LIVER DIGEST

September 25, 2023

A bi-weekly update of PLRC happenings

PITTSBURGH LIVER RESEARCH CENTER
A partnership of University of Pittsburgh & UPMC

In this issue:

Please acknowledge all support from the PLRC in your publications and presentations. Note the grant number and all CORES used. (NIH/NIDDK P30DK120531)

Please share your relevant accolades (grants, publications, awards and other news worthy items) with us, as it relates to the PLRC mission, so we can share with all of our members.

Visit the PLRC website (www.livercenter.pitt.edu) for up-to-date news, seminar and event information.
Contact Aaron Bell (bellaaro@pitt.edu) if you have specific questions or suggestions.

Our mailing address is:

Pittsburgh Liver Research Center
S414 Biomedical Science Tower
200 Lothrop St. | Pittsburgh, PA 15261

Faculty Highlight

Dr. Paul Monga, MD., Director of PLRC, co-authored a publication in Life Science Alliance on the impact of Huntingtin gene loss on liver function, entitled ***"Huntingtin loss in hepatocytes is associated with altered metabolism, adhesion, and liver zonation".***

Bragg RM, Coffey SR, Cantle JP, Hu S, Singh S, Legg SRW, McHugh CA, Toor A, Zeitlin SO, Kwak S, Howland D, Vogt TF, Monga SP, Carroll JB. bioRxiv [Preprint]. 2023 Jun 26:2023.06.24.546334. doi: 10.1101/2023.06.24.546334. PMID: 37425835; PMCID: PMC10327156.

Huntington's disease arises from a toxic gain of function in the *huntingtin* (*HTT*) gene. As a result, many HTT-lowering therapies are being pursued in clinical studies, including those that reduce HTT RNA and protein expression in the liver. To investigate potential impacts, we characterized molecular, cellular, and metabolic impacts of chronic HTT lowering in mouse hepatocytes. Lifelong hepatocyte HTT loss is associated with multiple physiological changes, including increased circulating bile acids, cholesterol and urea, hypoglycemia, and impaired adhesion. HTT loss causes a clear shift in the normal zonal patterns of liver gene expression, such that pericentral gene expression is reduced. These alterations in liver zonation in livers lacking HTT are observed at the transcriptional, histological and plasma metabolite level. We have extended these phenotypes physiologically with a metabolic challenge of acetaminophen, for which the HTT loss results in toxicity resistance. Our data reveal an unexpected role for HTT in regulating hepatic zonation, and we find that loss of HTT in hepatocytes mimics the phenotypes caused by impaired hepatic β-catenin function.

Young Investigator Highlight

Mathew Carson, postdoc in the lab of **Dr. Kari Nejak-Bowen**, was awarded a $2500.00 pre-pilot & feasibility grant funded by the *Pittsburgh Liver Institute* to evaluate perturbations in the liver-bone axis, secondary to cholestatic liver disease with a focus on primary sclerosing cholangitis. Congratulations!

His grant is entitled, **"Evaluating the role of hepatic β-catenin on dysregulated liver-bone signaling in cholestatic liver disease."**

Abstract: Osteoporosis is a frequent comorbidity in patients with cholestatic liver diseases. While lower bone mass has been demonstrated in the Mdr2 knockout model of cholestatic liver disease, the underlying mechanisms causing bone loss remain unclear. Wnt/β-catenin signaling in the liver regulates bile acid and vitamin C metabolism, which have been shown to impact bone cell differentiation and function. Considering knockdown of β-catenin aggravates liver injury in the MDR2 knockout model, we hypothesize that knockout of hepatic β-catenin may exacerbate bone loss attributed in part to changes in circulating bile acids and vitamin C.

