Chung Owyang, MD
Division Chief/Professor

Emeritus Faculty
Keith S. Henley, MD (active)
William O. Dobbins III, MD
Arthur B. French, MD
Jorge J. Gumucio, MD

Professor
John Del Valle, MD
Grace H. Elta, MD
Anna S.F. Lok, MBBS
Juanita L. Merchant, MD, PhD
Richard H. Moseley, MD
Timothy T. Nostiant, MD
James M. Scheiman, MD
Rebecca W. Van Dyke, MD
John A. Williams, MD, PhD

Adjunct Professor
Tadataka Yamada, MD

Associate Professor
William D. Chey, MD
Robert J. Fontana, MD
William L. Hasler, MD
Philip S. Schoenfeld, MD
Grace L. Su, MD
Andrea Todisco, MD
John W. Wiley, MD
Ellen M. Zimmermann, MD

Adjunct Associate Professor
Joseph C. Kolars, MD

Clinical Associate Professor
Frederick K. Askani, MD, PhD
D. Kim Tungeon, MD

Assistant Professor
Michelle A. Anderson, MD
Ezra Burstein, MD
Hari S. Conjeevaram, MBBS
Duyen Dang, MD
Peter D. Higgins, MD, PhD
Willemijn Hoogerwerf, MD
John Y. C. Kao, MD
Jorge A. Marrero, MD
Leslie B. Aldrich, MD
Laurel R. Fisher, MD
Raf Rizk, MD
Mimi S. Takami, MD
Eric-Jan Wamsteker, MD

Clinical Lecturer
Matthew J. DiMagno, MD
Hellan Kang, MD
Richard Kwon, MD
Stacy B. Menees, MD
Cyrus Piraka, MD
Joel H. Rubenstein, MD
Richard Saad, MD

Research Associate Professor
Ying Li, MD

Research Assistant Professor
Roberto Towns, PhD

Research Investigator
Longchuan Bai, PhD
Kadinos Calevski, PhD
Gintautas Grabauskas, PhD
Shuangsong Hong, PhD
Yana Zavros, PhD
Shi-1i Zhou, PhD
Preparing for the Coming Rise in Liver Cancer

For doctors who specialize in liver disease, it’s like watching a giant wave roll toward them, and waiting for it to crash onto shore. And while the wave seems to be moving in slow motion, it will be here soon enough that there isn’t a moment to spare.

The wave is a dramatic increase in the number of cases of liver cancer. It is expected to crest in the next decade or so, as more and more patients suffer the long-term effects of liver damage caused by hepatitis C infection, alcohol and/or obesity.

National statistics already show it’s the cancer with the fastest rate of increase over the last 10 years. And specialists at U-M are among those seeing a rise in the number of new patients—which spurred this year’s decision to create a new multi-disciplinary liver cancer clinic at the U-M Comprehensive Cancer Center.

The hepatitis B and C epidemics of the past three decades are major culprits in the anticipated wave of liver cancer, with more than 3.5 million Americans now living with chronic infection of those two viruses. Over time, the viruses scar the liver, causing cirrhosis that can give rise to uncontrolled cell growth and cancer. Fatty liver disease, whether brought on by alcohol abuse or by obesity and metabolic syndrome, can produce the same effect, especially if combined with hepatitis C infection.

No matter what its cause, liver cancer is hard to find—and the longer it goes undetected, the worse the patient’s chance of survival. But if it’s found early, the outlook is very positive.

That’s why U-M hepatologist Jorge A. Marrero, MD (right), and his colleagues are working toward a critical goal: to develop a better way of finding early signs of liver cancer, so that patients can get specialized treatment as soon as possible.

Marrero is the principal investigator of a national liver-cancer study funded by the National Cancer Institute. Over the past two years, it has recruited nearly 1,000 liver disease patients to participate—including many patients in the earliest stages of cancer.

The study is designed to validate a promising blood test for a liver cancer biomarker—a telltale protein that may reveal the presence of cancer.

The biomarker is called DCP, for des-gamma carboxyprothrombin. In 2003, Marrero and his hepatology colleague Grace Su, MD, published initial results suggesting that DCP may be better for early detection than the standard blood test, called alpha-fetoprotein or AFP. That led to the current national study that—if successful—could lead to DCP’s acceptance as a broadly used test.

