LIVER DIGEST

February 23, 2024

A monthly 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



The CBRPC directors Drs. Aatur Singhi and David Geller along with PLRC director Paul Monga were integral contributors to the collaborative publication in Nature by Torok etal. entitled, "***Matrix viscoelasticity promotes liver cancer progression in the pre-cirrhotic live***r".

Fan W, Adebowale K, Váncza L, Li Y, Rabbi MF, Kunimoto K, Chen D, Mozes G, Chiu DK, Li Y, Tao J, Wei Y, Adeniji N, Brunsing RL, Dhanasekaran R, Singhi A, Geller D, Lo SH, Hodgson L, Engleman EG, Charville GW, Charu V, Monga SP, Kim T, Wells RG, Chaudhuri O, Török NJ. Nature. 2024 Jan 31. doi: 10.1038/s41586-023-06991-9. Epub ahead of print. PMID: 38297127 .https://rdcu.be/dxSJu

ABSTRACT:

Type 2 diabetes mellitus is a major risk factor for hepatocellular carcinoma (HCC). Changes in extracellular matrix (ECM) mechanics contribute to cancer development[1,2], and increased stiffness is known to promote HCC progression in cirrhotic conditions[3,4]. Type 2 diabetes mellitus is characterized by an accumulation of advanced glycation end-products (AGEs) in the ECM; however, how this affects HCC in non-cirrhotic conditions is unclear. Here we find that, in patients and animal models, AGEs promote changes in collagen architecture and enhance ECM viscoelasticity, with greater viscous dissipation and faster stress relaxation, but not changes in stiffness. High AGEs and viscoelasticity combined with oncogenic β-catenin signalling promote HCC induction, whereas inhibiting AGE production, reconstituting the AGE clearance receptor AGER1 or breaking AGE-mediated collagen cross-links reduces viscoelasticity and HCC growth. Matrix analysis and computational modelling demonstrate that lower interconnectivity of AGE-bundled collagen matrix, marked by shorter fibre length and greater heterogeneity, enhances viscoelasticity. Mechanistically, animal studies and 3D cell cultures show that enhanced viscoelasticity promotes HCC cell proliferation and invasion through an integrin-β1–tensin-1–YAP mechanotransductive pathway. These results reveal that AGE-mediated structural changes enhance ECM viscoelasticity, and that viscoelasticity can promote cancer progression in vivo, independent of stiffness.

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Drs. Mark Miedel, PhD and Alex Soto-Gutierrez, MD, PhD of the PLRC were awarded an MPI grant from the NIH-NIDDK for their project entitled, "***Implementing A Quantitative Systems Pharmacology Platform to Predict and Test Drugs for Metabolic Associated Fatty Liver Disease Genetic Variants in an iPSC-cell Based Human Biomimetic Liver Microphysiology System***".

Project Narrative: The lack of approved drugs for treatment of MAFLD is due to the heterogenous pathology of disease progression and the limitation that animal models do not fully recapitulate the human disease. The use of a combined QSP and iPSC-derived Micro-Physiology-System experimental platform to examine mechanistic detail of key disease-related genetic variants and to use for testing predicted drugs serves as a starting point to identify optimized therapeutics that will advance the approach to MAFLD drug discovery. The more detailed analysis of the best drugs and drug combinations in an optimized biomimetic model will refine the selection of drugs/combinations for select patient cohorts.