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Faculty Highlight



Dr. Silvia Liu | Dr. Kari Nejak-Bowen | Dr. Dean Yimlamai

PLRC GSBC Core Director Dr. Silvia Liu along with **Dr. Kari Nejak-Bowen** and former PLRC member Dr. Dean Yimlamai who moved to the Yale Liver center in the Eastern Alliance published a study which began here at the University of Pittsburgh, in Science Translational Medicine entitled, "*Hepatocyte CYR61 polarizes profibrotic macrophages to orchestrate NASH fibrosis.*"

Mooring M, Yeung GA, Luukkonen P, Liu S, Akbar MW, Zhang GJ, Balogun O, Yu X, Mo R, Nejak-Bowen K, Poyurovsky MV, Booth CJ, Konnikova L, Shulman GI, Yimlamai D. Hepatocyte CYR61 polarizes profibrotic macrophages to orchestrate NASH fibrosis. Sci Transl Med. 2023 Sep 27;15(715):eade3157. doi: 10.1126/scitranslmed.ade3157. Epub 2023 Sep 27. PMID: 37756381.

Abstract:

Obesity is increasing worldwide and leads to a multitude of metabolic diseases, including cardiovascular disease, type 2 diabetes, nonalcoholic fatty liver disease, and nonalcoholic steatohepatitis (NASH). Cysteine-rich angiogenic inducer 61 (CYR61) is associated with the progression of NASH, but it has been described to have anti- and proinflammatory properties. We sought to examine the role of liver CYR61 in NASH progression. CYR61 liver-specific knockout mice on a NASH diet showed improved glucose tolerance, decreased liver inflammation, and reduced fibrosis. CYR61 polarized infiltrating monocytes promoting a proinflammatory/profibrotic phenotype through an IRAK4/SYK/NF-κB signaling cascade. In vitro, CYR61 activated a profibrotic program, including PDGFa/PDGFb expression in macrophages, in an IRAK4/SYK/NF-κB–dependent manner. Furthermore, targeted-antibody blockade reduced CYR61-driven signaling in macrophages in vitro and in vivo, reducing fibrotic development. This study demonstrates that CYR61 is a key driver of liver inflammation and fibrosis in NASH.

Faculty Highlight


Dr. Alex Soto-Gutierrez | **Dr. Lanuza Faccioli**

PLRC HSLBC Core Director Dr. Alex Soto-Gutierrez and his core scientist Dr. Lanuza Faccioli have recently published multiple articles, two of which are highlighted in this issue.

1) ***Evaluation of Human Hepatocyte Drug Metabolism Carrying High-Risk or Protection-Associated Liver Disease Genetic Variants.***

Int J Mol Sci. 2023 Aug 29;24(17):13406. doi: 10.3390/ijms241713406. PMID: 37686209; PMCID: PMC10487897.

Metabolic-dysfunction-associated steatotic liver disease (MASLD), which affects 30 million people in the US and is anticipated to reach over 100 million by 2030, places a significant financial strain on the healthcare system. There is presently no FDA-approved treatment for MASLD despite its public health significance and financial burden. Understanding the connection between point mutations, liver enzymes, and MASLD is important for comprehending drug toxicity in healthy or diseased individuals. Multiple genetic variations have been linked to MASLD susceptibility through genome-wide association studies (GWAS), either increasing MASLD risk or protecting against it, such as *PNPLA3*-s738409, *MBOAT7*-rs641738, *GCKR*-rs780094, *HSD17B13*-rs72613567, and *MTARC1*-rs2642438. As the impact of genetic variants on the levels of drug-metabolizing cytochrome P450 (CYP) enzymes in human hepatocytes has not been thoroughly investigated, this study aims to describe the analysis of metabolic functions for selected phase I and phase II liver enzymes in human hepatocytes. For this purpose, fresh isolated primary hepatocytes were obtained from healthy liver donors (n = 126), and liquid chromatography-mass spectrometry (LC-MS) was performed. For the cohorts, participants were classified into minor homozygotes and nonminor homozygotes (major homozygotes + heterozygotes) for five gene polymorphisms. For phase I liver enzymes, we found a significant difference in the activity of CYP1A2 in human hepatocytes carrying *MBOAT7* (p = 0.011) and of CYP2C8 in human hepatocytes carrying *PNPLA3* (p = 0.004). It was also observed that the activity of CYP2C9 was significantly lower in human hepatocytes carrying *HSD17B13* (p = 0.001) minor homozygous compared to nonminor homozygous. No significant difference in activity of CYP2E1, CYP2C8, CYP2D6, CYP2E1, CYP3A4, ECOD, FMO, MAO, AO, and CES2 and in any of the phase II liver enzymes between human hepatocytes carrying genetic variants for *PNPLA3*-rs738409, *MBOAT7*-rs641738, GCKR-rs780094, *HSD17B13*-rs72613567, and *MTARC1*-rs2642438 were observed. These findings offer a preliminary assessment of the influence of genetic variations on drug-metabolizing cytochrome P450 (CYP) enzymes in healthy human hepatocytes, which may be useful for future drug discovery investigations.

