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Assistant Director
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**Clinical-Translational
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- Guadalupe Garcia-Tsao, MD
Director
- Loren Laine, MD
Associate Director
- Dhanpat Jain, MD
Associate Director
- Randolph de la Rosa Rodriguez
Clinical Studies Coordinator

2015-2016 Pilot Project Awards

In January, 2015, applicants submitted their proposals for the 2015-2016 Yale Live Center Pilot Project Grant program. Four applicants were awarded \$25,000 each beginning September 2015.

Romina Fiorotto, PhD

"CFTR-defective biliary cells from h-iPSCs as a model to study the role of innate immunity in CFLD"

Cystic Fibrosis (CF) is a common and severe genetic disease, caused by mutations in CFTR, a protein that regulates fluid secretion in a number of organs. In CF patients the disease can be complicated by liver disease (CFLD), a condition that can compromise survival and quality of life of these patients. Unfortunately a cure is not yet available. Defective CFTR function impairs the ability of liver biliary cells (i.e cholangiocytes) to produce bile in the proper amount and quality. However we have found that the recovery of bile secretion is not sufficient to ameliorate liver damage in an experimental model in which CFTR-defective cholangiocytes are exposed to endotoxins. Using an animal model of CF we have demonstrated that lack of CFTR has a profound impact on the biliary epithelial innate immunity. We have generated preliminary evidence in a CF rodent model, showing the mechanistic link between CFTR and the regulation of epithelial innate immunity and we have identified the protein tyrosine kinase Src as an important target. Thus, translating our knowledge and the therapeutic applications in a human model would represent a distinct advantage. Lately the advance in stem cell technology has improved the ability to reprogram somatic cells into pluripotent stem cells (iPSC) to provide a unique platform for generating cells from patients with different human genetic diseases. In this study we will use human induced pluripotent stem cells (iPSC) to model the effects of Cystic Fibrosis (CF) in the liver. Starting from iPSCs derived from a control subject and a CF patient carrying the most common CFTR mutation $\Delta F508$ we will generate human biliary cells. We will investigate the impact of this mutation on the innate immune response to endotoxins and test compounds able to inhibit the activity of the protein tyrosine kinase Src as a new therapeutic target. This project will represent a pilot study aimed at increasing the availability of cell models of human origin to perform studies on the efficacy of new drugs for the liver disease in CF and possibly other cholangiopathies.

Silvia Vilarinho, MD

"Genomic Architecture of Biliary Atresia"

Biliary Atresia (BA) is a progressive fibro-obliterative cholangiopathy of infancy and if untreated, these children die from liver failure within the first 2 years of life. Timely diagnosis within first 3 months of life can be treated with Kasai hepatoportoenterostomy to restore bile flow. However, even with a successful timely surgical intervention, progressive hepatic inflammation and cirrhosis occurs, and approximately 50% of these patients will require a liver transplant by 2 years of age. Despite advances in surgical management of BA, its etiology remains elusive and lack of non-invasive diagnostic tools and therapies represent a major unmet need. The devastating nature of BA during infancy, its association with additional congenital malformations in 20% of the cases, and its predilection to affect children of Asian and African ancestries, launch our premise that genetic factors underpin the etiopathogenesis of BA. To investigate this hypothesis, we performed whole exome sequencing of germ line DNA from 108 unrelated BA patients, including 23 syndromic cases, from a national pediatric liver center managed by a single surgeon. As expected in a complex disease, our initial unbiased analysis revealed no single gene mutated across samples. Thus, taken advantage of the recent advances in large genomic data analytic tools, we are currently pursuing the following three specific aims: (1) Identify genes and pathways specifically altered in the germ line DNA of BA probands; (2) Investigate potential liver-specific somatic gene alterations in BA patients, and (3) Establish genotype-phenotype correlations using whole exome alterations and accurate phenotyping of BA probands. We believe that identification of high-risk genetic variants for BA will likely provide the first steps to develop non-invasive diagnostic tools and to identify novel therapeutic targets to halt the inevitable development of cirrhosis and need for liver transplantation. Lastly, as more BA patients achieve adulthood, an improved understanding of genetic basis of BA will facilitate optimal genetic counseling.

