The first prophylactic hepatitis C vaccine to reach human trials could enter phase II testing this year, a landmark for a field that has faced many technical challenges since the virus was identified in 1989. If this vaccine—or one of several other candidates—is successful, the public health impact could be substantial. Hepatitis C is a major cause of liver disease, including hepatocellular carcinoma, a leading cause of cancer deaths worldwide. The vaccines being developed are meant to prevent primary infection with the hepatitis C virus.

The vaccine in human trials is Chiron Corporation’s product, a recombinant version of the viral envelope proteins E1 and E2. In a phase I trial at St. Louis University Medical School, all 45 healthy volunteers given the vaccine produced neutralizing antibodies to hepatitis C. Phase II planning is under way and should be finalized in 2006, according to Michael Houghton, Ph.D., vice president of virology research at Chiron, which is based in Emeryville, Calif.

Although Chiron’s candidate is the farthest along in development, it is by no means alone in the field. There are at least half a dozen other candidates that take many different approaches to meet the particular challenges of this virus.

**Challenges**

One intrinsic difficulty in developing a vaccine to hepatitis C is that the virus itself does not always stimulate a strong natural immune response in humans. In fact, hepatitis C is “quite clever at evading the immune response,” said T. Jake Liang, M.D., head of the liver diseases branch at the National Institute of Diabetes and Digestive and Kidney Diseases, part of the National Institutes of Health. Consequently, understanding the mechanisms of viral infection...
and the immune response has been a major task. Another challenge has been the difficulty of growing the virus in cell culture, a problem overcome only last year. There is also no small-animal model—chimpanzees are the only laboratory animal that can be infected with hepatitis C virus. And finally, the virus has six genotypes and hundreds of subtypes, so developers must aim for a vaccine that protects against all of them—or at least the most common types.

“We went into this area with some trepidation and realizing that there would be some major challenges,” said Chiron’s Houghton, speaking at the American Association of Cancer Research’s annual prevention meeting last fall in Baltimore. “But I think today we have reason for a little more optimism that a prophylactic vaccine can be developed against many of the hepatitis C viral genomes.”

Reasons for optimism come in part from animal studies. In chimpanzees, the Chiron vaccine has prevented chronic infection in most animals, including those who produced only low antibody concentrations in response to vaccination. And at NIH, Liang said that his group has “very promising preliminary data” showing that a candidate vaccine based on virus-like particles provides at least partial protection against chronic infection in chimpanzees. Chronic hepatitis C infection is what leads to liver disease, so preventing the chronic phase is what most vaccine developers are aiming for.

There is also some promising data on a vaccine’s potential to protect against various strains of the virus, according to Houghton. “We know that our [Chiron] vaccine neutralizes HCV pseudotypes containing envelope glycoproteins from many of the major genotypes. This finding suggests that our vaccine could be broadly cross-protective,” he said in an e-mail interview. Chiron also has some evidence of cross-protection from a study in chimps.

Finally, the ability to replicate the virus in cell culture, announced just last year by NIDDK and several other groups, will make it easier to study the virus and to test potential antiviral compounds. It also opens the door for a vaccine based on an attenuated version of the virus, similar to many other common vaccines. Researchers are already beginning to work on an attenuated vaccine at NIH and elsewhere, Liang said.

Other Strategies

In the meantime, work continues on other hepatitis C vaccine strategies. These include protein-based approaches, a category that includes Chiron’s recombinant envelope proteins and NIH’s virus-like particles, which are based on both the envelope and core proteins. Several DNA-based approaches are also under study. Some use plasmid DNA encoding the envelope, core, and/or nonstructural viral proteins to serve as antigens. Others use a variety of viral and bacterial vectors to express and deliver the DNA for these antigens. The aim of all the candidates is to elicit both antibody and T-cell immune responses, since both appear to be important in preventing chronic infection.

A few of these candidates have already been tested in chimpanzees and are now being refined. At NIH, for instance, Liang said that next steps would focus on boosting the efficacy of the vaccine based on virus-like particles. One possibility may be to combine it with a novel adjuvant or perhaps a DNA vaccine. “It will probably require a combination of candidate vaccines for full protection,” he said.

—Caroline McNeil