Yale Liver Center
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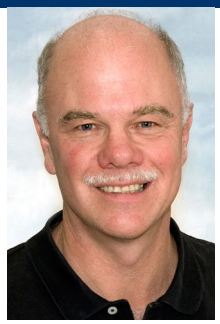
NEW MEMBER SPOTLIGHT



James Duncan, PhD

Ebenezer K. Hunt Professor of Radiology and Biomedical Imaging and Professor of Biomedical Engineering;
Director of Undergraduate Studies in Biomedical Engineering;
Vice Chair, Bioimaging Sciences in the Department of Diagnostic Radiology

What are your core research interests?

Medical Image Processing and analysis, statistical pattern recognition, computer vision, machine learning: basically quantitative analysis of biomedical images focused on image segmentation, non-rigid motion/deformation tracking and image-guided intervention.

How does your research connect to Liver Disease?

Our group is primarily working on the analysis of multiparameter MR images to both perform tissue classification (into classes of active tumor, necrosis, vessels, normal parenchyma) and develop image-based biomarkers for outcome prediction. We are primarily working with pre-clinical and patient data related to both baseline imaging and treatment by transarterial chemoembolization (TACE), but are looking to expand into other liver diseases/disorders.

Tell us about your vision on how Image analysis, data science and machine learning can help us address the most pressing issues in liver cancer?

Our hope is that quantitative information derived from noninvasive imaging can be related to other (e.g. phenotypical, pathological and/or genomic) information to help study longitudinal changes in liver disease as well as understand the effects of different therapies (such as TACE). In addition, by registering certain information (e.g. voxel-wise tissue class labels from multiparameter MRI) with intra-procedural imaging (e.g. Cone beam CT), the interventional radiologist or oncologist would be able to perform image-guided therapeutic procedures more accurately and reliably. Finally, we hope to be able to take this same quantitative information at baseline and/or after initial treatment and use it to predict response to therapy, either with respect to overall survival or possibly even tumor burden. Our work uses both statistical/geometric model-based strategies and/or data-driven (machine or deep learning) strategies to label or classify image information, as well as to predict outcomes.

Can you - in a few words - tell us more about the IPAG and the faculty that work with you?

The Image Processing and Analysis Group (IPAG) was formed around 1997 within the Department of Radiology & Biomedical Imaging and currently is made up of 6 faculty members, all with backgrounds in Electrical Engineering, Biomedical Engineering, Applied Mathematics and/or Computer Science. All faculty also hold fully joint or secondary appointments in one or more departments in Yale's School of Engineering and Applied Science (including Biomedical Engineering, Electrical Engineering and Statistics & Data Science). Including postdoctoral researchers, Ph.D. students, MS students, undergraduate researchers and staff there are about 30 people within the Group, who reside on the first, second and third floors of The Anlyan Center and work closely with other colleagues in MRI, MRS and PET within Radiology's Division of Bioimaging Sciences.

How do you plan to support the liver center physician-scientists in their efforts to bridge basic science and clinical application?

In addition to working closely on new and continuing NIH R01 funding on image-derived biomarkers for use in studying, diagnosing and predicting changes in liver disease, members of IPAG have recently formed the center for Translational Image Analysis and Machine Learning (TIAML). This center is intended to work more closely with clinical and hospital-based colleagues to assemble and analyze clinical image data for use in data-driven research, intending to bridge clinical hypotheses to image-derived quantitative parameters whose measurement is motivated from basic research. One of the key initial areas whose data are being studied and analyzed is liver disease. This resource will be made available to liver center members.

How many members of your group are involved in research of liver disease?

Four faculty members and about 4 PhD students are currently involved in liver disease research, with more becoming interested each month. Several Yale College (BME) undergraduates have also been involved.

What's your favorite college football / hockey team?

Ever since my middle daughter attended and graduated from Michigan State a few years ago, I've been avidly following their football and basketball teams. As for hockey, I love going to Yale games when I can.