2015-2016 New Liver Center Members

- [Choukri Ben Mamoun, PhD](#)
- [Ying Chen, MD, PhD](#)
- [Jeff Geschwind, MD](#)
- [Martin Kriegel, MD, PhD](#)
- [Zhaoxia Sun, PhD](#)
- [Vasilis Vasilou, PhD](#)
- [Silvia Vilarinho, MD](#)
- [Narendra Wajapeyee, PhD](#)

If you are interested in becoming a member of the Yale Liver Center, please contact [Christine Abu-Hanna](#) for an application.

[Membership Criteria](#)

Events Calendar

- 1/19/16**
Augusto Villanueva, MD, PhD
"New Trends in Molecular Stratification of Liver Cancer Patients."
TAC S247 5:00-6:00PM
- 2/2/16**
Christopher Bowlus, MD
"The Known and Unknowable Unknowns of Primary Sclerosing Cholangitis"
TAC S247 5:00-6:00PM
- 6/24/16-6/26/16**
PSC Partners Seeking a Cure's 12th annual conference at the Omni Hotel

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Dr. Michael Nathanson

Director's Corner

The Yale Liver Center (YLC) is one of 18 Digestive Diseases Research Core Centers ([DDRCC](#)) supported by NIH/NIDDK. The YLC has been funded continuously for over 30 years and is one of only four that focus on the liver.

[Full story >](#)



At the AASLD Meeting on November 15, 2015, Dr. Guadalupe Garcia-Tsao was awarded the Distinguished Clinician Educator/Mentor Award, one of the highest honors bestowed upon an AASLD member. This award recognizes the skills of outstanding clinicians and educators who have made momentous contributions to hepatology over an extended period. Dr. Garcia is Professor of Medicine at Yale University School of Medicine and Chief of Digestive Diseases at the VA-CT Healthcare System. She has served the AASLD in many capacities, notably as president of AASLD in 2012 and currently as Associate Editor of HEPATOLOGY and Chair of the ACT-First program, an online educational program

for primary care providers.

Dr. Garcia-Tsao is a consummate clinician, researcher and educator. As some of her colleagues have expressed "her observations have changed the way we look at cirrhosis and portal hypertension." Her ability to add clarity to complicated concepts and her passion and enthusiasm for the study of liver diseases make her a respected and sought after mentor and lecturer. She has mentored, taught and collaborated with clinicians and researchers from all over the world. Her commitment to improving the care of patients is evident through her many contributions to AASLD and the field of hepatology in general.

Dr. Michael H. Nathanson, Gladys Phillips Crofoot Professor of Medicine and Cell Biology, Chief of the Section

of Digestive of Diseases at Yale University School of Medicine, and Editor of HEPATOLOGY, was given the honor of presenting this award to Dr. Garcia at the AASLD meeting. He pointed out that Dr. Garcia has been invited to give nearly 400 talks in 35 countries, including over a dozen named lectureships. She has also served as a mentor to nearly 70 trainees in 12 countries, some of which who were featured in the video that Dr. Nathanson presented. The video showed interviews from some of her current/former trainees that captured the essence of Dr. Garcia's unique and engaging style of teaching and mentorship.

For those who wish to see the video, please contact [Christine Abu-Hanna](#).

CLINICAL-TRANSLATIONAL CORE

Guadalupe Garcia-Tsao, MD
Director

Loren Laine, MD
Associate Director

Dhanpat Jain, MD
Associate Director

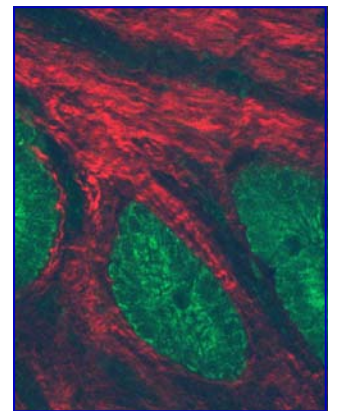
Randolph de la Rosa Rodriguez
Clinical Studies Coordinator

The Clinical-Translational Core provides an infrastructure for patient-oriented research by streamlining regulatory and compliance processes, obtaining and storing high-quality samples linked to extensive clinical phenotypic information, offering expert consultation in the design and implementation of patient-oriented trials, and supplying statistical expertise for application of innovative analytic methods in translational and patient-oriented research. The Core was established to

facilitate the performance of patient oriented research to Core members. The Clinical-Translational Core has been extremely effective in accomplishing its goals, generating a large number of original publications and establishing numerous collaborations with facilities and investigators that have increased or supplemented the available services (e.g. the Office of Research Services of the Yale Center for Clinical Investigation that has been assisting Liver Center investigators, at no cost, in preparing and submitting new research projects), and provide additional sources of support for Core activities (support for inpatient data collection from the National Consortium for the Study of Endstage Liver Disease) as well as increasing the number of core members.