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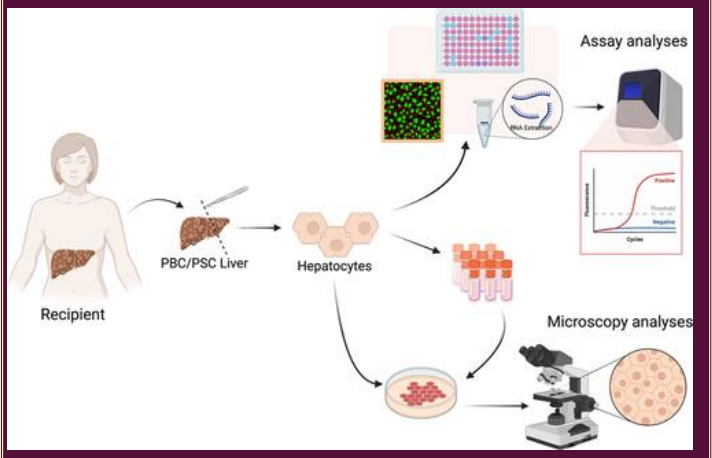
Faculty Highlight (Cont'd)

Dr. Alex Soto-Gutierrez

Dr. Lanuza Faccioli

2) *Human Hepatocellular response in Cholestatic Liver Diseases.* Organogenesis 2023 Dec 31;19(1):2247576.

Ortiz K, Cetin Z, Sun Y, Hu Z, Kurihara T, Tafaleng EN, Florentino RM, Ostrowska A, Soto-Gutierrez A, Faccioli LAP. Human Hepatocellular response in Cholestatic Liver Diseases. Organogenesis. 2023 Dec 31;19(1):2247576. doi: 10.1080/15476278.2023.2247576. PMID: 37598346; PMCID: PMC10444014.



ABSTRACT: Primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), the most common types of cholestatic liver disease (CLD), result in enterohepatic obstruction, bile acid accumulation, and hepatotoxicity. The mechanisms by which hepatocytes respond to and cope with CLD remain largely unexplored. This study includes the characterization of hepatocytes isolated from explanted livers of patients with PBC and PSC. We examined the expression of hepatocyte-specific genes, intracellular bile acid (BA) levels, and oxidative stress in primary-human-hepatocytes (PHHs) isolated from explanted livers of patients with PBC and PSC and compared them with control normal human hepatocytes. Our findings provide valuable initial insights into the hepatocellular response to cholestasis in CLD and help support the use of PHHs as an experimental tool for these diseases.

COMMUNITY LIVER ALLIANCE™
GLOBAL AWARENESS. LOCAL IMPACT.