Project Summary: Nonalcoholic fatty liver disease (NAFLD), recently renamed metabolic dysfunction associated fatty liver disease (MAFLD), is a worldwide public health problem. Despite major investments by the pharmaceutical industry, there are no approved drugs for the treatment of MAFLD, reflecting the heterogeneous pathophysiology of this disease. We have implemented a platform focused on a human vascularized liver acinus microphysiology system (vLAMPS) biomimetic that incorporates four human liver cell types and uses genomic, biochemical, and phenotypic metrics, and quantitative systems pharmacology (QSP) to identify mechanisms of disease progression that can be used to inform new or repurposed drugs for MAFLD. Genome- wide association studies (GWAS) have identified several variants that are associated with MAFLD susceptibility, including mutations in PNPLA3, TM6SF2, and MBOAT7. In contrast to these variants that increase MAFLD risk, recent studies have identified two novel protective variants, HSD17B13 and MTARC1, that are linked to lower risk of MAFLD. However, little is currently known regarding the biological function of these protective variants. Thus, our goal is to harness the computational and experimental QSP platform with genome-edited iPSC-derived liver cells to experimentally test probe drugs and drug combinations predicted by computational analysis to normalize key disease phenotypes and to provide mechanistic insight into the role novel protective variants have in both alleviating MAFLD progression and as attractive new pharmacological targets; thus, linking specific genetic variant risk factors with successful intervention on druggable pathways. We will test the following Specific Aims: (1) Implement optimized biomimetic vLAMPS to recapitulate both normal liver function and MAFLD disease progression using iPSC-derived liver cells harboring clinically relevant variants (2); Test the response to drugs predicted to halt or reverse MAFLD disease phenotypes using iPSC-derived high-risk variants in vLAMPS; (3) Test the response to drugs predicted to halt or reverse MAFLD disease phenotypes using iPSC-derived high-risk variants in vLAMPS. The lack of approved drugs for treatment of MAFLD is due to the heterogenous pathology of disease progression and the limitation that animal models do not fully recapitulate the human disease. The use of a combined QSP and iPSC-derived MPS experimental platform to examine mechanistic detail of key disease- related genetic variants and to use for testing predicted drugs serves as a starting point to identify optimized therapeutics that will advance the approach to MAFLD drug discovery.

Young Investigator Highlight

Brandon Lehrich, MD-PhD trainee in Dr Paul Monga's lab, will be giving the ASIP Young Investigator Keynote Seminar virtually on March 21st @ 1:00PM. The title of his talk is: "***Beta-catenin Activity Drives Immunosuppression and is a Targetable Therapeutic Vulnerability in Hepatocellular Carcinoma*** ". Register online @ **ASIP-Keynote** to get the link for the seminar.

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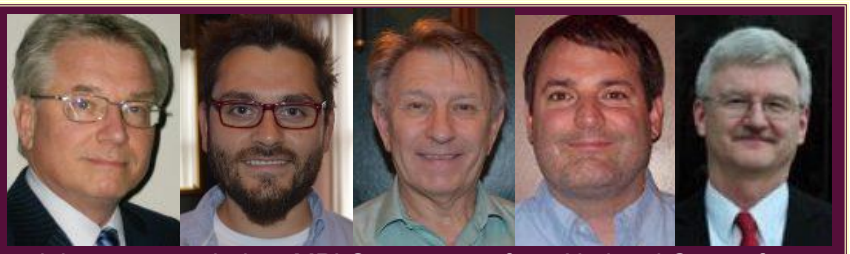

Lans Taylor, Co-director of the Human Synthetic Liver Biology Core (HSLBC) and director of the Drug-discovery Institute along with Alex Soto-Gutierrez, co-director of the HSLBC, and Lawrence Vernetti, as well as PLRC members-elect Mark Miedel and Mark Schurdak were awarded an MPI Center grant from National Center for Advancing Translational Sciences (NCATS). CONGRATULATIONS!

The Title of the Grant is: "***Qualification of Patient-Derived Biomimetic Liver MPS as Drug Discovery Tools for Drug Metabolism, Toxicity, Drug Efficacy Testing and Clinical Trial Cohort Selection***"

The University of Pittsburgh TraCe MPS Center's (Pitt-TraCe) qualified, patient-derived, structured, biomimetic liver Microphysiology Systems (MPS) platform will deliver qualified DDTs that will dramatically improve the efficiency and accuracy in liver safety and efficacy for drug development decisions, especially for complex heterogeneous diseases in precision medicine. These commercially available, qualified DDTs will benefit the drug development process for the pharmaceutical industry and FDA regulatory oversight. In addition, the Automated Biomimetic Analytic MPS (ABAMPS) platform employing commercially available materials from can be harnessed to qualify new organ structured, biomimetic MPS in the future.

