Advances in Hepatitis Research
With its large hepatology program, the Division of Gastroenterology maintains a heavy focus on understanding and treating liver disease. Faculty within the hepatology group are working at the forefront of research into viral hepatitis, specifically hepatitis B and C (HBV and HCV, respectively). Unfortunately, these two infections together affect well over five million Americans and over 500 million individuals worldwide.

With both viruses, initial, acute infections progress to a chronic form that, in time, can cause irreparable harm to the liver. The damage can lead to scarring, or cirrhosis, as well as organ failure and cancer. About half of all liver transplants performed in western countries are due to HCV, with another five to 10 percent due to HBV. Even after transplant, infection can recur, presenting numerous clinical and research challenges.

Halting Hepatitis C
The University of Michigan is one of 10 clinical sites for the National Institutes of Health Hepatitis C Antiviral Long-term Treatment against Cirrhosis, or HALT-C, clinical trial. The 11-year study of more than 1,000 patients is the largest prospective cohort study of HCV in the United States. HALT-C investigators, including Anna Lok, MBBS (left) and Robert Fontana, MD, set out to determine whether maintenance treatment with interferon, a type of antiviral medication that also boosts the body’s immune response, would prevent progression, scarring, cancer and the need for liver transplantation in patients unable to clear the virus after standard treatment. With one year still to go, it appears the investigative regimen doesn’t provide significant benefit; still, the study is providing many valuable insights, including the discovery of serum and genetic markers that may one day allow doctors to predict how the disease will progress in particular patients and why some patients progress more rapidly than others.

In April 2008 Dr. Lok presented HALT-C data on liver cancer at the Annual Meeting of the European Association for the Study of the Liver in Milan, Italy, reporting a lower percent of patients who developed cancer compared to hepatitis C patients in Europe and Japan. “This data is very important, highlighting the need for accurate data in each country. In this study, despite close monitoring, one quarter of the patients had advanced cancer at the time of diagnosis,” she says. “Therefore, research into biomarkers for early diagnosis of liver cancer is badly needed.” Several studies are ongoing to test blood samples collected in the HALT-C trial to discover new markers that would allow liver cancer to be diagnosed early, when a cure is possible.

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Preventing Recurrence of Hepatitis B After Liver Transplantation

In a seven year, 15-center Hepatitis B-Orthotopic Liver Transplantation (HBV-OLT) study, also supported by the National Institutes of Health, researchers explored cost-effective ways to reduce recurrence of the virus after transplant. In the past, recurrence rates were in the 80 percent range, and patients with recurrent disease often died within two years of transplant. Giving patients hepatitis B immunoglobulin, or HBIG, from the time of transplant has lowered recurrence rates to about 30 percent over a three year period, a dramatic improvement but still too high for researchers to rest. Dr. Lok served as principal investigator of the HBV-OLT study supervising all the clinical centers and the central virology laboratory. She recently reported that using oral antiviral agents prior to transplant, and HBIG right after, achieved even better results. The use of oral antiviral agents also allowed much lower doses or shorter durations of HBIG to be used while keeping the recurrence rate to seven percent after five years. These findings were presented at the American Association for the Study of Liver Diseases annual meeting in November 2008. A key to success is careful monitoring of virus response and resistance. Dr. Lok’s laboratory was responsible for the virus testing for the entire study. The Hepatology Program is also one of 13 participating centers of the Hepatitis B Clinical Research Network, another National Institutes of Health initiative. The seven-year venture was launched in October 2008 to look more closely at why some patients remain inactive carriers and others develop liver failure or liver cancer. This network will also look at the best time to start treatment. Current therapies can reduce the concentration of virus in the bloodstream and normalize liver enzymes, but less is known about whether these drugs actually stem disease progression to cirrhosis and cancer and improve survival rates. “It’s important to know that we’re not just suppressing numbers but that we’re preventing complications, such as cancer,” says Dr. Lok, who is chairing the steering committee to oversee this newly formed network.
Existing Weapons, New Fronts

The hepatology group is participating in several industry-sponsored studies, too, including use of a protease inhibitor against hepatitis C. Researchers at U-M are also looking at drug therapies to increase platelet counts so that HCV patients with cirrhosis—those most in need of treatment—can receive standard treatment, which decreases blood counts.

Researchers are also studying a drug commonly used to treat diabetes to improve insulin resistance in people with HCV. Insulin resistance has been associated with a lower response to standard treatment, according to principal investigator Hari Conjeevaram, MBBS. The HALT-C Trial showed that HCV patients with insulin resistance are more likely to develop liver failure. With the increasing epidemic of obesity and diabetes, these studies may have a major impact on the outcome of patients with HCV.

A New Home for Focused Efforts

Plans are underway for a new Center for Hepatitis Research and Education, within the Division of Gastroenterology. The center will provide additional infrastructure to support basic, translational and clinical research endeavors; to train fellows and faculty and to provide optimal care and education to patients with hepatitis and other liver diseases. “Unfortunately many treatments are efficacious, but not always as effective as we would like,” says Dr. Lok. “And there’s often a trade-off between side effects and efficacy. Patients wonder if they can tolerate the treatment and if the benefits will offset the risks. We’re working on interactive tools to help them make those difficult decisions.” And on ways to help make those questions irrelevant with novel therapies and, hopefully one day, an easy cure.

First Alice Lohrman Andrews Research Professor Appointed

Anna Suk-Fong Lok, MBBS, has been appointed the Alice Lohrman Andrews Research Professor of Gastroenterology by the University of Michigan Board of Regents. Dr. Lok is a professor of internal medicine, director of clinical hepatology and associate chair for clinical research in the Department of Internal Medicine.

The professorship, made possible by a generous gift from the TUKTAWA (pronounced “tucked away”) Foundation, was established to further U-M’s internationally renowned research and to help its investigators continue making strides towards more effective treatments and potential cures for liver disease. The endowed professorship provides support for exploratory research to test new concepts and treatments and to launch new programs.

From Left to Right: Chung Owyang, MD; Anna Lok, MBBS; and Chuck Andrews.