HEPATITIS C

Hepatitis C virus (HCV) has infected more than 170 million people worldwide, including 3.9 million people in the United States.[35] HCV continues to emerge as a serious infectious disease in the United States and worldwide. About 25,000 new U.S. infections occur each year, and liver failure resulting from HCV infection is the leading cause of liver transplants in the United States.[36] Before 1990, patients who received blood transfusions were vulnerable to an unknown infectious agent of liver disease then known only as non-A, non-B hepatitis. However, after being cloned and genetically sequenced more than a decade ago, HCV was identified as the cause of most of these unidentified, transfusion-related liver infections.

Fortunately, rapid improvements in HCV diagnostics, including tests that can detect both antibodies to the virus and the virus itself, have made the supply of blood and blood products in this country safe from HCV contamination. Today, injection drug users are at highest risk of infection. Sexual transmission also occurs, especially among people with multiple partners, and other transmission routes are also possible, including exposure to contaminated blood. Approximately 55 to 85 percent of infected people become chronic carriers of the virus.[37] However, because people with chronic HCV infection often show no overt symptoms even as their livers are being attacked by the virus, many current carriers do not know they are infected.

NIAID has aggressively expanded its HCV research program through its Framework for Progress on Hepatitis C. In collaboration with participating Institutes and Centers, NIAID developed an NIH-wide framework that incorporates the different missions of NIH into a cohesive global plan for hepatitis C research. The final plan was reviewed by outside experts and has been approved by NIH Institute and Center Directors and the NIH Director. The plan identified the following research goals:

- Understand transmission modes to develop effective intervention strategies;
- Understand pathogenic mechanisms and disease progression to develop new treatments;
- Characterize host immune responses to infection to develop new vaccines and therapies;
- Define viral replication and recovery during therapy;
- Investigate clinical manifestations in order to develop methods to noninvasively evaluate disease state, predict outcomes, and prevent or reverse disease progression; and
- Define effective prevention and intervention strategies to improve health.

The tools needed to achieve these goals include tissue culture systems, small animal models, well-defined clinical cohorts, and research and reference reagents and tools.

NIAID supports a robust hepatitis C research portfolio that encompasses a range of critical areas, from cell culture systems to animal model development, virus replication to gene expression, crystal structure determination to rational drug development, and immune responses to vaccine development. These research activities are supported through grants to individual investigators and cooperative agreements via a network of Hepatitis C Cooperative Research Centers, in which a fusion of basic and clinical research is achieved so that laboratory observations can be clinically validated and clinical observations can be investigated at the molecular level. Through this network, NIAID supports clinical research that emphasizes studies

in special populations heavily affected by HCV such as African-Americans.

Current hepatitis C therapies include various forms of interferon and long-lasting forms of interferon (pegylated interferon), alone or in combination with the antiviral drug ribavirin. The success rates of these therapies, determined by the achievement of sustained elimination of virus, vary, depending on several factors—primarily, the genotype of the infecting virus (there are six distinct genotypes of HCV, all of which are globally distributed but with variable geographic predominance). Genotype I, the predominant strain in the United States, is the least responsive to interferon treatment, with only a 50 percent overall response rate. Also, African-Americans are considerably less responsive to therapy than are Caucasians. NIAID funds studies to understand these racial disparities in treatment responses. NIAID also supports research, new drug development, and the identification of new molecular targets for therapy, e.g., HCV polymerase, protease and helicase proteins, as well as other viral components critical for replication, such as the internal ribosome entry site (IRES).

Extramural investigators recently developed efficient HCV replication systems that can produce virus that is infectious in both human hepatocytes in cell cultures and in chimpanzees. These systems will soon close a huge gap in *in vitro* drug discovery programs supported by NIAID contracts and in the pharmaceutical industry. Information on these resources, which are accessible to both academic and corporate scientists, is available at *www.niaid.nih.gov/dmid/viral*.

Impressive advances are being made in understanding some of the mechanisms by which HCV subverts innate immunity and the adaptive immune responses to establish chronic infection. These advances are crucial to the rational design of vaccines and immunotherapies. The identification of the immune responses that define the rare natural ability to clear acute infection spontaneously remains a major goal. This is an area of intense interest and effort for continued NIAID-supported HCV research and drug development.

Efforts are in progress to develop and test preventive and therapeutic HCV vaccines (for use in chronically infected patients). In FY 2004, NIAID concluded a phase I trial of Chiron Corporation's prototype E1E2 HCV vaccine, intended to evaluate the safety, tolerability, and immunogenicity of this vaccine candidate in healthy, uninfected human subjects. Other trials are in preparation.

