Yale SCHOOL OF MEDICINE

YALE LIVER CENTER

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Yale Liver Center Retreat

The 2016 Yale Liver Center Retreat will be held on Saturday, November 19, 2016 at the New Haven Country Club located at 160 Hartford Turnpike, Hamden, CT 06517.

The following speakers will be presenting at the Retreat:

"Liver, Inflammation and Metabolism"	Ruslan Medzhitov, PhD
Pilot Project Report 1 *"The role of Wnt/ TCF7L2 in regulation of Liver Fat, Inflammation and fibrosis*	Arya Mani, MD, FACC, FAHA
Pilot Project Report 2 *"CFTR-defective biliary cells from human induced pluripotent-stem cells (iPSC) as a model to study the role of innate immunity in cystic fibrosis liver disease"*	Romina Fiorotto, PhD
"Biomedical Innovations in Liver Transplantation"	Manuel Davalos-Rodriguez, MD, FACS
Pilot Project Report 3 *"Genomic Architecture of Biliary Atresia"*	Silvia Vilarinho, MD
Pilot Project Report 4 *"Redox-based regulatory role of glutathione in the pathogenesis of fatty liver disease"*	Ying Chen, PhD
"Clinical HCC research at Yale"	Jeff Geschwind, MD
"Mouse Models to Study the Role of Alcohol Metabolism in Liver Toxicity"	Vasilis Vasiliou, PhD
"Establishing Casual Connections Between Gut Microbiota Composition and Human Disease"	Noah Palm, PhD
"Cirrhosis: Progression and Regression"	Guadalupe Garcia-Tsao, MD
"Regulating Inflammation in NASH"	Wajahat Mehal, MD, PhD
"New Tricks for Digoxin to treat NASH"	Xinshou Ouyang, PhD
"HCC surveillance, detection, and treatment - tales from the real world."	Tamar Taddei, MD
"Liver Repair and Fibrosis"	Carlo Spirli, PhD
"Update on Autoimmune Liver Disease Research at the Yale Liver Center"	Davis Assis, MD
"Histological features of Autoimmune Hepatitis: A critical appraisal"	Dhanpat Jain, MD

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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 >

2016-2017 Pilot Project Recipients

Romina Fiorotto, Ph.D.

Associate Research Scientist
Department of Digestive Diseases

CFTR-defective biliary cells from h-iPSCs as a model to study the role of innate in cystic fibrosis liver disease (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 the liver, CFTR is expressed in the biliary epithelium, where it promotes the transmembrane efflux of chloride and bicarbonate. A percentage of patients with CF present liver disease (CFLD), a chronic cholangiopathy that can compromise survival and quality of life.

Using an animal model of CF we have demonstrated that lack of CFTR has a profound impact on the innate immunity and on the cytoskeletal architecture of biliary cells and we have identified the protein tyrosine kinase Src as an important target.

A major obstacle to design new therapies is the lack of an experimental model that matches the human CF biliary phenotype. In this project we will exploit the novel technology of human induced pluripotent stem cells (iPSC) to translate our knowledge and the therapeutic applications in a model that closely resemble the human disease.

During the first year of the project we have developed a protocol for differentiation of human iPSCs, derived from a healthy control and from a CF patient with ΔF508CFTR mutation, into mature and functional biliary cells. Preliminary evidence shows that the mutated cholangiocytes present a similar phenotype compare to the mouse model previously described (i.e increased TLR4/NF-kB response, increased Src activation, altered F-actin distribution).

Based on our findings, during the second year of the project we will test in iPSC-derived biliary cell model new therapeutic approaches to target inflammation and restore the integrity of the actin cytoskeleton. The integrity of the actin cytoskeleton is crucial for the stability of CFTR protein at the membrane. In combination with the small molecules that partially correct the ΔF508 defect (i.e VX-809 and VX-770), we might improve CFTR recycling and retention at the plasma membrane therefore increasing the efficacy of the therapies in use to correct the basic ΔF508 defect.

Carol Soroka, Ph.D.