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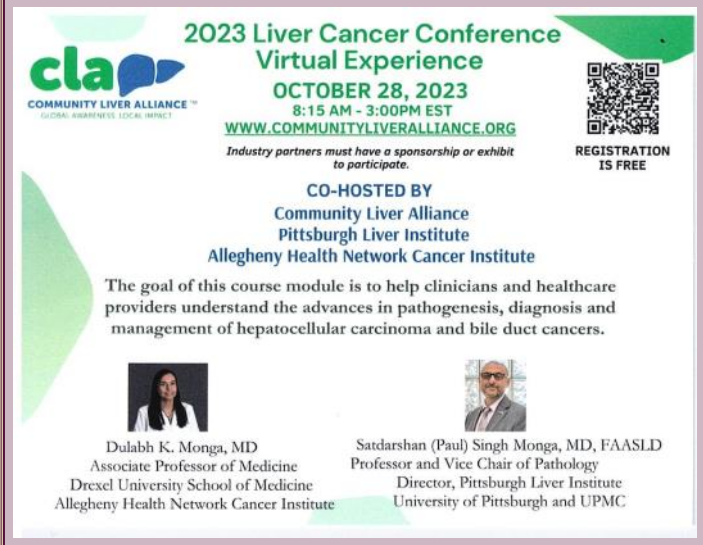
2023 Liver Cancer Conference

"Virtual Experience"

October 28, 2023,

8:15AM—3:00PM,EST



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PLRC Seminars

Oct 3rd @ 12:00 pm – 1:00 pm in S120 BST

Dr. Mitchell Lazar, MD, PhD

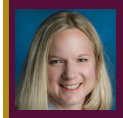
Willard and Rhoda Ware Professor in Diabetes and Metabolic Diseases; Director Penn Diabetes Research Center; Perelman School of Medicine
Philadelphia, PA
Website URL

Seminar Title: Hepatic Nuclear Receptors and the circadian regulation of transcription and metabolism

Oct 10th @ 12:00 pm – 1:00 pm in S120 BST

PLRC INJURY SIG Roundtable

Dr. Naudia Jonassaint, MD



Dr. Kari Nejak-Bowen, PhD, MBA

Topics: Modeling Biliary Injury in Mice
Biliary Disorders in Patients

Oct 17th @ 12:00 pm – 1:00 pm in Univ. Club Ballroom

PLRC Retreat "KEYNOTE LECTURE"

Dr. Rebecca Wells, MD, PhD

Professor of Medicine, Vice Chief for Research, Division of Gastroenterology and Hepatology University of Pennsylvania Perelman School of Medicine

Seminar Title: The impact of lipids and cholesterol on hepatocyte and liver mechanics: new mechanisms for MASLD?"

Oct 31st @ 12:00 pm – 1:00 pm in S120 BST

Andreas Villunger, PhD
Professor
Biocenter, Medical university of Innsbruck
Division of Developmental Immunology

Seminar Title: TBD

Announcement

PLRC Pilot & Feasibility Grants
2024 Application Cycle NOW OPEN!
Full application Due: October 13th, 2023

More details on the PLRC P&F Website

Funding Opportunities

Notice of Special Interest (NOSI): Administrative Supplements for Research on Sexual and Gender Minority (SGM) Populations (Admin Supp Clinical Trial Optional): https://grants.nih.gov/grants/guide/notice-files/not-od-22-032.html
Notice of Special Interest (NOSI): Research on the Health of Sexual and Gender Minority (SGM) Populations: https://grants.nih.gov/grants/guide/notice-files/not-md-22-012.html

ALPHA-1 Foundation: The Alpha-1 Foundation is committed to finding a cure for Alpha-1 Antitrypsin Deficiency and to improving the lives of individuals affected by Alpha-1 worldwide.

6 Funding Categories: Bridge/Ethics-Legal-Social/ Career Devel./Pilot & Feasibility/ Postdoc/ Research

LOI due Sept 29….Grants Due Nov
Alpha-1 Grant Website

NOFOs:

RFA-DK-22-023 Ancillary Studies to the NIDDK Inflammatory Bowel Disease Genetics Consortium (R01 Clinical Trial Not Allowed)

Next Due Date: November 8, 2023.

To see all NIH Grants sorted by week, please visit:
NIH Guide: 2023

Or click below for recent weeks:

Week of: **Sept 8:** **Sept 15:** **Sept 22:**

Click here for all current **NIDDK** Funding opportunities

NOTICE!

