

### Administrative Core

Michael H. Nathanson, M.D., Ph.D.  
Director

Mario Strazzabosco, M.D., Ph.D.,  
FACG  
Deputy Director

James L. Boyer, M.D.  
Emeritus Director

### Morphology Core

Michael H. Nathanson, M.D., Ph.D.  
Director

Carol Soroka, Ph.D.  
Technical Director

Albert Mennone, M.S.  
Research Director

### Cellular and Molecular Physiology Core

James L. Boyer, M.D.  
Director

Shi-Ying Cai, Ph.D.  
Assistant Director

Carlo Spirli, Ph.D.  
Assistant Director

### Clinical and Translational Research Core

Guadalupe Garcia-Tsao, M.D.  
Director

Joseph Lim, M.D.  
Associate Director

Judy Cho, M.D.  
Associate Director

### Inside this issue:

YLC /YCC Clinical Study 2

Feature — Morphology 2  
Core

### Yale Liver Center

The Anlyan Center for Medical  
Research & Education  
300 Cedar Street, Room S241  
New Haven, CT 06520  
Telephone: 203-785-6140  
Fax: 203-785-7273

### 2011-2012 Pilot Project Award

In January 2011 27 applicants submitted their proposals for the 2011-2012 Yale Liver Center Pilot Project grant program. Five applicants were awarded approximately \$20,000 each beginning September 2011.

**David Assis, M.D.:** "Macrophage Migration Inhibitory Factor (MIF) in Autoimmune Liver Disease". Autoimmune Hepatitis (AIH) is a chronic relapsing disease of unclear pathogenesis, in which an unbalanced immune system plays a crucial but poorly understood role. Preliminary analysis of blood samples from patients with AIH at Yale revealed markedly elevated levels of serum MIF and soluble CD74 receptor, compared to health controls. Circulating soluble CD74 levels were found to be elevated in patients with AIH and more so in patients with Primary Biliary Cirrhosis (PBC) and Primary Sclerosing Cholangitis (PSC), as compared to controls. The goal of this project is to further develop these findings to elucidate the role of MIF and CD74 in pathogenesis and disease activity of AIH and relate autoimmune liver diseases.

**Violeta Popov, M.D.:** "The role of beta-catenin in liver lipid metabolism and insulin resistance". Wnt signaling has been implicated in functionally linking cellular metabolism to tissue development and function. Beta-catenin is the chief downstream regulator of the canonical Wnt pathway. The aim of her study is to investigate the effect of disrupting beta-catenin signaling in the liver and white adipose tissue on hepatic lipid metabolism, insulin sensitivity, energy expenditure and inflammation in rodent models.

**Carlo Spirli, Ph.D.:** "Mechanism of fibrosis in fibrocystin-deficiency associated cholangiopathies". This is the second year for this project. Morbidity, mortality and medical costs associated with cholangiopathies are significant. Cholangiopathies represent the indication for up to 80% pediatric and 20% adult liver transplants. In Dr. Spirli's proposal, they will study the mechanisms of portal fibrosis in a mouse model of CHF/CD, harboring a deleting mutation in Pkhd1.

**Zhaoxia Sun, Ph.D.:** "Function of Cilia in Zebrafish Liver Development". The cilium is an important sensory organelle for the vertebrate cell. Cilia defects have been implicated in the pathogenesis of polycystic liver disease and nephronophthisis but the precise mechanisms remain unclear. Using cilia markers and zebrafish cilia mutants we previously developed, this pilot will ask whether zebrafish can be used as a model system to address this question. Specifically, Dr. Sun will analyze the dynamics of cilia formation during zebrafish liver development and further investigate whether or not cilia mutants display liver associated phenotypes, particularly bile duct dilation, cell over-proliferation and fibrosis. Results will reveal the role of cilia during liver development and help establish zebrafish as a model system for future genetic, chemical and functional studies on liver development in general and HRFCDs in particular.

**Narendra Wajapeyee, Ph.D.:** "Characterization and Therapeutic Targeting of New HCC Oncogenes". This is the second year for this project. Hepatocellular carcinoma accounts for more than 700,000 new cases of cancer each year worldwide. During the first year of this application, a genome-wide human RNAi screen was performed and i30 genes as regulators of HHIP gene silencing were identified. The plan is to characterize these genes as new hepatocellular carcinoma oncogenes and then evaluate genetic and pharmaceutical means to target them with the ultimate aim of developing new methods for hepatocellular carcinoma treatment.



### Director's Corner

The Yale Liver Center (YLC) is one of 16 Digestive Diseases Research Core Centers (DDRCC) supported by NIH/NIDDK. The YLC has been funded continuously for 28 years and is one of only four that focus on the liver.

[Full story >](#)

### Events Calendar

March 14, 2012—Samuel D. Kushlan -- [Visiting Professorship—Peter Green, M.D.](#)

April 11, 2012— [26th Annual Klatskin Lecture — William Balistreri](#)

Digestive Diseases Seminars Series

- [Seminars](#)
- [GI Journal Club](#)
- [Liver Journal Club](#)

### 2011-2012 New Liver Center Members

[Erol Fikrig, MD](#)  
[Alan Garen, Ph.D.](#)  
[Yang Zhao](#)

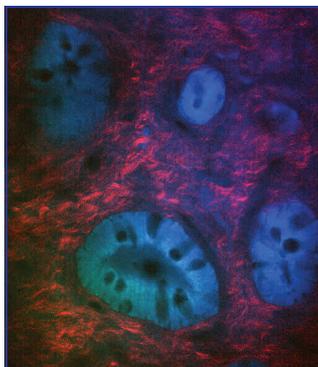
If you are interested in becoming a member of the Yale Liver Center, please contact Kathleen Weisgable at [kathleen.weisgable@yale.edu](mailto:kathleen.weisgable@yale.edu) for an application.