The Clinical-Translational Core offers the following specific activities and services, plus associated training and technical support:

1. a clinical core coordinator that facilitates regulatory processes (obtaining and maintaining IRB approval for the performance of patient-oriented research
2. clinical registries consisting mainly of a patient and a sample registry, as well as disease-specific databases that have been collected by different center investigators over the years
3. statistical support, including study design and implementation and data analysis.



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.

2015-2016 Pilot Project Awards (continued)

In January, 2015, applicants submitted their proposals for the 2015-2016 Yale Live Center Pilot Project Grant program. Four applicants were awarded \$25,000 each beginning September 2015.

Choukri Ben Mamoun, PhD

"Elucidating the role of the organic transporter OSTα/SCL51A in malaria infection"

Malaria, caused by intraerythrocytic protozoan parasites of the genus *Plasmodium*, is by far the most pernicious and among the most prevalent of the parasitic diseases. The World Health Organization has recently estimated that malaria is responsible for approximately 240 million annual clinical cases and about 860 thousand deaths. Most fatalities can be ascribed to infection by *P. falciparum*. *Plasmodium* exhibits a complex life cycle consisting of a sexual phase within the *Anopheles* mosquito vector and an asexual phase in hepatocytes and red blood cells of the human host. We have identified expression of the bile acid/sterol Organic Solute Transporter (OSTα-OSTβ (SLC51A-SLC51B)) as a potential modifier of parasite load in children with malaria. We hypothesized that variation in expression of this transporter could influence parasite growth by modifying the availability of cholesterol which is essential for parasite membrane synthesis, or by modifying cellular entry of immunomodulatory sterol molecules. In this study we aim to test experimentally whether the *in vivo* growth or killing of malaria parasites differ between wild type mice and mice deficient in *Osta*.

Ying Chen, PhD

"Redox-Based Regulatory Role of Glutathione in the Pathogenesis of Fatty Liver Disease"

The goal of this project is to identify novel targets involved in protection against fatty liver disease (FLD) by elucidating novel functions of glutathione (GSH) as a signaling molecule that modulates pathways involved in the pathogenesis and progression of FLD. We have developed two unique transgenic mouse models in which hepatic GSH synthesis is repressed by preventing the expression of the catalytic (GCLC) or the modifier (GCLM) subunit of glutamate-cysteine ligase, the rate-limiting enzyme in GSH biosynthesis. Our previous studies show that these mice have GSH deficiencies at different levels but exhibit either resistance to alcoholic and nonalcoholic steatosis (GCLM knockout mice) or develop spontaneous liver fibrosis/cirrhosis featuring the advanced stage of FLD (liver-specific GCLC knockout mice). The proposed research project will utilize these animal models to expand upon these provocative findings and investigate our novel hypothesis that GSH biosynthesis plays an important regulatory role in mitochondrial redox signaling network, by which means it modulates key metabolic and stress response pathways that are mechanistically linked with FLD. We propose to use the redox proteomic approach to delineate target proteins of GSH-mediated redox modifications at the mitochondrial proteome level in GCLM KO and GCLC KO hepatocytes, which will be complemented by biochemical characterizations of cellular redox state and mitochondrial biogenesis.

MEMBERS RECENT PUBLICATIONS

Statins are Associated with a Decreased Risk of Decompensation and Death in Veterans with Hepatitis C-related Compensated Cirrhosis. Mohanty A, Tate J, **Garcia-Tsao G**. *Gastroenterology*, 2015, (15) 01476-6, PMID: 26484707.