LIVER CENTER THEMES

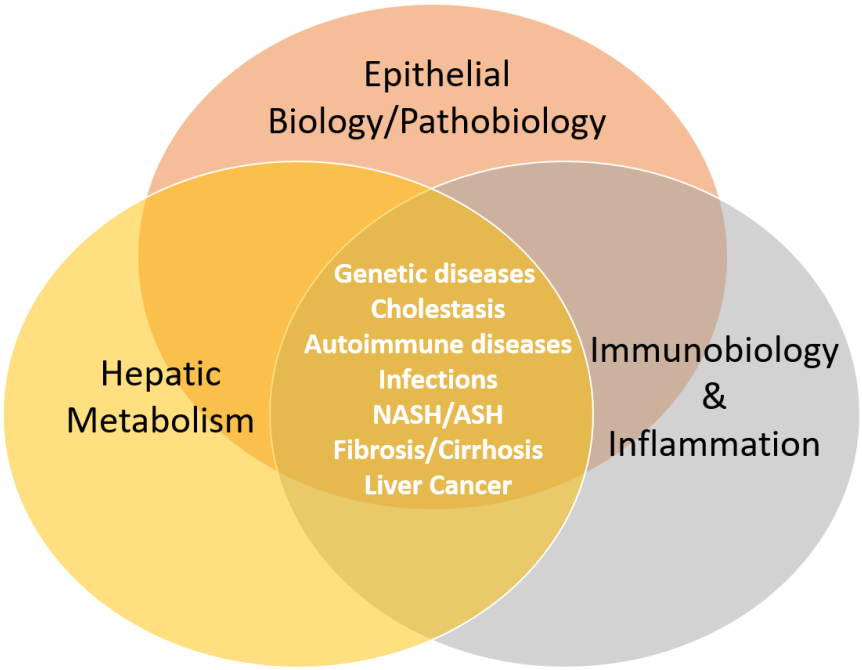
The Research Base of the Liver Center focuses on three broad translational themes. These include:

(1) Immunobiology and inflammation

(2) Hepatic metabolism

(3) Epithelial biology and pathobiology

The major areas of liver disease examined within these translational themes include autoimmune diseases, cholestasis, fibrosis/ cirrhosis, genetic diseases, infections, liver cancer, and NASH/ASH. Many of our investigators have research interests that span multiple themes.



2019-2020 PILOT PROJECT AWARDS

Jittima Weerachayaphorn, PhD
Visiting Assistant Professor
Internal Medicine, Digestive Diseases

" Role of inositol 1,4,5-trisphosphate receptors in alcoholic hepatitis"

John Onofrey, PhD
Associate Research Scientist
Radiology & Biomedical Imaging

"Automated Hepatic Lesion Detection and LI-RADS Prediction using Deep Learning for Clinical Decision Support"

Shi-Ying Cai, PhD
Senior Research Scientist
Internal Medicine, Digestive Diseases

"Role of Ca2+/NFAT signaling pathway in cholestatic liver injury"

