells. To overcome this problem, researchers have combined genes from HIV and SIV to construct a hybrid virus known as SHIV, which causes an AIDS-like disease in Indian rhesus macaques. Now, a team led by Shao Yiming, a virologist based at China's Center for Disease Control and Prevention (CDC) in Beijing, is tailoring a similar hybrid virus for Chinese macaques. As part of a larger project backed by a grant from the U.S. National

Institutes of Health, the researchers have just begun to test whether this virus reliably causes disease in animals in the primate center's shiny new biosafety labs.

Many researchers look askance at results from SHIV tests in Indian macaques, arguing that the hybrid virus doesn't mimic HIV in humans closely enough. But Shao hopes to avoid at least one critical drawback. HIV exploits a unique cellular receptor to estab-



Primate boost? AIDS vaccine developer Shao Yiming hopes to develop a new animal model with the Chinese macaque.



lish an infection and then typically switches to a different one. Unlike other SHIV makers, Shao relied on a recently infected person for an HIV strain and confirmed that it used the proper receptor. Ronald Desrosiers, head of the New England Regional Primate Research Center in Southborough, Massachusetts, says if Shao makes a better SHIV model, "that would be tremendously useful."

In addition to his SHIV work, Shao is constructing AIDS vaccines for human tests. Furthest along is one designed to deliver a one-two punch to the immune system. After priming the immune system with a vaccine made from HIV genes stitched into a ring of bacterial DNA, a second shot presents the same genes spliced into vaccinia, the smallpox vaccine virus. Several other teams have developed similar "prime-boost" vaccines, but Shao is customizing his for China with HIV genes from a strain of the virus isolated

in Xinjiang Uygur Autonomous Region and a strain of vaccinia called Tiantan (Temple of Heaven) that formed the backbone of China's smallpox vaccination program. He hopes to begin human tests early next year.

In a more radical venture, Shao has teamed up with virologist Shen Rongxian of the Harbin Veterinary Research Institute in Heilongjiang Province to study a vaccine Shen developed against equine infectious anemia virus (EIAV). An attenuated form of EIAV is the only effective vaccine ever developed against a lentivirus—the family that includes HIV and SIV. Over the past 30 years, it has protected 75 million horses and donkeys.

Shao, Shen, and co-workers from three U.S. universities will compare the vaccine virus to the "wild-type" strain to try to tease out which genetic factors make EIAV pathogenic. They will also try to deduce the immune responses that lead to protection, and how EIAV protein structures compare to their HIV counterparts. The goal is to apply the findings to the design of HIV vaccines. "It's an extremely important model to understand the mechanism of protective vaccine immunity," says collaborator Ronald Montelaro, an EIAV expert at the University of Pittsburgh in Pennsylvania. "It's an experiment we all should learn something from."

Ideally, Shao says he hopes the result will be a vaccine that uses only the HIV parts needed for protection. But if that strategy fails, he says they plan to move forward with a live, weakened HIV vaccine. This approach is highly controversial, in part because Desrosiers made attenuated SIV vaccines that seemed safe but then reverted to virulence. Shao says EIAV proves that it is possible to make a safe live lentivirus vaccine. He stresses that they would proceed cautiously, testing the vaccine extensively in monkeys. "It's pretty exciting to think about the possibilities," says Desrosiers. "It's not an unrealistic scenario."

Shao says the sense of urgency about developing an effective AIDS vaccine is far greater in China than in countries with more contained epidemics. "I think the live attenuated approach has been dropped too early in HIV research because of the safety concerns," says Shao. "In science, nothing should be considered impossible until we try it."

—JON COHEN