Pigment Epithelium-Derived Factor (PEDF) Inhibits Wnt/β-catenin Signaling in the Liver. **Protiva P**, Gong J, Sreekumar B, Torres R, Zhang X, Belinsky GS, Cornwell M, Crawford SE, **Iwakiri Y, Chung C**. *Cell Mol Gastroenterol Hepatol*. 2015;1(5):535-549. PMID:26473164

Canalicular membrane MRP2/ABCC2 internalization is determined by Ezrin Thr567 phosphorylation in human obstructive cholestasis. Chai J, **Cai SY**, Liu X, Lian W, Chen S, Zhang L, Feng X, **Cheng Y**, He X, He Y, Chen L, Wang R, Wang H, **Boyer JL**, Chen W. *J Hepatol*. 2015; 63(6):1440-8. PMID: 26212029

Stimulation of nuclear receptor peroxisome proliferator-activated receptor-γ limits NF-κB-dependent inflammation in mouse cystic fibrosis biliary epithelium. Scirpo R, **Fiorotto R**, Villani A, Amenduni M, **Spirli C, Strazzabosco M**. *Hepatology*. 2015; 62(5):1551-62. PMID: 26199136

Na(+)/H(+) exchanger regulatory factor 1 knockout mice have an attenuated hepatic inflammatory response and are protected from cholestatic liver injury. Li M, **Mennone A, Soroka CJ**, Hagey LR, **Ouyang X**, Weinman EJ, **Boyer JL**. *Hepatology*. 2015;62(4):1227-36. PMID: 26108984

Calcium signaling and secretion in cholangiocytes. Guerra MT, **Nathanson MH**. *Pancreatolgy*. 2015;15(4 Suppl):S44-8. PMID: 26100660

Nuclear Factor, Erythroid 2-Like 2 Regulates Expression of Type 3 Inositol 1,4,5-Trisphosphate Receptor and Calcium Signaling in Cholangiocytes. Weerachayaphorn J, Amaya MJ, **Spirli C**, Chansela P, **Mitchell-Richards KA, Ananthanarayanan M, Nathanson MH**. *Gastroenterology*. 2015; 149(1):211-222. PMID: 25796361

Hepatic arteriolosclerosis: a small-vessel complication of diabetes and hypertension. Balakrishnan M, **Garcia-Tsao G**, Deng Y, **Ciarleglio M**,

Jain D. *Am J Surg Pathol*. 2015; 39(7):1000-9. PMID: 25786083

Liver X receptor regulates hepatic nuclear O-GlcNAc signaling and carbohydrate responsive element-binding protein activity. Bindsøll C, Fan Q, Nørgaard RC, MacPherson L, **Ruan HB**, Wu J, Pedersen TA, Steffensen KR, **Yang X**, Matthews J, Mandrup S, Nebb HI, Grønning-Wang LM. *J Lipid Res*. 2015; 56(4):771-85.

Controlled-release mitochondrial protonophore reverses diabetes and steatohepatitis in rats. Perry RJ, Zhang D, Zhang XM, **Boyer JL, Shulman GI**. *Science*. 2015, (6227):1253-6. PMID:25721504

Fibrates and cholestasis. Ghonem NS, **Assis DN, Boyer JL**. *Hepatology*. 2015; 62(2):635-43. PMID: 25678132

The origins of hepatobiliary and gastrointestinal physiology. **Boyer JL**. *Hepatology*. 2015; 61(5):1452-4. PMID: 25677183

Hepatic acetyl CoA links adipose tissue inflammation to hepatic insulin resistance and type 2 diabetes. Perry RJ, Camporez JP, Kursawe R, Titchenell PM, Zhang D, Perry CJ, Jurczak MJ, Abudukadier A, Han MS, Zhang XM, **Ruan HB, Yang X, Caprio S**, Kaech SM, Sul HS, Birnbaum MJ, Davis RJ, Cline GW, **Petersen KF, Shulman GI**. *Cell*. 2015; 160(4):745-58. PMID: 25662011

TAM receptor-dependent regulation of SOCS3 and MAPKs contributes to proinflammatory cytokine downregulation following chronic NOD2 stimulation of human macrophages. Zheng S, Hedl M, **Abraham C**. *J Immunol*. 2015;194(4):1928-37. PMID: 25567680

Immunohistochemical pitfalls in the diagnosis of hepatocellular adenomas and focal nodular hyperplasia: accurate understanding of diverse staining patterns is essential for diagnosis and risk assessment. Kakar S, Torbenson M, **Jain D**, Wu TT, Yeh M, Ferrell LD. *Mod Pathol*. 2015; 28(1):159-60. PMID: 25560413

Post-translational regulation of the type III inositol 1,4,5-trisphosphate receptor by miRNA-506. **Ananthanarayanan M**, Banales JM, Guerra MT, **Spirli C**, Munoz-Garrido P, **Mitchell-Richards K**, Tafur D, Saez E, **Nathanson MH**. *J Biol Chem*. 2015; 290(1):184-96. PMID: 25378392