Senior Research Scientist
Department of Digestive Diseases

Use of Human Organoids in the Study of Liver Disease: A Model for Maintaining PSC Patient Progenitor Cells in Long-term Culture with the Potential Ability to Screen for the Efficacy of Drug Therapies

Primary sclerosing cholangitis (PSC) is a rare, progressive, and often fatal cholestatic liver disease of unknown etiology. Understanding the mechanisms of the disease and how to treat it is hampered by the diversity seen in the clinical population, the rarity of the disease, and the lack of a reproducible in vitro culture system that can focus on the bile duct cell that represents a very small percent of all hepatic cells. In this Pilot grant study, we will isolate and culture progenitor cells (organoids) directly from the liver of patients with PSC. These cells have a biliary phenotype and can be maintained long-term in culture. Furthermore, they can be frozen down in order to create a biobank of cells that can be used for future studies, including pharmacotherapeutic testing of drugs. The organoids from controls (healthy and diseased) and PSC patients will be compared by genetic analysis and drug therapies will be tested in a personalized fashion, tailored to the phenotype-genotype detected. It is the hope that the use of organoids will provide insight into the diversity seen in the patient population and allow future studies into the mechanisms of this rare disease.

2016-2017 Pilot Project Recipients

Adam Arterbery, Ph.D.
Associate Research Scientist
Department of Pediatrics

Inflammasome, Unfolded Protein Response, and T cell Immunity in DAIH

Chronic liver allograft dysfunction is a leading cause of patient morbidity and late allograft loss after liver transplantation. An Important cause of chronic liver allograft dysfunction is de novo autoimmune hepatitis (DAIH) seen in 4-7% of pediatric and adult liver transplant recipients. The long term goal of the proposed research is to provide insights into the etiology and pathogenesis of DAIH to inform prevention and management strategies. The main objective of this project is to begin to identify the molecular mechanisms through which monocytes induce Tregs from patients with DAIH to differentiate towards a pro-inflammatory phenotype and lose suppressive function. The rationale is that identification of intrinsic cellular pathways involved in Treg dysfunction in DAIH could lead to potentially new therapies, improve patient care and lower health care costs. If our hypothesis is correct, completing the specific aims will provide attractive new targets for preventive and therapeutic interventions in addition to advancing our understanding of the pathogenesis of DAIH. We will investigate if inflammasome activation (IL-1b, IL-18, caspase-1, and NLRP3) in CD14+ monocytes from patients with DAIH drives the enhanced production of pro-inflammatory polarizing cytokines (IL-12/IL-6). In addition, we will assess whether inflammasome activation in monocytes drives Treg polarization. We seek to determine if the inflammasome induces proinflammatory signaling in monocytes/macrophages from patients with DAIH; and determine if activation of the UPR via ATF6 induces a pro-inflammatory signature in Tregs from patients with DAIH and drives reduced regulatory function. Gene silencing of caspase-1 in CD14+ monocytes and ATF6 in CD127-CD25highCD4+ Tregs using lentiviral shRNA will allow us to (i) confirm activation of the inflammasome (caspase-1, (pro)IL-1b, (pro)IL-18, and NLRP3) in DAIH and establish if inhibition of the inflammasome in monocytes influences the subsequent production of effector cytokines in Tregs when co-cultured and (ii) to verify a functional role for ATF6 in the production of pro-inflammatory cytokines by Tregs, and establish if UPR activation compromises the regulatory capacity of Tregs.

Dana Peters, Ph.D.
Assistant Professor
Department of Radiology and Biomedical Imaging

Magnetic Resonance Biomarkers of Acidosis in the Liver Tumor

Liver cancer is the only cancer with growing incidence rates worldwide, with over 800,000 new cases every year of primary and 300,000 cases of metastatic disease. Transarterial chemoembolization (TACE) is a minimally invasive, image-guided, catheter-based therapy which significantly improves patient survival. However, TACE is still only palliative but could possibly become curative if problems due to imperfect drug delivery—especially for large tumors—were solved. Multiparameter MRI (mpMRI) –MRI which combines several measures of the tumor--could ultimately guide therapies. Our team combines unique expertise in liver cancer therapies, and MR imaging. Liver tumor progression is known to occur in acidic tumor microenvironments (1,2) which stimulate vascularity. Increased cellularity is also a marker of tumor progression. Vascularity, cellularity, and importantly, acidity, can be quantified using MRI methodologies. We are developing mpMRI tools to quantify acidity, vascularity, cellularity, with the goal of employing them to identify post-TACE response of increased tumor aggression, in future studies.