The University of Pittsburgh TraCe (Pitt-TraCe) proposal is rooted in strong expertise and experience in large program Administration, management of Resources and early steps toward Qualification of Drug Development Tools (DDTs). The Pitt-TraCe proposal addresses multiple Food and Drug Administration (FDA) needs that will expand the FDA's ability to progress regulatory science and decision-making capabilities using our extensive expertise and experience. The overall goal of the Pitt-TraCe proposal is to qualify our patient-derived structured, biomimetic liver Microphysiology Systems (MPS) platform in 4 contexts of use (CoUs) as DDTs that are being made commercially available. To reach this goal, the Pitt-TraCe includes strong administrative, MPS resources and qualification sections to accelerate the translational application of our liver MPS for specific CoUs. We will qualify our externally validated, structured, biomimetic liver MPS that recapitulates critical liver structures and functions with 4 liver cell types mimicking the liver acinus as DDTs. Induced pluripotent stem cell (iPSC)-derived liver cells from non-alcoholic fatty liver disease (NAFLD) patients enrolled in the University of Pittsburgh Medical Center Fatty Liver, Obesity, and Wellness Clinic (UPMC FLOW Clinic) that exhibit heterogeneity based on genetics, environment, and lifestyle will be used to define the role of patient heterogeneity in drug discovery, development, and clinical trials. NAFLD patient-derived liver MPS will serve as the disease background for developing the DDTs since this heterogeneous and progressive disease impacts >25% of the world population. This is a critical platform to define mechanisms of action (MOA) in the liver MPS in medium throughput to complement other high throughput, but simpler liver MPS for other CoU applications. We will qualify 4 CoU liver MPS that can be applied as DDTs including 1) quantifying hepatic clearance and identifying major metabolites; 2) quantifying liver toxicity; 3) drug testing for safety and efficacy; and 4) selecting clinical trial cohorts. Collaborations with pharmaceutical and biotechnology companies will yield materials including cells, media, and reagents critical for the qualification of the DDTs. Through a collaborative effort with Nortis Inc. and BioSystics, Inc., we will implement a medium throughput, high content and automated platform called the Automated Biomimetic Analytic MPS (ABAMPS) platform. The ABAMPS platform will deliver a more efficient and accurate use of structured, biomimetic MPS for MOA studies that will result in commercially available, FDA qualified DDTs.

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PLRC Seminars

Feb 27th @ 12:00 pm – 1:00 pm in S120 BST

Anand S. Mehta, PhD

Professor of Cell & Molecular Pharmacology
SmartState Endowed Chair in Proteomic Biomarkers
Medical University of South Carolina,SC

Seminar Title: **The use of Spatial-omics to find biomarkers for HCC .**

Mar 12th @ 12:00 pm – 1:00 pm in S120 BST

Wolfam Goessling, MD, PhD

Chief, Division of Gastroenterology
Jules L. Dienstag, M.D. and Betty and Newell Hale Endowed Chair in Gastroenterology
Robert H. Ebert Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Seminar Title: **Regulation of Liver Metabolism and Regeneration**

Mar 19th @ 12:00 pm – 1:00 pm in S120 BST

Wen Wei Wang, PhD

Deputy Director – Center for Cancer Research , Co-Director – Liver Cancer Program, Deputy Chief – Laboratory of Human Carcinogenesis NIH – National Cancer Institute

Seminar Title: **Molecular landscape of liver cancer and its clinical implications**

