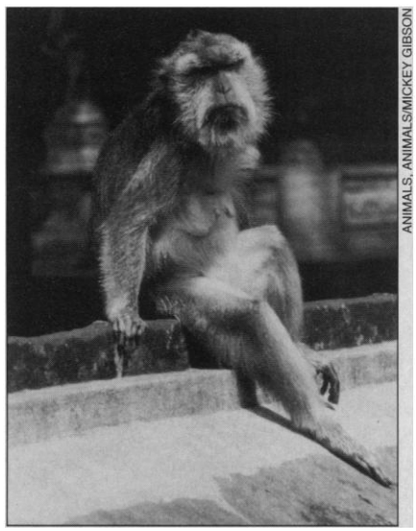
AIDS RESEARCH

Monkey-Human Viral Hybrid Is New Weapon in AIDS Fight

On the eve of the Eighth International Conference on AIDS in Amsterdam, researchers at Boston's Dana-Farber Cancer Institute have announced that they have made a combination human-monkey AIDS virus, which they believe will be a powerful new weapon in the battle against the pandemic. Called "SHIV" by the group, the weapon is a hybrid of the human AIDS virus, HIV-1, and its simian cousin, SIV. In the June issue of the *Journal of Acquired Immune Deficiency Syndrome* (*JAIDS*), the team reports that a genetically engineered SHIV has persistently infected four cynomolgus monkeys, a relatively plentiful species.

Dana-Farber's Joseph Sodroski—whose graduate student, John Li, engineered the SHIV—adds that if these monkeys end up getting sick from SHIV, the model may help solve the mystery of how the AIDS virus savages the immune system. "I'm ecstatic," says Sodrowski's colleague William Haseltine, who is both a coauthor of the SHIV paper and an editor of *JAIDS*. "What this does is break a bottleneck in vaccine testing." But at Amsterdam, Haseltine's enthusiasm could be tempered a bit by a competing group of Japanese researchers —who claim they developed a similar combination virus first but had trouble publishing their results while the Americans hustled into print.



ANIMALS, ANIMALS/MICKEY GIBSON

A better AIDS model? The cynomolgus monkey appears to be persistently infected by the hybrid virus.

The bottleneck Haseltine refers to is the fact that the only animal model so far available for testing HIV-1 vaccines has been the chimpanzee, a rare and expensive species that can be infected with HIV-1 but does not seem to develop AIDS. The chimp model, in fact, has so many limitations that most AIDS vaccine work has been done in monkeys using the monkey virus, SIV. Though SIV handily infects several monkey species and causes disease, as a model for human infection it has the handicap of having significant genetic and functional differences from HIV-1.

So does SHIV, but the Dana-Farber group argues that it has enough in common with HIV-1 to be, as they write, "a valuable model for study of the efficacy of anti-HIV-1 vaccines." And in that view they have supporters, one of whom is Alan Schultz of the National Institute of Allergy and Infectious Diseases: "It's so sweet, it's so fantastic," says Schultz, acting director of the vaccine branch at the Division of AIDS. Schultz is particularly elated because real-life tests of AIDS vaccines are right around the corner and SHIV could be the route to revealing which vaccines have the best chance of working—a route researchers desperately need. "There's virtually no way right now to evaluate the efficacy of HIV-1 vaccines in an animal model," laments Schultz.

Masanori Hayami, head of the Japanese group developing chimerics at Kyoto University's Institute for Virus Research, agrees the SHIV data "looks good." But his group came up with the original idea for a chimeric SIV-HIV-1 virus—a point that the Dana-Farber team concedes—and has made several variations. Hayami's group even came up with a hybrid much like SHIV, which they call NM-3n, that they have isolated from a cynomolgus monkey that was infected 37 weeks ago. But the Americans have published their animal data and the Japanese haven't, and that has produced some ill feelings.

Hayami contends his group was on the verge of publishing their animal data after 4 years of work and that the Dana-Farber group "hurried their publication" in *JAIDS* because they "know what we are doing." He adds: "It is our surprise [that] Dr. Sodroski's paper was received [by JAIDS] May 1, accepted on May 7 and published in the June issue. Usually we must wait for the answer for 2 to 3 months and it takes a half year for publication." The Japanese paper is now in press at the *Journal of General Virology*.

Sodroski acknowledges that "to be in a competitive position" his lab turned on the afterburners. "Were we interested in rapid publication?" he asks. "Sure we were." But both Sodroski and Haseltine emphasize that their paper was peer reviewed and they believe their chimeric is better. "We have a great deal of respect for Dr. Hayami," adds Haseltine. Attendees at the Amsterdam meeting will have a chance to hear the American and Japanese teams describe their chimerics and, perhaps, divvy up credit.

They will also hear more about the fact that SHIV is not the only recent development that could help break the AIDS vaccine testing bottleneck. Only weeks ago, a University of Washington research team working with pigtail macaque monkeys reported they have a promising new model for testing HIV-1 vaccines (*Science*, 19 June, p. 1630 and 3 July, p. 103). But some researchers doubt that the macaque model will pan out. And in any case, some researchers think introducing SHIV into readily available species of monkeys could be more practical than attempting to infect the pigtail with HIV-1 since the latter, though not endangered, are still in short supply.

SHIV is essentially the monkey virus SIV dressed in the outer, or envelope, proteins of the human AIDS virus. It contains two critical genes from HIV-1—*tat* and *rev*—that help to regulate viral replication. The value of this "chimeric" virus lies in the fact that envelope proteins are key components of many experimental HIV-1 vaccines. HIV-1 cannot infect cynomolgus monkeys, but a vaccine made from HIV-1 envelope proteins should stimulate their immune systems. If the vaccine works, then when the monkeys are later "challenged" with the chimeric virus, they should be able to resist infection.

Of course, it will be a while before anyone can say whether SHIV has proven out. Norman Letvin of Harvard's New England Regional Primate Research Center, who infected monkeys with SHIV and continues to evaluate them, says the animals have had the virus in their blood cells for more than 3 months now. "We're hoping they will remain viremic and get sick and die," says Letvin. "If both of those occur, we'll be in great shape."

And what if both the SHIV model and the pigtail macaque work hold up? A debate between partisans of each school likely will follow, because, to anticipate only one argument, since the current chimeric model is based on HIV-1 envelope proteins only, it cannot be used to test vaccines that rely on HIV-1's inner, or core, proteins. Indeed, this point has already led Washington's William Morton to assert that the pigtail system holds more promise. "You want to try to come as close as you can to human disease and pathogenesis," says Morton. "If you can use the whole HIV-1 in the monkey model, that's the best of all possible worlds." Then again, partisans on both sides would much prefer to join in such a debate than to find either or both of these approaches falling by the wayside.

–Jon Cohen

Jon Cohen is a science writer living in Washington, D.C.