FOR MORE INFORMATION ON THESE PROJECTS, PLEASE VISIT OUR WEBSITE

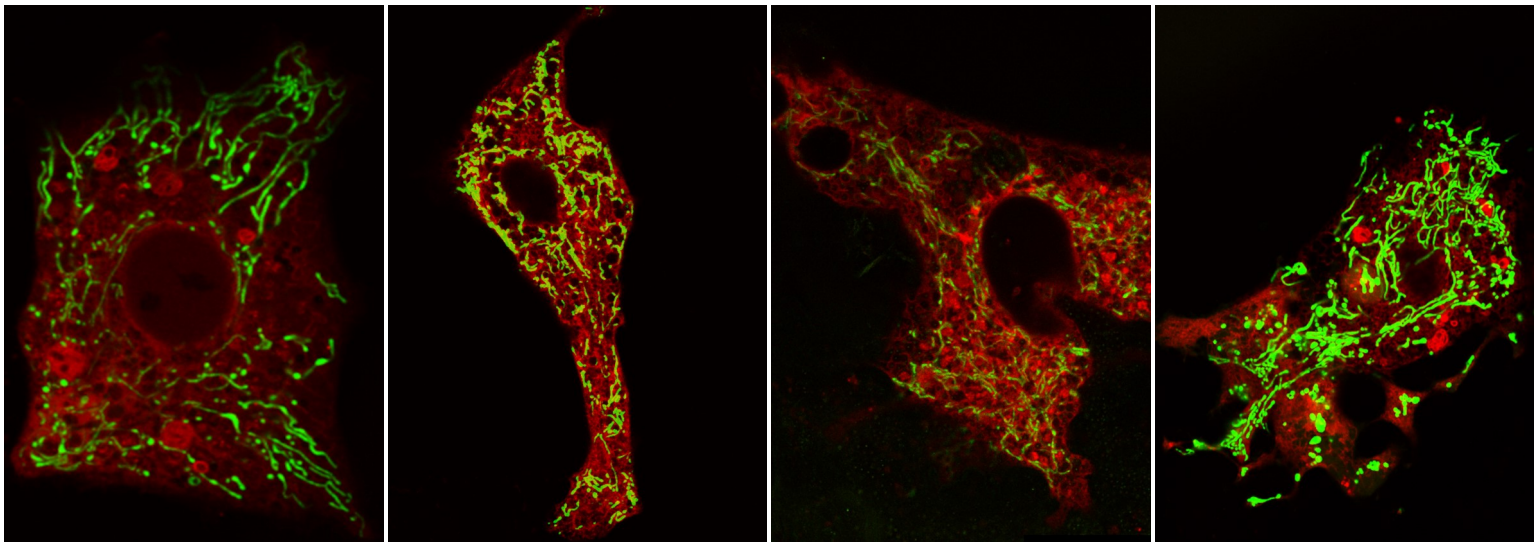
FEATURED PUBLICATIONS

Glucagon stimulates gluconeogenesis by $InsP_3R$-I mediated hepatic lipolysis

Rachel J. Perry, Dongyan Zhang, **Mateus T. Guerra,** Allison L. Brill, Leigh Goedeke, Ali R. Nasiri, Aviva Rabin-Court, Yongliang Wang, Liang Peng, Sylvie Dufour, Ye Zhang, Xian-Man Zhang, Gina M. Butrico, Keshia Toussaint, Yuichi Nozaki, Gary W. Cline, **Kitt Falk Petersen, Michael H. Nathanson, Barbara E. Ehrlich, and Gerald I. Shulman**

Nature. 2020; Accepted for publication

While it is well-established that alterations in the portal vein insulin/glucagon ratio play a major role in causing dysregulated hepatic glucose metabolism in type 2 diabetes (T2D)1-3, the mechanisms by which glucagon alters hepatic glucose production and mitochondrial oxidation remain poorly understood. Here we show that glucagon stimulates hepatic gluconeogenesis by increasing hepatic adipose triglyceride lipase activity, intrahepatic lipolysis, hepatic acetyl-CoA content, and pyruvate carboxylase flux, while also increasing mitochondrial fat oxidation, mediated by stimulation of the inositol triphosphate receptor-1 (InsP3R-I). Chronic physiological increases in plasma glucagon concentrations increased mitochondrial hepatic fat oxidation and reversed diet-induced hepatic steatosis and insulin resistance in rats and mice; however, the effect of chronic glucagon treatment to reverse hepatic steatosis and glucose intolerance was abrogated in InsP3R-I knockout mice. These results provide new insights into glucagon biology and suggest that InsP3R-I may be a novel therapeutic target to reverse nonalcoholic fatty liver disease and T2D.



Glucagon has something to say to the mitochondria
Human hepatocytes (hepG2) imaged using super-resolution STED microscopy showing the close association between mitochondria (green) and endoplasmic reticulum (ER; red). Images obtained by Allison Brill and Dr. Barbara Ehrlich.