2016-2017 Pilot Project Recipients

Arya Mani, M.D.
Associate Professor of Medicine and Genetics
Department of Cardiovascular Medicine

The role of Wnt/ TCF7L2 in regulation of Liver Fat, Inflammation and fibrosis

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease, which begins with steatosis and advances to steatohepatitis (NASH), steatofibrosis, and cirrhosis. The pathways involved in disease progression are not well understood. Loss-of-function mutations in Wnt coreceptor LDL receptor-related protein 6 (LRP6) underlie NASH and metabolic syndrome in humans (Mani, Science 20071). Mice with the human disease-associated LRP6R611C mutation exhibit hyperlipidemia, steatohepatitis and steatofibrosis. These traits are associated with increased activation of the noncanonical Wnt pathways and its downstream kinase NLK, which phosphorylates Wnt transcription cofactor TCF7L2 and results in its ubiquitination. The causal link between altered Wnt/TCF7L2 signaling, hyperlipidemia and NASH is supported by normalization of TCF7L2 expression and the rescue of the hyperlipidemia and NASH upon Wnt3a administration to LRP6mut/mut mice. These studies identify diverse disease pathways that underlie a spectrum of NASH-related liver diseases and are triggered by a single human genetic mutation and underscore the importance of TCF7L2 in protection against NASH. Most notable, genetic variants in TCF7L2 gene have been associated with increased risk for NAFLD3,4 and diabetes. Our current focus is on studying the role of TCF7L2 in regulation of liver fat, inflammation and fibrosis and plasma lipids in mice overexpressing TCF7L2 and mice haploinsufficient for TCF7L2.

LIVER CENTER ANNOUNCEMENTS

Yale Liver Center Retreat

Please join us for the bi-annual Yale Liver Center Retreat:

Date: Saturday, November 19th, 2016

Location: New Haven Country Club
160 Hartford Turnpike, New Haven, CT 06517

Start time: 8:00AM

Please RSVP to Christine Abu-Hanna.

2016-2017 New Liver Center Members

Christopher Ibarra
Xuchen Zhang

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

Membership Criteria

Featured Publications

Insulin Receptor Thr^{1160} Phosphorylation Mediates Lipid-Induced Hepatic Insulin Resistance

Petersen MC, Madiraju AK, Gassaway BM, Marcel M, Nasiri AR, Butrico G, Marcucci MJ, Zhang D, Abudukadier A, Zhang XM, Philbrick W, Hubbard SR, Jurczak MJ, **Samuel VT**, Rinehart J, and **Shulman GI**.