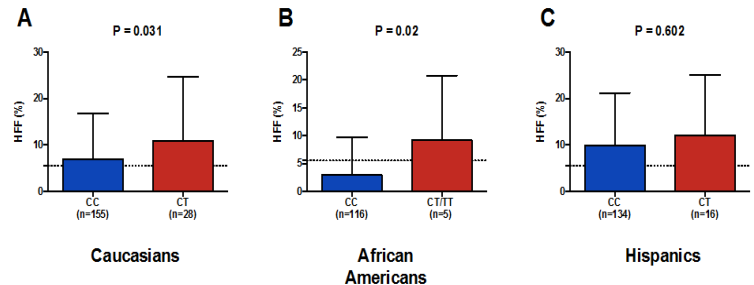
Feature Publications

Role of the TM6SF2 rs58542926 in the pathogenesis of non-alcoholic pediatric fatty liver disease (NAFLD): A multiethnic study.

Goffredo M, Caprio S, Feldstein AE, D'Adamo E, Shaw MM, Pierpont B, Savoye M, Zhao H, Bale AE, Santoro N. *Hepatology* 2016

This study explored the association between the single-nucleotide polymorphism (SNP) rs58542926 in the transmembrane 6 superfamily member 2 (TM6SF2) gene and fatty liver disease in obese youth. The minor allele of the rs58542926 SNP was associated with high hepatic fat content (HFF%) in Caucasians and African Americans (all $P < 0.05$), with high ALT levels in Hispanics ($P < 0.05$) and with a more favorable lipoprotein profile (lower LDL, small dense LDL and very small LDL) in Caucasians and Hispanics (all $P < 0.05$). The liver biopsy showed a higher prevalence of fibrosis ($P = 0.04$) and a higher NAFLD Activity Score ($P = 0.05$) in subjects carrying the minor allele than in those

homozygous for the common allele. Moreover, a joint effect among the TM6SF2 rs58542926, the PNPLA3 rs738409 and the GCKR rs1260326 SNPs in determining intrahepatic fat accumulation ($P < 0.05$) was observed. These data show that the rs58542926 SNP in the TM6SF2 gene is associated with pediatric NAFLD, but may confer protection against cardiovascular risk.



Effect of Oral Eliglustat on Splenomegaly in Patients With Gaucher Disease Type 1 The ENGAGE Randomized Clinical Trial

Pramod K. Mistry, MD, PhD, FRCP; et al. *JAMA* 2015

This paper was featured on [Yale News](#)

Gaucher disease type 1 is a chronic disorder that causes disability, reduced life expectancy, and life-threatening complications in patients. Until recently, the main treatment option consisted of enzyme replacement therapy, provided intravenously on a biweekly basis.

To determine the utility of a novel oral therapy, eliglustat, first author Dr. Pramod K. Mistry, professor of medicine, pediatrics and cellular & molecular physiology at Yale School of Medicine, collaborated with a multinational team of researchers to conduct a study known as ENGAGE. It was the first placebo-controlled and largest randomized trial in patients with this rare genetic disease. The study was published online Feb. 17 in *JAMA*.

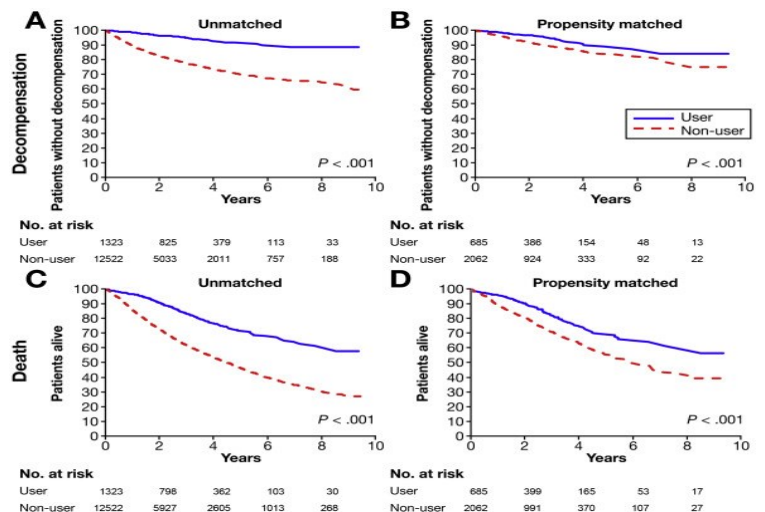
During the nine-month research period, study participants received either eliglustat or a placebo. Compared to those taking the placebo, participants taking the oral therapy showed marked improvements in GD complications. "Patients who received eliglustat had reduction in the enlargement of the spleen and liver, and improvement of platelet count, hemoglobin, inflammatory markers, and measures of bone involvement," said Mistry.