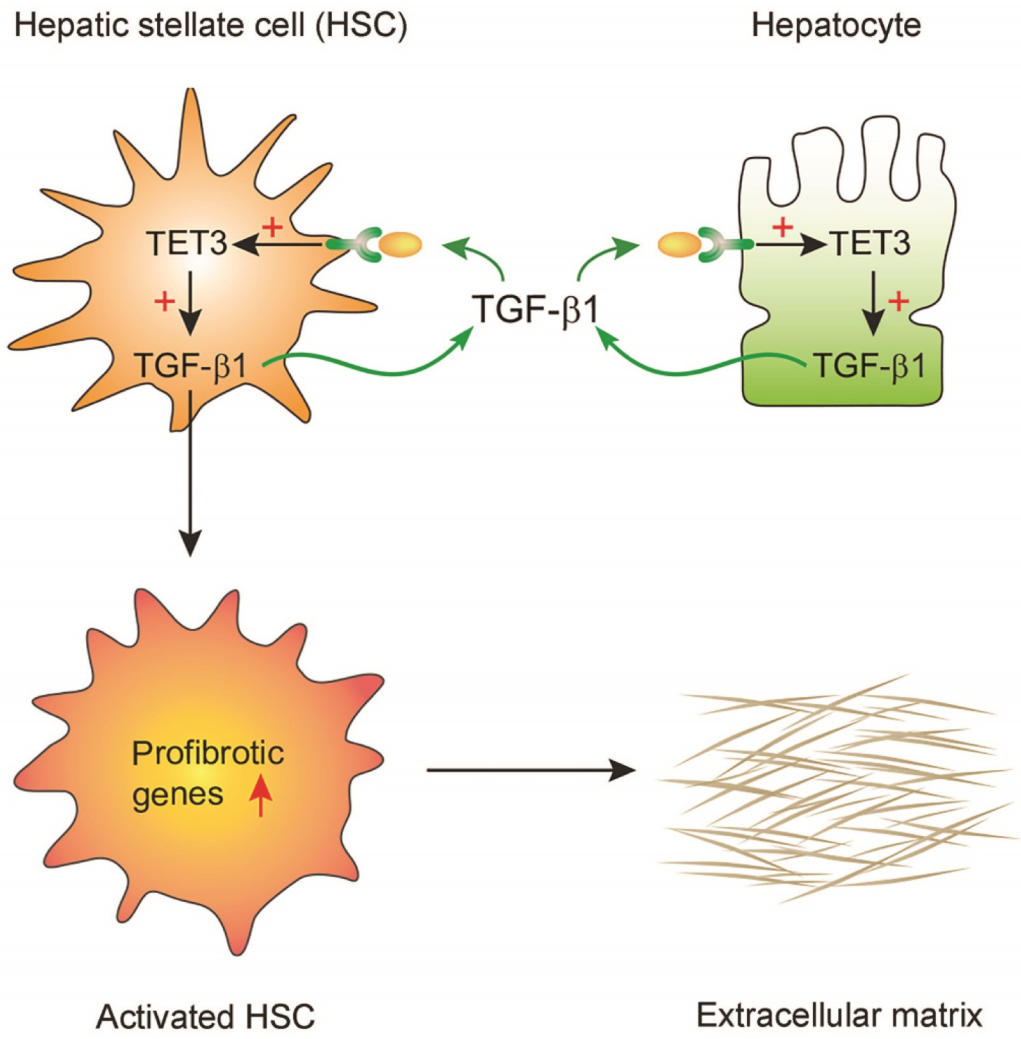
FEATURED PUBLICATIONS

A Positive Feedback Loop of TET3 and TGF-β1 Promotes Liver Fibrosis

Xu Y, Sun X, Zhang R, Cao T, **Cai SY, Boyer JL**, Zhang X, Li D, **Huang Y.**

Cell Rep. 2020; 30:1310-1318.e5

Pathological activation of TGF-β signaling is universal in fibrosis. Aberrant TGF-β signaling in conjunction with transdifferentiation of hepatic stellate cells (HSCs) into fibrogenic myofibroblasts plays a central role in liver fibrosis. Here we report that the DNA demethylase TET3 is anomalously upregulated in fibrotic livers in both humans and mice. We demonstrate that in human HSCs, TET3 promotes profibrotic gene expression by upregulation of multiple key TGF-β pathway genes, including TGFB1. TET3 binds to target gene promoters, inducing demethylation, which in turn facilitates chromatin remodeling and transcription. We also reveal a positive feedback loop between TGF-β1 and TET3 in both HSCs and hepatocytes. Furthermore, TET3 knockdown ameliorates liver fibrosis in mice. Our results uncover a TET3/TGF-β1 positive feedback loop as a crucial determinant of liver fibrosis and suggest that inhibiting TET3 may represent a therapeutic strategy for liver fibrosis and perhaps other fibrotic diseases.



A positive feedback model in liver fibrosis. Stressed hepatocytes upregulate TET3 leading to increased production of TGF-β1 from hepatocytes. TGF-β1 acts on both hepatocytes and HSCs to stimulate more TGF-β1 production via the TET3/TGF-β1 positive feedback mechanism. In HSCs, TET3 also promotes profibrotic gene expression and subsequent ECM production via increasing expression of multiple TGF-β pathway genes.