Published in: Journal of Clinical Investigation, 2016

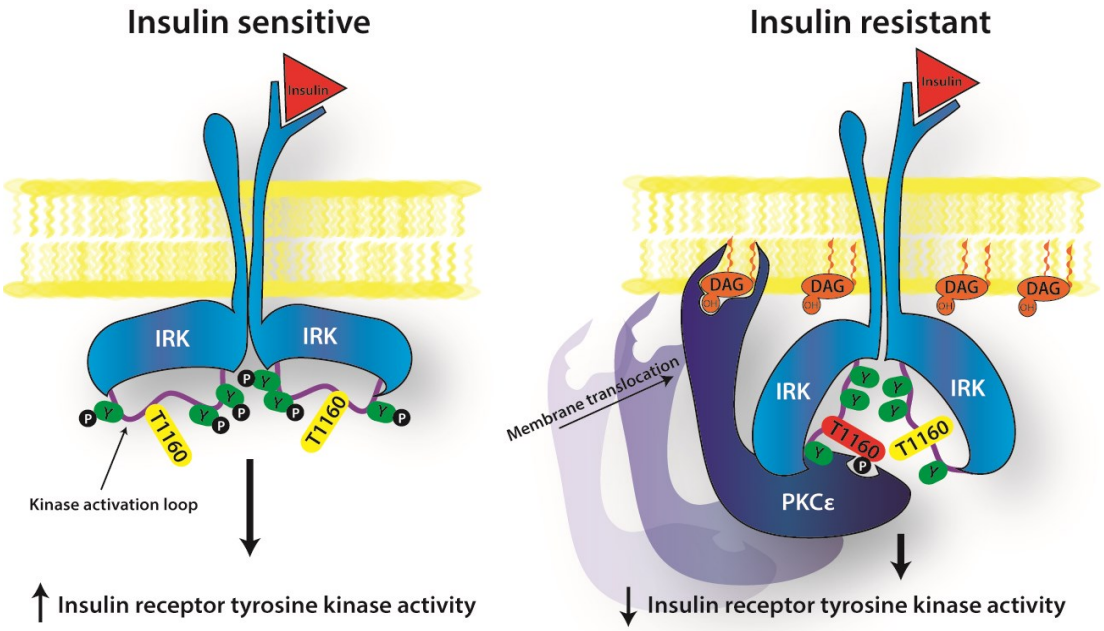


Figure: Mechanism of DAG-PKCe induced Hepatic Insulin Resistance

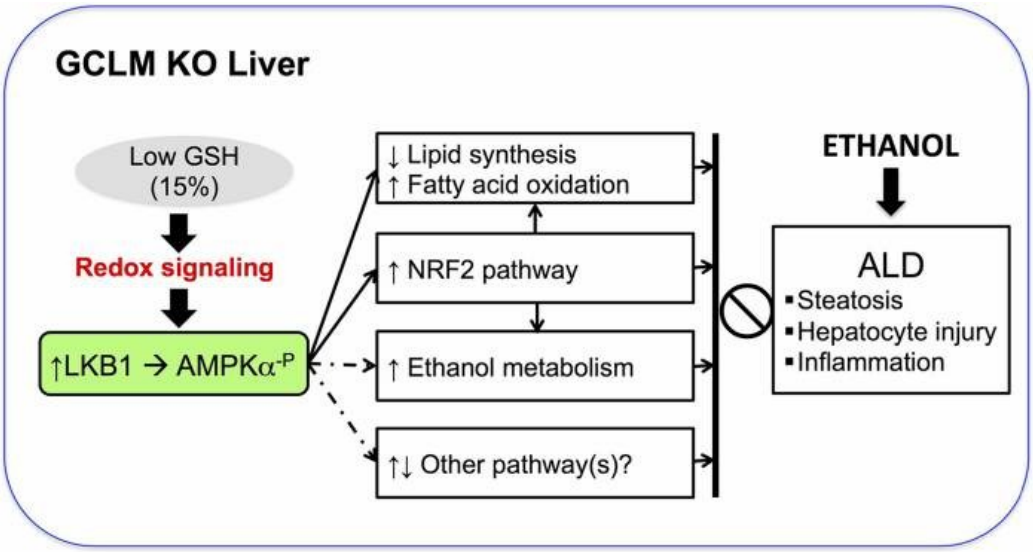
Nonalcoholic fatty liver disease (NAFLD) is a risk factor for type 2 diabetes (T2D), but whether NAFLD plays a causal role in the pathogenesis of T2D is uncertain. One proposed mechanism linking NAFLD to hepatic insulin resistance involves diacylglycerol-mediated (DAG-mediated) activation of protein kinase C-ε (PKCε) and consequent inhibition of insulin receptor (INSR) kinase activity. However, the molecular mechanism underlying PKCε inhibition of INSR kinase activity is unknown. In this study Max Petersen, a Yale MSTP student, studying in the lab of Gerald Shulman (George R. Cowgill Professor of Medicine and Cellular & Molecular Physiology) used mass spectrometry to identify the phosphorylation site Thr^{1160} as a PKCε substrate in the functionally critical INSR kinase activation loop in collaboration with Jesse Reinhart (Associate Professor of Cellular & Molecular Physiology). They hypothesized that Thr^{1160} phosphorylation impairs INSR kinase activity by destabilizing the active configuration of the INSR kinase, and their results confirmed this prediction by demonstrating severely impaired INSR kinase activity in phosphomimetic T1160E mutants. Conversely, the INSR T1160A mutant was not inhibited by PKCε in vitro. Furthermore, mice expressing INSR with a threonine-to-alanine mutation at the homologous residue Thr^{1150} (*Insr*^{T1150A} mice) were protected from high fat diet-induced hepatic insulin resistance. *Insr*^{T1150A} mice also displayed increased insulin signaling, suppression of hepatic glucose production, and increased hepatic glycogen synthesis compared to wild-type controls during hyperinsulinemic clamp studies. These data reveal a critical pathophysiological role for INSR Thr^{1160} phosphorylation and provide further mechanistic links between PKCε and INSR in mediating NAFLD-induced hepatic insulin resistance.

Featured Publications

Chronic Glutathione Depletions Confers Protection against Alcohol-induced Steatosis: Implication for Redox Activation of AMP-activated Protein Kinase Pathway

Chen Y, Singh S, Matsumoto A, Manna SK, Abdelmegeed MA, Golla S, Murphy RC, Dong H, Song BJ, Gonzalez FJ, Thompson DC, **Vasiliou V.**

A new study from the Yale School of Public Health has identified a novel mechanism that protects the liver against the accumulation of fats and may represent a promising new therapeutic approach for treating and/or preventing alcoholic liver disease (ALD) and other fatty liver diseases.