NIH GRANT SUBMISSION DEADLINES ARE **NOT AFFECTED** BY GOVERNMENT SHUTDOWN AS OF NOW.

Please submit by the standard dates.

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2023 PLRC RETREAT PROGRAM

2023 PLRC/PLI RETREAT October 17 University Club, Ballroom B

9:30-10:00	Continental Breakfast: Registration & Onsite badge pick up	
10:00	Welcome Paul Monga (Director) and Kari Nejak-Bowen (Enrichment Program Director)	
10:10-10:45	**Pilot & Feasibility overview and presentations (Paul Monga)**	
	10:15-10:30	**Dr. Rodrigo Florentino:** Understanding Mechanisms of Progressive Familial Intrahepatic Cholestasis Type 1 (PFIC1) Using Patient-Specific Inducible Pluripotent Stem Cells
	10:30-10:45	**Dr. Chris Chiu:** Deep learning-based prediction of drug repurposing and genetic vulnerabilities in hepatocellular carcinoma
10:45-11:45	**PLRC Core Updates**	
	10:45-11:00	Dr. Alan Watson:Advanced Cell and Tissue Imaging Core
	11:00-11:15	Dr. Aatur Singhi: Clinical Biospecimen Repository and Processing Core
	11:15-11:30	Dr. Silvia Liu: Genomics and Systems Biology Core
	11:30-11:45	Dr. Alex Soto-Gutierrez: Human Synthetic Liver Biology Core
11:45-12:00	Collect lunch	
12:00-1:00	**Keynote Presentation by Dr. Rebecca Wells from the University of Pennsylvania (Moderator: Kari Nejak-Bowen)** **"The impact of lipids and cholesterol on hepatocyte and liver mechanics: new mechanics for MASLD?"**	
1:00-1:10	BREAK	
1:10-2:00	**Efforts to Translate and Commercialize at PLI**	
	1:10-1:20	Panel Discussion: combined vision for translation and commercialization pipeline initiative. **Drs. Paul Monga, Naudia Jonassaint**
	1:20-1:35	Clinical Trials Development and Operations. Developing infrastructure for promoting clinical trials in liver space. **Dr. Pat Corby**
	1:35-1:50	Commercialization of Your Discovery With the Office of Innovation and Entrepreneurship. **Dr. Evan Facher**
	1:50-2:00	Clinical Trials in Hepatology: Current state and aspirations. **Dr. Jaideep Behari**
2:00-2:30	**PLRC/PLI FEATURES: Showcasing unique human-based systems to study liver diseases**	
	2:00-2:05	Dr. Amanda Clark: Liver on a Chip for Metastasis
	2:05-2:10	Dr. Mo Ebrahimkhani: hiPSC based organoids
	2:10-2:15	Dr. Lans Taylor: Human microphysiological systems for studying liver disease
	2:15-2:20	Dr. Alex Soto-Gutierrez: hiPSC, mini-liver, inducible gene-editing systems
	2:20-2:25	Dr. Haitao Guo: Cell culture models to study HBV
	2:25-2:30	Dr. Andrew Duncan: Humanized Mice
2:30-3:00	**PLRC/PLI FEATURES: Showcasing unique animal models of human diseases for SRAs.**	
	2:30-2:35	Dr. Paul Monga: Hepatocellular cancer models
	2:35-2:40	Dr. Ed Prochownik: Hepatoblastoma models
	2:40-2:45	Dr. Sungjin Ko: Cholangiocarcinoma models
	2:45-2:50	Dr. Juliane Beier: Environmental Toxicant + MASLD/HCC
	2:50-2:55	Dr. Kari Nejak-Bowen: Alagille, BA, PSC
	2:55-3:00	DR. Donghun Shin: Hepatobiliary repair in Zebrafish
3:05-3:15	**BREAK**	
3:15-3:35	**PLRC/PLI FEATURES: Showcasing translational opportunities for clinic**	
	3:15-3:20	Dr. Henry Dong: Pharmacologic inhibition of FOX-O1: Treating Type-2 Diabetes
	3:20-3:25	Dr. Bharat Bhushan: EGFR inhibition in MASLD and DILI
	3:25-3:30	Dr. Francisco Schopfer: Lipid mediators as therapeutic agents for metabolic diseases
	3:30-3:35	Dr. Eric Lagasse: Ectopic Hepatocyte Transplantation Therapy
3:40-4:00	**PLRC/PLI FEATURES: Use of computational and AI based systems**	
	3:40-3:45	Dr. Chris Chiu: In silico drug discovery for liver cancer
	3:45-3:50	Dr. Dooman Arefan: Radiomics application in HCC molecular characterization
	3:50-3:55	Dr. Riyue Bao: Image-based AI for liver cancer
	3:55-4:00	Dr. Silvia Liu: Spatial Transcriptomics Pipeline
4:05-4:20	**PLRC/PLI FEATURES: Unique services for local and outside collaborations**	
	4:05-4:10	Dr. Aatur Singhi: Multispectral Imaging
	4:10-4:15	Dr. Michael Jurczak: in vivo and ex vivo hepatocyte mitochondrial metabolism
	4:15-4:20	Dr. Matt Steinhauser: Imaging Mass Spec Platform
4:25-4:35	**Clinical Trials in Liver Tumors: Current State and Opportunities, Dr. Aanwar Saeed**	
4:45-5:15	Drinks and Hors d'oeurves	
5:15-6:30	Poster Session with Drinks & hors d'oeurves.	

