Recombinant vaccine shows promise against dengue fever

Scientists this week reported progress in genetically engineering a vaccine for dengue fever, a severe viral disease of global significance that is beginning to spread to North America. Public health officials in the United States and abroad have expressed increasing concern about the mosquito-borne disease, which is endemic to much of Asia, Africa and South and Central America. Development of a vaccine has been hampered, however, by a peculiar characteristic of the dengue virus: Antibodies against dengue tend to promote rather than prevent re-infection with closely related strains of the dengue virus.

Ching-Juh Lai, a researcher with the National Institute of Allergy and Infectious Diseases in Bethesda, Md., reported at a National Institutes of Health seminar that a novel approach to vaccine development has so far conferred complete protection against dengue in mice. The vaccine is now being tested on rhesus monkeys.

Most viral antibodies — whether naturally occurring or vaccine induced — recognize and bind to the outer envelope of a target virus. But strains of the dengue virus can bind to such antibodies and subvert them to *enhance* the virus's ability to infect human monocytes, a kind of white blood cell. Moreover, such antibody-enhanced infections tend to be much more severe than the original infection, which is characterized by fever, headache and joint pain. Antibody-enhanced infection can lead to a potentially fatal syndrome involving internal bleeding, severe dehydration and shock.

Lai's approach is based on work by scientists at the University of Rochester (N.Y.), who found that antibodies against a so-called nonstructural protein, produced inside the monocytes to help assemble new viruses, can protect against dengue without enhancing re-infection later. The nonstructural protein, dubbed NS-1, is produced in monocytes after a dengue virus "hijacks" the cells' genetic machinery. It is critical to virus replication but is never actually incorporated into new viral offspring. Although the mechanism of protection is not well understood, there is evidence that NS-1 antibodies recognize dengue-infected monocytes and destroy them before the virus has a chance to reproduce.

Anti-NS-1 antibodies have proved effective against dengue in mice and against yellow fever, a closely related disease, in mice and monkeys, according to Jacob Schlesinger and Michael Brandriss, who performed those experiments at the University of Rochester. The production of those antibodies was cumbersome, however, because it required the culturing and purification of large volumes of live virus. In contrast, Lai is splicing relevant parts of the dengue genome into other viruses that can be used to mass produce NS-1.

"The recombinant approach is nicer both in practice and in theory," Brandriss told SCIENCE NEWS. However, he says, it is difficult to predict the vaccine's efficacy in humans because the dengue virus behaves differently in monkeys and mice than it does in people. Because of the lack of good animal models, says Schlesinger, "you're probably going to have to consider doing human trials sooner than you would normally."

More than 100 million cases of dengue fever and its more severe form, dengue hemorrhagic fever, are estimated to occur each year worldwide. Few cases have occurred in the United States to date, but severe epidemics have occurred in the past few years both in Asia and in the Americas. Concern about its spread to the North American continent was spurred by the recent introduction into 17 states of *Aedes albopictus*, a mosquito that can transmit the disease very efficiently (SN: 8/23/86, p. 119). — *R. Weiss*

New lung cancer vaccine may double survival rates

Just-completed clinical trials of an experimental anticancer vaccine suggest that it can double survival rates in early-stage lung cancer and provide a way to predict within months which patients will do well on this regimen, scientists reported this week. Other cancer researchers are praising the work for its potential significance but caution that more evidence is needed.

Although referred to as a vaccine, the antigen product used in this study is not a vaccine in the classic sense, since it does not prevent disease but instead fights existing disease by boosting the patient's immune response. Among 34 patients with early-stage squamous-cell and adenocarcinoma lung cancers, the immunotherapy increased five-year survival rates to between 53 and 75 percent, depending on how the vaccine was given after surgery, compared with 33 percent in those treated with surgery alone. Ariel C. Hollinshead and her co-workers at George Washington University in Washington, D.C., developed the vaccine by isolating and purifying an antigen found on the surface of lung cancer cells, which they believe is a specific marker for lung tumor cells. They then injected these tumor-associated antigens into patients once a month for three months.

They noted that within five to six months after treatment, the patients who did not respond to the vaccine had very low or no serum-antibody responses to the antigen, as well as poorer cell-mediated immunity responses. By assaying these responses, clinicians can predict the vaccine's effect, says Hollinshead.

She reported the latest clinical trials this week at the American Cancer Society's 30th annual science writers' seminar in Daytona Beach, Fla. The studies, done in collaboration with Roswell Park Memorial Institute in Buffalo, N.Y., appear promising. However, the results — to appear in the JOURNAL OF CANCER — apply only to people diagnosed during the early stages of disease, a group that includes only 20 to 25 percent of squamous-cell lung cancers. Squamous-cell cancers account for 80 percent of all lung cancers seen in the United States and are associated with tobacco smoking.

Until more data are collected, the results should be viewed with "suppressed enthusiasm," says John P. Minton of the Ohio State University College of Medicine in Columbus. Commenting on Hollinshead's work during the seminar, Minton pointed out that effective treatments for lung cancer have been elusive, despite the importance of the disease — 152,000 new cases are expected this year, with a five-year survival rate of only 13 percent for all types combined. But Minton calls the vaccine results a "new bright light of hope."

Hollinshead's study should be regarded as a "state-of-the-art" effort that can point the way to related efforts against cancer, agrees Frank J. Rauscher, the American Cancer Society's senior vice-president for research. He does, however, say that he will have reservations about the findings until the work is duplicated by other researchers. "I'm not so sure the data are good enough to call these antigens unique [to lung tumors]," he says. But he cites the "remarkable" three-shot regimen and the immune-response-monitoring aspects of the work as significant.

Although Rauscher admits he is "nervous" about the study, he says he believes the results are valid "until proven otherwise" and that "an awful lot of other cancers may be amenable [to this approach]." For decades researchers have been looking at tumor-associated antigens as possible cancer markers and as signposts to better therapy, without the dramatic results reported this week. However, even if the new antigen were to enter the commercial-production pipeline soon, says Rauscher, it likely would be five to seven years before it would be widely available. — *D.D. Edwards*