Although the pathogenesis of ALD is poorly understood, it is believed that oxidative stress (caused by the overproduction of free radicals associated with decreased levels of the antioxidant glutathione) plays a critical role. The study showed that mice genetically engineered to have much lower levels of glutathione in the liver are more resistant to alcohol-induced accumulation of fatty cells in the liver (steatosis, a major symptom of ALD) despite having increased levels of oxidative stress in the liver.

"This is an amazing finding that reveals an unanticipated capacity of oxidative stress to elicit beneficial cellular responses," said Vasiliou, who specializes in alcohol-related illnesses. "This should advance the field by providing a new direction for preventing and/or treating alcoholic liver disease and, potentially, other fatty liver diseases."

The researchers showed the involvement of activation of the AMP-activated protein kinase (AMPK) pathway in the liver, which, in turn, promoted beneficial changes in fat and lipid mobilization. The next step is to develop a new class of drugs that mimic the effects of this process on AMPK. This possibility is particularly exciting because there is currently no effective therapeutic treatment for ALD.

"Developing such drugs may revolutionize the treatment of this disease," Vasiliou said.

ALD accounts for over 30,000 deaths annually in the United States alone. The disease results in a variety of complications, including bleeding, coma, sepsis, cirrhosis, liver failure and death. There are no effective therapies for any form of ALD, making this an area of great unmet need. With advanced disease simply stopping drinking does not result in reversal of ALD.

Featured Publications

ACOX 2 deficiency: A disorder of bile acid synthesis with transaminase elevation, liver fibrosis, ataxia, and cognitive impairment

Vilarinho S, Sari S, Mazzacuva F, Bilguvar K, Esendagli-Yilmaz G,
Jain D, Akyol G, Dalgic B, Gunel M, Clayton PT, Lifton RP

Liver disease of unknown cause represents an unmet medical need. Using exome sequencing, we have described a new syndrome associated with homozygous loss of ACOX2 featuring intermittently elevated transaminases, liver fibrosis, mild ataxia and cognitive impairment. ACOX2 encodes the peroxisomal branched-chain acyl-CoA oxidase and is involved in the bile acid biosynthetic pathway. Importantly, this disorder is potentially reversible, because the bile acid synthetic pathway can be suppressed with exogenous bile acids, diminishing the production of the likely toxic metabolites causing liver and neurologic dysfunction. To date, most peroxisomal disorders have been diagnosed via the identification of probands with severe phenotypes with marked biochemical abnormalities, followed by investigation leading to identification of the genetic defect. It is noteworthy that our patient presented with a relatively non-specific clinical presentation, and that a primary defect in bile acid biosynthesis was not considered prior to identification of the ACOX2 mutation. Particularly because of the potential for mitigation of the clinical consequences of ACOX2 deficiency, this diagnosis should be considered in children with unexplained transaminase elevations and neurologic abnormalities, and raise the question of whether ACOX2 mutation might also contribute to cases of cryptogenic cirrhosis later in life.