AVAILABLE CENTER CORE SERVICES

ADMINISTRATIVE

PILOT FEASIBILITY PROGRAM
Pilot grants given annually to promote studies of liver disease

ENRICHMENT PROGRAM
Weekly seminar series, annual Klatskin Lectureship, bi-annual Center retreat

CELLULAR-MOLECULAR

ISOLATED CELL PREPARATIONS
Hepatocytes, cholangiocytes, endothelial cells, stellate cells, portal fibroblasts and hepatic lymphocytes, primarily from mice and rates. Human hepatocytes when available.

PROTEIN & GENE EXPRESSION
Quantitative real time PCR and infrared imaging detection . Altering gene expression in these cells using siRNA transfection and adenovirus infection technologies

IPSC/LIVER ORGANOID
On request, PBMCs are transferred to the Yale Stem Cell Center (YSCC) for reprogramming into iPSC. YSCC will generate at least 3 clones of iPSCs for each PBMC sample. iPSCs can be differentiated into liver cells (biliary cells or hepatocytes) and made available. Liver organoids available upon request

CELL CULTURE FACILITIES
Available for short– and long–term cultures and cell lines

MORPHOLOGY

CONFOCAL, SUPER-RESOLUTION, MULTIPHOTON IMAGING
Leica SP5
Swept-field (Opterra II, Bruker)
Zeiss LSM 710 duo
Vutara 252 super-resolution
Leica SP8 gated STED 3X
Zeiss LSM 880 AiryScan Fast
Bruker Luxendo MuVi SPIM

EPIFLUORESCENCE MICROSCOPY INCLUDING QUANTITATIVE & RATIO IMAGING
Zeiss Axio Observer epifluorescence microscope
Olympus BX51 multi-headed brightfield microscope
Dissecting microscope
Zeiss Discovery 8 SteReo

ELECTRON MICROSCOPY
Tecnai 12. biotwinFEI Tecnai TF20 FEG

CLINICAL-TRANSLATIONAL

BIOSTATISTICAL SUPPORT
Two biostatisticians available for expertise in the design, conduct, and analysis of patient-oriented studies, as well as methodological development, education, and training

BIOSPECIMEN & LIVER BIOPSY REPOSITORY
Recruitment of patients and collection of blood samples

PATIENT REGISTRY
Patient databases on diagnoses including: chronic hepatitis C, cirrhosis, chronic hepatitis B, PBC, autoimmune hepatitis, PSC, hepatocellular carcinoma, NAFLD, and cholangiocarcinoma

Members' Original Recent Publications

Polycystin 2 is increased in disease to protect against stress-induced cell death.
Brill AL, Fischer TT, Walters JM, Marlier A, Sewanan LR, Wilson PC, Johnson EK, Moeckel G, Cantley LG, Campbell SG, Nerbonne JM, Chung HJ, Robert ME, Ehrlich BE. Sci Rep. 2020;10:386. PMID: 31941974

Distinct Hepatic PKA and CDK Signaling Pathways Control Activity-Independent Pyruvate Kinase Phosphorylation and Hepatic Glucose Production.
Gassaway BM, Cardone RL, Padyana AK, Petersen MC, Judd ET, Hayes S, Tong S, Barber KW, Apostolidi M, Abulizi A, Sheetz JB, Kshitiz, Aerni HR, Gross S, Kung C, Samuel VT, Shulman GI, Kibbey RG, Rinehart J. Cell Rep. 2019; 29:3394-3404.e9. PMID: 31825824

Type 3 inositol 1,4,5-trisphosphate receptor: A calcium channel for all seasons.
Mangla A, Guerra MT, Nathanson MH. Cell Calcium. 2020; 85:102132. PMID: 31790953