The extramural program of NIAID supports a contract for the acquisition and provision of HCV research reagents, currently housed in the AIDS Research and Reference Reagent Program (*www.aidsreagent.org*). This program is to be expanded; with the large numbers of reagents now being developed, many are expected to become reference standards for wide use in the research community, to allow uniformity and comparability of data from different laboratories and clinical research sites. Other HCV-related reagents are available through the NIH Tetramer Facility (*www.niaid.nih.gov/reposit/tetramer/index.html*) and the NIAID Reference Reagent Repository (*www.kamtekinc.com/niaid.php*).

NIAID also owns and maintains an annotated HCV sequence database and an HCV immunology database through a contract with the Los Alamos National Laboratories (*hcv.lanl.gov/content/hcv-db/index*).

In 2002, NIAID cosponsored a Consensus Development Conference entitled "Management of Hepatitis C: 2002". The meeting was convened to provide an update to a 1997 conference on the same topic. Among the recommendations for future research in its report, the panel gave top priority to the development of reliable and reproducible HCV cultures to advance

understandings of HCV biology and mechanisms of drug resistance and aid vaccine development.[38] The panel also urged the establishment of a hepatitis research network that would conduct research into the natural history, prevention, and treatment of hepatitis C. In 2005, NIAID organized a workshop, "Vaccines for Hepatitis C Virus", to discuss various issues and problems in the development of vaccines for HCV. A major outcome of the workshop was the recognition that, despite gaps in understanding protective immune responses, it is necessary to bring vaccine candidates to the fore and begin the iterative process of vaccine development and testing. A partnership initiative has since been developed to encourage and solicit the participation of private companies, in collaboration with academic institutions and with NIAID support, to produce vaccines that can be advanced to preclinical and early clinical trials within a few years.

NIAID also continues to help support the ancillary studies of the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) trial of the National Institute of Diabetes and Digestive and Kidney Diseases. This trial is evaluating the impact of long-term therapy on disease progression, and seeks to correlate virologic parameters and immunologic responses with recovery.

Scientists in NIAID's Division of Intramural Research are conducting research to answer key questions about HCV pathogenesis and the host immune response in order to develop an effective HCV vaccine and better hepatitis C treatments. Along the way, they are improving the tools used in hepatitis research. They are also developing critical research reagents and sharing them with researchers around the country.

For example, NIAID scientists previously collaborated with colleagues in France to demonstrate that a new *in vitro* test to detect and quantify virus neutralizing antibodies worked as well as a more cumbersome test that requires the use of chimpanzees.[39] This test is now helping researchers identify the specific portions of HCV that induce protective antibodies and can be used to promote the development of an effective hepatitis C vaccine.

In 2005, NIAID scientists and their colleagues used this new method to further their studies of HCV neutralizing antibodies. Using this assay, they defined the role of neutralizing antibodies in acute and chronic HCV infections and demonstrated significant cross-genotype neutralization. The detection of high-titer neutralizing antibodies with cross-genotype reactivity has important implications for the development of vaccines and immune-based therapies against HCV.[40]

In addition, NIAID intramural scientists and their colleagues continued their research to develop anti-HCV immune globulin preparations—similar to those used successfully to treat hepatitis B virus infection—that might be useful in preventing or controlling HCV infections. In recent work, they studied five monoclonal antibodies derived from the bone marrow of a healthy chronic carrier of HCV who was infected more than two decades ago. This patient was shown previously to possess serum neutralizing antibodies to HCV and has been the source of well-characterized HCV. The results of the research demonstrated that one or more of these monoclonal antibodies could be useful in preventing infections by HCV belonging to genotype 1 or 2, the most medically important HCV types worldwide. The scientists' goal is to produce these monoclonal antibodies in sufficient quantity to allow their evaluation in chimpanzees. Ultimately, such antibodies could be used to prevent recurrent HCV infection among liver transplant recipients. In HCV infection, re-infection of the transplanted liver is universal, and new therapies that enhance transplant and patient survival are sorely needed.[41]

This basic research, as well as vaccine and therapeutic development, would be greatly aided by the development of a small animal model in which to study HCV and to fine-tune candidate vaccines and antibody therapies. To this end, NIAID researchers are working to determine whether GB virus B, a monkey virus that is the closest relative of HCV, is a suitable surrogate for HCV in experimental studies. If so, the tamarin monkey could be used for *in vivo* studies and greatly reduce the need for chimpanzees for HCV research. Work is this area has been encouraging.