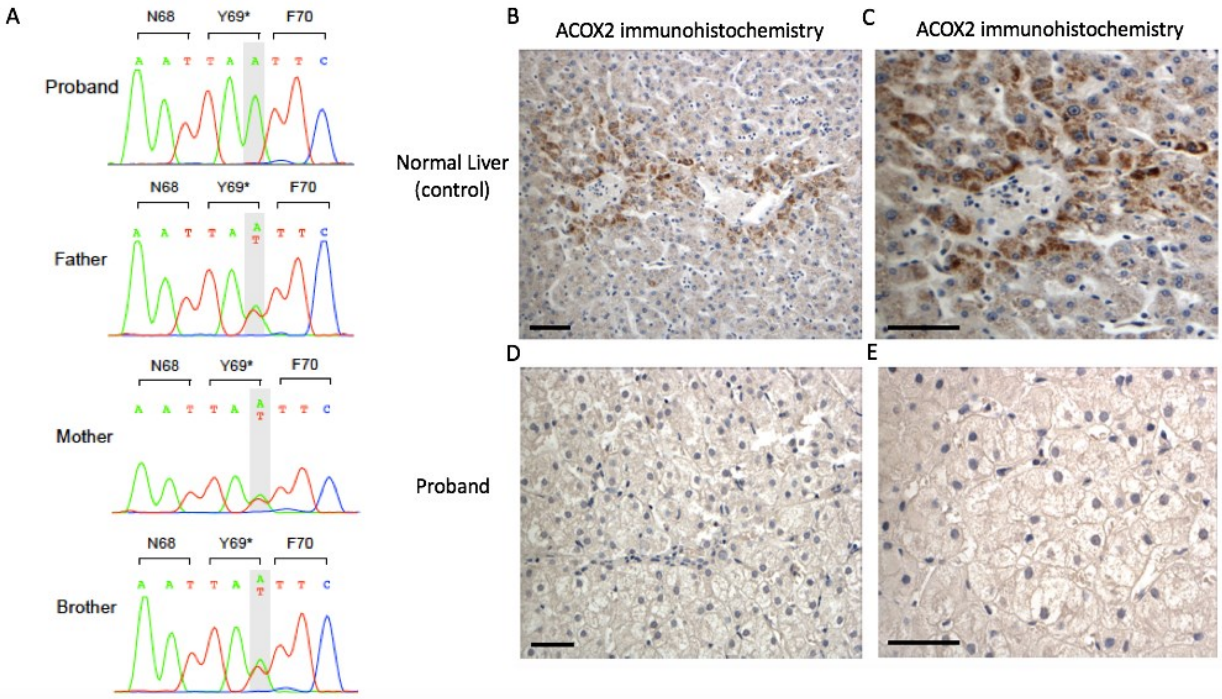


Figure 1. ACOX2 mutation in a subject with an unrecognized bile acid synthesis disorder and absence of ACOX2 in proband's liver. (A) Sanger sequencing chromatograms of the proband, his unaffected parents and brother. The ACOX2 p.Y69* mutation is homozygous in the proband and heterozygous in the unaffected parents and sibling. (B, C) Immunohistochemistry for ACOX2 in normal liver shows intense granular staining in the pericentral (zone 3) hepatocytes. The staining in remaining hepatocytes is faint. (D, E) Immunohistochemistry for ACOX2 in the proband's liver biopsy, showing complete absence of staining. Scale bars, 50μm.

Featured Core: Cellular & Molecular Physiology Core

James Boyer, MD
Director

Shi-Ying Cai, PhD	Carlo Spirli, PhD	Meena Ananth, PhD	Kathy Harry
Assistant Director	Assistant Director	Assistant Director	Research Assistant

The Cellular and Molecular Physiology Core is the "work horse" of the Center and is organized to provide technical expertise, equipment, and personnel to Liver Center investigators in order to provide them with state of the art research resource in an efficient, quality controlled, and cost effective manner. The facility is divided in to two components:

Cell Isolation, Cell Culture, & Organ Perfusion

- Isolated cell preparations including: Hepatocytes, Cholangiocytes, Endothelial cells, Stellate cells, Portal fibroblasts, Hepatic lymphocytes
- Equipment and expertise for isolated liver perfusion preparations in rats and mice for studies using the whole perfused organ
- Cell culture facilities for short– and long-term cultures and cell lines.

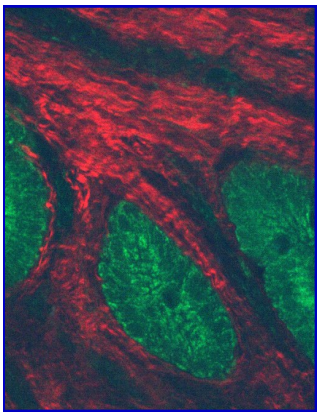
Molecular

Maintains the latest models of equipment for protein and gene expression using Quantitative real time PCR and infrared imaging detection and pro-vides technology and expertise for altering gene expression in cells and tis-sues using siRNA transfection and adenovirus infection.

NEW! Animal Models of Disease

Several new animal models of disease have been added to the Core's resources: Cystic fibrosis, Alagille syndrome, Autosomal Dominant Polycystic Kidney Disease, Autosomal Recessive Polycystic Kidney Disease, Autoimmune hepatitis, and Biliary Atresia.

Additional Resources: Keck Biotechnology Resource Laboratory, Yale Center for Genome Analysis (YCGA)



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.

MEMBER'S RECENT PUBLICATIONS

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Continued on Next Page

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