Bacteriophage targeting of gut bacterium attenuates alcoholic liver disease.
Duan Y, Llorente C, Lang S, Brandl K, Chu H, Jiang L, White RC, Clarke TH, Nguyen K, Torralba M, Shao Y, Liu J, Hernandez-Morales A, Lessor L, Rahman IR, Miyamoto Y, Ly M, Gao B, Sun W, Kiesel R, Hutmacher F, Lee S, Ventura-Cots M, Bosques-Padilla F, Verna EC, Abraldes JG, Brown RS Jr, Vargas V, Altamirano J, Caballería J, Shawcross DL, Ho SB, Louvet A, Lucey MR, Mathurin P, Garcia-Tsao G, Bataller R, Tu XM, Eckmann L, van der Donk WA, Young R, Lawley TD, Stärkel P, Pride D, Fouts DE, Schnabl B. Nature. 2019; 575:505-511. PMID: 31723265

O-GlcNAc transferase suppresses necroptosis and liver fibrosis.
Zhang B, Li MD, Yin R, Liu Y, Yang Y, Mitchell-Richards KA, Nam JH, Li R, Wang L, Iwakiri Y, Chung D, Robert ME, Ehrlich BE, Bennett AM, Yu J, Nathanson MH, Yang X. JCI Insight. 2019;4. pii: 127709. PMID: 31672932

Clinical outcome indicators in chronic hepatitis B and C: A primer for value-based medicine in hepatology.
Strazzabosco M, Cortesi PA, Conti S, Okolicsanyi S, Rota M, Ciaccio A, Cozzolino P, Fornari C, Gemma M, Scalone L, Cesana G, Fabris L, Colledan M, Fagiuoli S, Ideo G, Zavaglia C, Perricone G, Munari LM, Mantovani LG, Belli LS. Liver Int. 2020; 40:60-73. PMID: 31654608

Molecular Imaging of Extracellular Tumor pH to Reveal Effects of Locoregional Therapy on Liver Cancer Microenvironment.
Savic LJ, Schobert IT, Peters D, Walsh JJ, Laage-Gaupp FM, Hamm CA, Tritz N, Doemel LA, Lin M, Sinusas A, Schlachter T, Duncan JS, Hyder F, Coman D, Chapiro J. Clin Cancer Res. 2020;26:428-438. PMID: 31582517

Epidermal growth factor (EGF) triggers nuclear calcium signaling through the intranuclear phospholipase Cδ-4 (PLCδ4).
de Miranda MC, Rodrigues MA, de Angelis Campos AC, Faria JAQA, Kunrath-Lima M, Mignery GA, Schechtman D, Goes AM, Nathanson MH, Gomes DA. J Biol Chem. 2019; 294:16650-16662. PMID: 31537645

GDF15 Is an Inflammation-Induced Central Mediator of Tissue Tolerance.
Luan HH, Wang A, Hilliard BK, Carvalho F, Rosen CE, Ahasic AM, Herzog EL, Kang I, Pisani MA, Yu S, Zhang C, Ring AM, Young LH, Medzhitov R. Cell. 2019; 178:1231-1244.e11. PMID: 31402172

Type 3 Inositol 1,4,5-Trisphosphate Receptor Is Increased and Enhances Malignant Properties in Cholangiocarcinoma.
Ueasilamongkol P, Khamphaya T, Guerra MT, Rodrigues MA, Gomes DA, Kong Y, Wei W, Jain D, Trampert DC, Ananthanarayanan M, Banales JM, Roberts LR, Farshidfar F, Nathanson MH, Weerachayaphorn J. Hepatology. 2019. doi: 10.1002/hep.30839. [Epub ahead of print] PMID: 31251815

Pathobiology of inherited biliary diseases: a roadmap to understand acquired liver diseases.
Fabris L, Fiorotto R, Spirli C, Cadamuro M, Mariotti V, Perugorria MJ, Banales JM, Strazzabosco M. Nat Rev Gastroenterol Hepatol. 2019; 16:497-511. Review. PMID: 31165788

Pathophysiology of Cystic Fibrosis Liver Disease: A Channelopathy Leading to Alterations in Innate Immunity and in Microbiota.
Fiorotto R, Strazzabosco M. Cell Mol Gastroenterol Hepatol. 2019; 8:197-207. Review. PMID: 31075352

Clinical utility of genomic analysis in adults with idiopathic liver disease.
Hakim A, Zhang X, DeLisle A, Oral EA, Dykas D, Drzewiecki K, Assis DN, Silveira M, Batisti J, Jain D, Bale A, Mistry PK, Vilarinho S. J Hepatol. 2019; 70:1214-1221. PMID: 31000363