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ANNOUNCEMENTS

- **Communityliveralliance.org**
  DeLIVERing HOPE campaign: Liver Disease Awareness
- **2023 Liver Cancer Conference "Virtual Experience" October 28, 2023, 8:15AM—3:00PM,EST "Free Event" Website link Register Here (or use QR code on page 2) Hosted by CLA, PLI, AHN, UPMC**
- **PLRC Pilot & Feasibility Grant Program Open NOW! More details and info available on Website,** Applications Due **October 13, 2023 Link to RFA**
- **2nd INTERNATIONAL LIVER CANCER RESEARCH CONFERENCE 2023 "Novel Directions in Liver Cancer Research" Oct. 11-13, 2023** @ Heidelberg, Germany Detail-Flyer Conference Program
- **First International Conference of Liver Pathobiology: From Bench to Bedside.** CRETE, GREECE **OCTOBER 11-16, 2023 CONFERENCE SCHEDULE / SPEAKERS / REGISTRATION**
- **PLRC/PLI Annual RETREAT Oct. 17th, 2023 9:30AM-6:30PM** See previous page for Program **Register here to attend**
- **ASIP "Tissue, Matrix, and Pathobiology: Joint Meeting of ASMB, HCS and ASIP" Oct. 22-25, 2023** @ Salt Lake City Utah. **Meeting Registration Site**
- **AASLD "THE LIVER MEETING" Nov. 10-14, 2023** @ Boston, MA. Meeting Registration open Now!
- **Pittsburgh Liver Institute/PLRC Reception @ The AASLD LIVER MEETING** in Boston**. Saturday November 11th, 7:30pm-9:30pm** @ Sheraton Hotel Boston **"Save the Date"**
- **DDRCC Annual Director's Meeting** @ Cincinnati Childrens Hospital, Cincinnati Ohio**, Nov. 6-7, 2023**

WANT ADS

This section is available for PLRC members to communicate wants or needs in your laboratories.
Available positions / Collaboration ideas / Equipment needs
Please send any "wants/needs" to be advertised to Aaron Bell (bellaaro@pitt.edu)

OPEN POSITIONS:

- Postdoc/Technician: Bone cell Differentiation $45K; PI: Harry Blair: US citizen ONLY! Contact: 412-383-9616 or hcblair@pitt.edu

JOB SEEKERS:

- Postdoctoral Associate Pathology Dept, With experience in proteomics, genomics, molecular biology, histology, animal studies. schudhry@pitt.edu link to CV