Mar 26th @ 12:00 pm – 1:00 pm in S120 BST

Stacey Huppert, PhD

Associate Professor, Dept of Pediatrics

Cincinnati Children's Hospital

Seminar Title: **TBD**

Funding Opportunities

Notice of Participation of NIDDK in PAR-23-309 Health and Health Care Disparities Among Persons Living with Disabilities (R01 - Clinical Trials Optional) (NOT-DK-24-006) National Institute of Diabetes and Digestive and Kidney Diseases

Stephen I. Katz Early Stage Investigator Research Project Grant PAR-24-075 (innovative project that represents a change in research direction for an early stage investigator (ESI) and for which no preliminary data exist) 1/26 or 5/29 due dates

Diabetes: JDRF Grant Opportunities URL/LINK

Improving Predictability of Food-Drug and Drug-Drug Interaction Risks by Utilizing In Vitro Simulated Gastrointestinal Dissolution Model for High-Risk Oral Drug Products (U01) Clinical Trial Optional **RFA-FD-24-009**
Open: 1/15/24 LOI 2/15/24

NOSI: Advancing Genomic Technology Development for Research and Clinical Application
NOT-HG-24-012 (NHGRI) applications focused on developing novel laboratory-focused tools and technologies that enable new lines of scientific inquiry and advance research or clinical applications in human genomics

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

Or click below for recent weeks:

Week of: **Feb 2:** **Feb 9:** **Feb 16:**

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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Farewell Dr Feranchak

The PLRC Administration would like to thank Dr. Drew Feranchak for his commitment and service as Associate Director of the PLRC. We are grateful for the years you dedicated to the PLRC , as you were an integral part of the success we have experienced as a new liver center. We thank you for all that you have done throughout your professional journey with us, and we wish you all the best in your retirement. Enjoy the next chapter of your life!

Sincerely,

Paul Monga and the PLRC Administration

ANNOUNCEMENTS & Meetings

- Communityliveralliance.org
- **ASIP Annual Meeting "Pathobiology: Mechanisms of Disease 2024": Baltimore, MD: April 20-23, 2024: Registration: event Program**
- **THE LIVER SINUSOID MEETING @ Chicago, IL April 24-26, 2024 Program: Registration**
- **Digestive Disease Week 2024: Washington D.C May 18-21, 2024 Registration: Details**
- **The FASEB Liver Meeting is now the Summer Liver Academy Meeting (SLAM).@ Cape Coral, FL June 16-20, 2024 Website**
- **National Institute on Minority Health & Health Disparities (NIMHD) hosting "Health Disparities Research Institute" August 5-9, 2024: Bethesda, MD For ESI investigators/Application period open 2/8/24-3/14/24 @ Application: Learn More**

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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:

JOB SEEKERS:

* PhD, Senior Researcher at Hormel Institute, interested in Senior Lab role @ Pitt/UPMC. Experience with HCC, CCA, Mol. Biology, metabolism, signal transduction. Link to CV Email: kpant@umn.edu

* MD, PhD Researcher with extensive experience in cholangiocyte biology, strong PI references. Link to CV. Email: Qin.Li7@chp.edu

* Res.Asst.Prof. Highly experienced researcher in many disciplines including bioinformatics, proteomics, genomics and molecular biology. Link to CV Email: liz45@pitt.edu

* Sr. Postdoc from UPENN (Wells-Lab), Hepatobiliary toxicity, environmental toxins, organ-on-a-chip, mechanobiology and biomaterials. Link to CV Email: Kapish.Gupta@Pennmedicine.upenn.edu

* Postdoc/Research Associate from Wash U with experience in Immunology & cytokine signaling of liver diseases and liver regeneration. Interest in gene editing research. Link to CV Email: ramavathnareshnaik@gmail.com

* Res. Asst. Prof. Experience in hepatocyte-biliary trans-differentiation, Cholestatic liver diseases, gut-liver axis. Link to CV Email: chhavi@pitt.edu