Statins are Associated with a Decreased Risk of Decompensation and Death

Arpan Mohanty, MD, Janet Tate, ScD, Guadalupe Garcia-Tsao, MD. *Gastroenterology*. 2015

This is a large nationwide study in a cohort of veterans with compensated cirrhosis related to hepatitis C that shows that statin use is associated with a decreased risk of decompensation and death. In this retrospective study, we used propensity score matching that balanced important variables at baseline between statin users and (up to five) statin non-users, so as to emulate a randomized controlled trial. These results are very important and although we cannot yet conclude that statins should be used in patients with compensated HCV cirrhosis (and results can probably be extended to cirrhosis of all etiologies), it is important that practitioners recognize that, rather than being harmful, statins may be beneficial and should not be avoided in these patients.



LIVER CENTER ANNOUNCEMENTS

NEW! Super-resolution Microscope

The Liver Center recently purchased a new Leica Gated STED super-resolution microscope, the first of its kind at Yale and one of the first in the country. This microscope permits collection of images with spatial resolution approximately five-fold below the diffraction limit. For training and access to this microscope, please contact [Al Mennone](#).

Mindfulness-Based Stress Reduction (MBSR)

In January Yale Digestive Diseases will begin offering Mindfulness-Based Stress Reduction (MBSR) as adjunctive therapy for patients with liver disease and GI disorders. Patients are referred to this program through their liver or GI providers. A brochure describing the program is available by contacting [Gina Clark](#) at (203) 747-6063.

Yale Liver Center Will Host Two Key PSC (Primary Sclerosing Cholangitis) Meetings in June 2016

The [PSC Partners Seeking a Cure](#) group will bring its annual national patient and caregiver meeting to New Haven, from 6/24 - 6/26. More than 300 patients and caregivers will be in attendance. The meeting will include several educational sessions in large and small group settings, given by a multi-disciplinary group of Yale providers in addition to an international group of leading PSC experts. It is considered the premier patient meeting for this disease, and represents an unparalleled opportunity for Connecticut patients and caregivers to come together with clinicians and researchers to seek support and promote new approaches to PSC management. The second gathering is the 4th workshop of the [International PSC Study Group](#) (IPSCSG), a biennial meeting of the world's leading experts in clinical and basic science research in the field of PSC. This is the first time in which this state-of-the-art meeting will be held outside Europe, thus providing a unique opportunity for the Yale Liver Center to assume a leadership role in promoting greater participation and collaboration among North American centers. The meeting will take place on 6/26-6/27, and will include a joint session with the PSC Partners meeting on the morning of the 26th in which researchers, clinicians, and patients will extensively interact and exchange ideas for how to best move the field forward. For more information about these meetings, please contact [Jennifer Horn](#).

NOW ACCEPTING LETTERS OF INTENT: 2016-2017 Pilot Feasibility Grant

The NIH P30 Liver Center grant provides for the annual submission of pilot projects (up to \$25,000 direct costs each) from both Yale and non-Yale Liver Center investigators as approved by the Executive Committee.

The purposes of the pilots are to fund new initiatives, not ongoing research, and to support new investigators to pursue liver related research that should lead to a R01-type funding or other support at a later date. Projects utilizing Core Facilities and supporting young investigators are given priority if the science is equally meritorious. **Investigators should meet one of the following criteria, in order of priority:**

1. Senior fellows or junior faculty at Yale, currently not funded by NIH grants and in need of funds to help prepare for R01-type applications.
2. Established University investigators not currently funded for work related to the Center's focus but who wish to apply their areas of expertise to subjects of Center interest.
3. Funded Center investigators who wish to pursue a project that is different from their current focus of interest, and who need to develop preliminary data to apply for new R01-type funding.

****We are also accepting submissions for special pilots specifically associated with some aspect related to the biology, pathogenesis, and/or therapy of primary sclerosing cholangitis including basic studies related to cholestasis****

For more information please click [here](#).