Meanwhile, the blood samples, liver biopsy tissue and other materials given by the study’s participants may help in the development of still another promising early-detection test. It’s based on blood levels of molecules called Golgi Glycoprotein GP73.

In late 2005, Marrero, along with his U-M colleague Anna Lok, MBBS and Drexel University scientists, published the first paper showing that GP73 might be a useful biomarker. Now, they are working toward further testing of novel glycoproteins as novel tests for the detection of early stage liver cancer.

Even as this blood-testing research continues to show great promise, U-M is demonstrating the usefulness of a medical-imaging approach to detect liver cancer in high-risk patients. Working with U-M radiologist Hero Hussain, MB ChB, FRCR, hepatologists Marrero, Lok and Robert J. Fontana, MD, have developed a protocol to use MRI imaging to see cancerous tumors and distinguish them from benign liver problems.

Continued on next page
When Medicines Harm Instead of Heal

Every day, tens of millions of Americans take a variety of medicines to help ease their symptoms, treat infections, or reduce their risk of disease. For the most part, these pills, tablets, syrups and injections do the job they’re intended to do. But once in a while, things can go very wrong, very fast. And for hundreds or perhaps thousands of patients each year, the medicine they thought would help them instead sends them into potentially severe liver failure. This phenomenon, called drug-induced liver injury or DILI, is a serious problem—but it’s not well understood by the medical community.

Why? Part of the difficulty in understanding DILI is its relatively low occurrence in the general population, with an estimated incidence of only 1 in 10,000 to 1 in 1,000,000 patients exposed to a given drug. In addition, there are currently no reliable laboratory tests to confirm a diagnosis of DILI, which is largely a diagnosis of exclusion. And finally, it’s currently impossible to predict which rare patient might be harmed by a drug that others can take safely—because doctors don’t understand the genetic, environmental, or disease factors that may contribute to an individual patient’s risk.

What is known for sure, however, is that liver damage is the most common reason for new medicines to be pulled from pre-market research or pulled from the market even after they have been tested in thousands of patients.

To address all of these issues, liver specialists including U-M hepatologist Robert J. Fontana, MD, are teaming up to identify cases of DILI and to address the special issue posed by the common painkiller acetaminophen (also known as Tylenol).

In late 2005, Fontana and his colleagues in the US Acute Liver Failure Study Group reported the results of their study of 275 consecutive acetaminophen-induced liver failure cases at 22 major medical centers.

The results were surprising. An increasing number of liver failure cases were traced directly to the painkiller over five years, and nearly half of those cases were unintentional overdoses caused by lack of understanding of acetaminophen’s risks and presence in a multitude of over the counter and prescription narcotic drugs. The study group also recently developed a blood test that may help doctors recognize and diagnose patients with acetaminophen-related liver injury.
But while acetaminophen’s liver-damaging properties are well understood, it’s the unpredictable damage from other medicines that forms the focus of another DILI study. Fontana is one of five national leaders participating in the NIH-sponsored DILI Network, which is compiling the most comprehensive bank of blood samples, clinical information, and data from non-acetaminophen DILI patients ever assembled.

Working with his U-M colleague Hari Conjeevaram, MBBS, and collaborators from six hospitals across lower Michigan, Fontana has created the Michigan Hepatotoxicity Network to cast the widest net possible to identify DILI patients and enroll them in a study focused on genetic and environmental risk factors for unexplained DILI.

Already, results have shown that 20 percent of the 250 DILI patients enrolled to date develop evidence of chronic liver disease during follow-up—a much higher percentage than anticipated. In addition, a wide range of drugs, from antibiotics to medications for epilepsy and depression, have been implicated as the source of liver injury. And in many cases, vitamins, dietary supplements or other alternative-medicines were found to have caused or contributed to the liver damage.

Now, the challenge is to find out why DILI develops in a minority of patients exposed to a given drug. The network researchers are beginning to analyze DNA samples from the DILI patients, and from healthy comparison volunteers, to look for differences. Recent advances in DNA analysis make it possible to scan thousands of genes, and hundreds of thousands of small variations within those genes, across hundreds of patients. Using this single nucleotide polymorphism (SNP) technique, Fontana and his colleagues may finally get to the bottom of why some people are harmed, and others helped, by the same drug.