Prospects Dim for Live AIDS Vaccine

Creating a live antiviral vaccine requires a delicate balance. The virus used must be sufficiently attenuated, or disabled, so that it doesn't cause disease. On the other hand, the vaccine needs to be strong enough to rouse the host into making antibodies or special immune cells. Ideally, such a balanced vaccine primes the immune system to kick in when it encounters the targeted disease.

AIDS, however, cares not for the ideal world. Even when stripped of key pieces of DNA to stymie its replication powers, a live attenuated AIDS vaccine can slowly recover its virulence and attack immune cells, scientists report. As a result, the search for a safe live vaccine against AIDS, which started with high hopes in the early 1990s, is sputtering.

"I think this current approach to generating a live attenuated AIDS vaccine is doomed," says Ruth M. Ruprecht, a virologist at Dana-Farber Cancer Institute and Harvard Medical School in Boston.

In the February NATURE MEDICINE, Ruprecht and her colleagues present the strongest evidence yet backing that assertion. In a study of rhesus macaque monkeys given attenuated SIV, the simian counterpart to HIV, the vaccine killed off many of the monkeys that received it.

Despite having three pieces of DNA deleted, the attenuated SIV vaccine proved fatal to 6 of 8 young monkeys that received it—2 others are still alive but have simian AIDS—and killed 5 of 16 adult monkeys. Two other adult monkeys died from unassociated causes.

Of the nine surviving adult macaques, only two appear healthy, now more than 3 years after getting the vaccine, Ruprecht says. The others have various signs of chronic SIV infection, including low immune-cell counts, opportunistic infections, rashes, anemia, a general failure to thrive, and a drop in concentrations of the blood platelets needed for coagulation.

Although the test vaccine uses live SIV that is missing segments of DNA thought necessary for replication, the virus managed to replicate anyway in most of the monkeys, Ruprecht says.

Meanwhile, a Dutch study of a similar "triple-delete" version of HIV finds that its virus can also restore the ability to replicate. In the February JOURNAL OF VIROLOGY, Ben Berkhout and his colleagues at the University of Amsterdam report "a dramatic gain of fitness" in their attenuated viruses as they evolved in a test tube. The researchers conclude that the safety of such a vaccine "cannot be guaranteed."

The findings raise hard questions for a scientific community under pressure to develop an AIDS vaccine for humans.

"With a live attenuated virus, you have to err on the side of safety," says immunologist David H. Schwartz of the Johns Hopkins Medical Institutions in Baltimore. "This virus has an extraordinary capacity to undergo mutations.

"For the foreseeable future, these kinds of results put the nails in the coffins of attenuated, live retroviral vaccines," he says.

The mechanism for recouping virulence remains puzzling. Ruprecht and her colleagues report that the virus didn't restore the deleted genes. Potency was regained "in some other fashion that's not clear, which means [the attenuated virus] has intrinsic virulence that, given enough time, reveals itself," says Schwartz.

Nevertheless, some scientists haven't given up on a live attenuated vaccine. "This work shows we don't have a good [live vaccine] candidate yet to pursue for human trials," says Margaret I. Johnston of the National Institute of Allergy and Infectious Diseases in Bethesda, Md. "That doesn't mean we shouldn't continue to evaluate [live-virus vaccines] with perhaps more deletions in other genes."

"The question is, if you continue to attenuate [the virus], do you really have a vaccine, or is the virus too weak?" asks Ruth I. Connor, a virologist at the Aaron Diamond AIDS Research Center in New York.

As an alternative to removing large numbers of genes, Ruprecht speculates that genetic pruning of an AIDS virus that would prevent it from targeting immune cells might still result in a safe vaccine. —*N. Seppa*

Fake sperm fool female butterflies

One of the great puzzles of butterfly sex—why males produce so much junk sperm—may be nearing a solution.

The dud sperm, skinny little strings that have lost their cell nuclei and can't fertilize anything, may be protecting a male's reproductive investment. A new study finds that the more this dummy sperm bulks up a female's sperm storage organ, the longer she waits before seeking a second mate and the less likely she is to bother at all.

The idea that infertile sperm discourage females from remating is old, but "this is the first evidence," says Penny A. Cook of Liverpool (England) John Moores University. In the Feb. 11 NATURE, she and Nina Wedell from the University of Stockholm describe tests with green-veined white butterflies, *Pieris napi*.

Many other species—other butterflies, stalk-eyed flies, fruit flies, and mollusks—produce infertile sperm along with the real stuff. Infertile molluscan sperm grow so huge that the fertile sperm hitch a ride on them.

British scientists Robin Baker and Mark Bellis even proposed a decade ago that human sperm take multiple forms, including kamikazes to destroy leftovers from other men. Cook, however, cautions that "we're not extending our findings to humans."

She and Wedell let butterflies mate, then provided females with a new male each day to allow second courtships. Pairs remain coupled for an hour, so during the 10-day experiment, the researchers dashed around the 36 cages every 15 minutes. Fortunately, the butterflies don't mate at night.

If a mating began, the scientists interrupted it and checked the sperm store from the earlier mating. They tested the other females at the end of the study.

From their first mating, all the females had received similar stores of around 1,000 fertile sperm. However, the storage organs held about 1,000 infertile sperm in females who accepted a second male versus 4,000 in females who didn't.

Cook speculates that infertile sperm amount to cheap knockoffs that ease the physical demands on a male. In adulthood, the butterflies exist on a sort of soda-and-junk-food diet of nectar. Drawing on protein stored from their larval days, the males produce sperm packets as big as their heads for each encounter.

Geoffrey A. Parker of the University of Liverpool, who developed much of sperm-competition theory, rates the new study as "quite good evidence." For butterflies, he says, "it's highly significant," though he warns against generalizing.

That same caution was voiced by Rhonda R. Snook of the University of Nevada, Las Vegas. She did a similar experiment to see if infertile sperm delay remating in fruit flies. As reported in the December 1998 ANIMAL BEHAVIOUR, they don't.

Snook laments the giggle factor associated with research in this area. Controlling sperm fertility might make a great way to control pest insects or aid inbred species, and insights into fertility might come from the mysterious process that generates two sperm types. "It's not just a gee-whiz thing," Snook says. —*S. Milius*