[Membership Criteria](#)

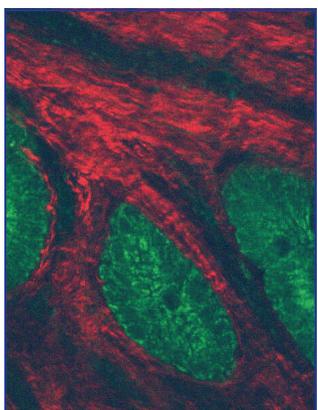
Yale Liver Center  
and  
Yale Cancer Center  
Sponsor

**A Multi-Center, Placebo-  
Controlled, Randomized Pilot  
Study of the Effect of Sorafenib ...**

— See page 2



Images of freshly excised rat common bile duct (CBDE) examined using 2-photon microscopy. Collagen fibers (red) surround ductular epithelium seen in green near the luminal surface of the CBD. Imaged deeper into the tissue, the ductules' (blue) columnar shape is more evident as well as mucous secreting epithelial cells.



The Yale Liver Center is built on a tradition established by the late Gerald Klatskin, one of the country's founders of the discipline of Hepatology and a member of Yale's faculty for over 50 years.

### Pilot study of the effect of Sorafenib

This is a multi-Center, placebo-controlled randomized pilot study of the effect of Sorafenib on portal pressure in patients with cirrhosis, significant portal hypertension and hepatocellular carcinoma treated with ablative therapy and/or transarterial chemoembolization.

This is a pilot proof-of-concept study that investigates the effect of sorafenib on portal pressure, as determined by the hepatic venous pressure gradient (HVPG), in patients with liver cirrhosis, portal hypertension and unresectable hepatocellular carcinoma (HCC) that have successfully responded to radiofrequency ablation and/or transarterial chemoemboliza-

tion, and have obtained a complete response.

The primary end-point of the study is the achievement of at least a 10% reduction in HVPG observed from baseline to three months after starting treatment with sorafenib. Secondary end-point is the mean change in HVPG over this period (three months after initiation of sorafenib/placebo) and safety of sorafenib. The trial is structured as a randomized double blind placebo controlled study. After a three-month period of therapy with sorafenib or placebo (double-blind phase), patients will be given open-label sorafenib for an additional

3-month period (open-label phase). A total of 44 patients will be randomized (in the initial phase) on a 1:1 ratio to sorafenib or placebo. Patients will be followed monthly and HCC follow-up will be according to standards of care. The study will be sponsored by Onyx, who will also provide the treatment medication (sorafenib and placebo). [Click here for detailed information about who can participate in the trial.](#) For more information about this trial, contact :

Guadalupe Garcia-Tsao, MD  
2 0 3 - 7 3 7 - 6 0 6 3  
[guadalupe.garcia-tsao@yale.edu](mailto:guadalupe.garcia-tsao@yale.edu)

### MORPHOLOGY CORE FACILITY

**Michael H. Nathanson**

*Director*

Carol Soroka

*Technical Director*

Albert Mennone

*Research Associate*

The Morphology Core Facility provides instrumentation and technical expertise for the preparation, acquisition and analysis of images of cells and tissues at the light microscopic level. Given the cost of such instrumentation and the high level of technical expertise required to perform these investigational techniques, this Core was established to ensure the availability of these techniques for Center members. In recognition of the broad usefulness of this Core facility, the School of Medicine has partnered with the Liver Center by making ongoing, major investments to ensure that the facility

remains state-of-the-art.

The Core has two confocal microscopes, plus a combined confocal and two-photon microscope. Both of our conventional confocal microscopes are Zeiss LSM 510 laser scanning microscopes. Both have three fluorescence detection channels, and one also has a meta-detector. The newest system is a Zeiss LSM 710 DUO NLO. This component allows two-photon excitation using a Spectra Physics MaiTai titanium sapphire laser. When coupled with the four high sensitivity external detectors (NDDs), the MaiTai is capable of deep tissue imaging. The 710 is also configured with a second "Live" scan head making it able to collect at very rapid acquisition rates. In addition, the stage is fitted with a temperature and CO2 controllable chamber for long-term imaging experiments.

There are two workstation computers in the facility, one dedicated to confocal image processing and the other for 3D rendering and volumetric analysis with Improvision's Volocity.

The Core maintains an epifluorescence microscope with a cooled high sensitivity Hamamatsu CCD camera, a camera equipped fluorescence dissecting microscope, a brightfield, multi-head microscope with a color CCD camera and an inverted epifluorescence microscopy for ratio imaging. The Core also maintains a microscope for video microscopy. A Lecai cryostat is available for frozen tissue sectioning. Interested investigators should contact Dr. Michael Nathanson or Mr. Al Mennone (5-3154) for access to the confocal microscopes or other light microscopic equipment.