LIVER DIGEST

April 19, 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

Dr. Mo Ebrahimkhani, MD, a PLRC researcher who's work combines synthetic biology and stem cell engineering to develop novel technologies and advance liver regenerative medicine was recognized for his stellar work and achievements thus far in his career with a "Health Sciences Ascending Star Award" for 2024 from the University of Pittsburgh School of Medicine. The award comes with 25,000 grant for research and a plenary lecture sponsored by the Deans Office. "The Ascending Star Award is just one tangible way in which we can recognize the excellence of faculty members whose career trajectories continue to offer great promise and to encourage them to continue that upward momentum, while also serving as role models and mentors to their junior colleagues."
Congratulations Mo! Well Deserved!

Faculty Highlight

PLRC researchers **Dr David Geller, MD.** and **Dr. Alex Soto-Gutierrez, MD., PhD.** were awarded a five year R24 grant from the NIDDK for the ***Human Liver Tissue & Hepatocytes Research Resource (HLTHRR)***. "Our overall goal is to be a core lab which provides normal human liver tissue and normal human hepatocytes (HC) and non-parenchymal cells (NPC) including NPC sub-fractions (Kupffer cells, sinusoidal endothelial cells, cholangiocytes, and stellate cells) to biomedical researchers across the USA."
For the past two years (2022-2024), the NIDDK has funded the Human HC Isolation and Distribution **(HHID)** in Dr. Geller's lab at Pitt with bridge funding as a supplement to our active University of Pittsburgh P30 DK120531 "Pittsburgh Liver Research Center" (PI- Dr. S. Monga) which has allowed us to maintain the current human HC core lab for the USA. Previously, Dr Geller's lab was part of the Liver Cell Tissue Distribution System (LTCDS) and Dr. Soto-Gutierrez's lab isolates and distributes liver cells from diseased livers as a service of the **Human Synthetic Liver Biology Core**. Cumulatively we have over 25 years of experience isolating human HC with great success and providing them to PIs around the country as the core NIDDK-funded lab in the USA.
Congratulations on securing funding for a much needed resource in the liver research community!

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Faculty Highlight

Drs. Silvia Liu and **Dr. Jianhua Luo** the Directors of the Genomics and Systems Biology Core of the PLRC published an article in Hepatology Communications entitled, "***Therapeutic targeting at genome mutations of liver cancer by the insertion of HSV1 thymidine kinase through Cas9-mediated editing.***"

Kader M, Sun W, Ren BG, Yu YP, Tao J, Foley LM, Liu S, Monga SP, Luo JH. Hepatol Commun. 2024 Mar 18;8(4):e0412. doi: 10.1097/HC9.0000000000000412. PMID: 38497929; PMCID: PMC10948134.

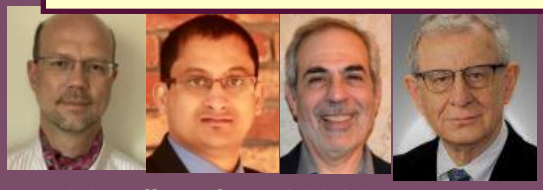
Background: Liver cancer is one of the most lethal malignancies for humans. The treatment options for advanced-stage liver cancer remain limited. A new treatment is urgently needed to reduce the mortality of the disease.

Methods: In this report, we developed a technology for mutation site insertion of a suicide gene (herpes simplex virus type 1-thymidine kinase) based on type II CRISPR RNA-guided endonuclease Cas9-mediated genome editing to treat liver cancers.

Results: We applied the strategy to 3 different mutations: S45P mutation of catenin beta 1, chromosome breakpoint of solute carrier family 45 member 2-alpha-methylacyl-CoA racemase gene fusion, and V235G mutation of SAFB-like transcription modulator. The results showed that the herpes simplex virus type 1-thymidine kinase insertion rate at the S45P mutation site of catenin beta 1 reached 77.8%, while the insertion rates at the breakpoint of solute carrier family 45 member 2 – alpha-methylacyl -CoA racemase gene fusion were 95.1%–98.7%, and the insertion at V235G of SAFB-like transcription modulator was 51.4%. When these targeting reagents were applied to treat mouse spontaneous liver cancer induced by catenin beta 1S45P or solute carrier family 45 member 2-alpha-methylacyl-CoA racemase, the mice experienced reduced tumor burden and increased survival rate. Similar results were also obtained for the xenografted liver cancer model: Significant reduction of tumor volume, reduction of metastasis rate, and improved survival were found in mice treated with the targeting reagent, in comparison with the control-treated groups.

Conclusions: Our studies suggested that mutation targeting may hold promise as a versatile and effective approach to treating liver cancers.

Faculty Highlight



Michael Oertel, PhD along with **Reben Raeman, PhD, Joeseph Locker, MD,** and **George Michalopoulos, MD, PhD** published a manuscript in the journal *Cells* entitled, "***Antagonizing Activin A/p15^{INK4b} Signaling as Therapeutic Strategy for Liver Disease.***"

Mekala S, Rai R, Reed SL, Bowen B, Michalopoulos GK, Locker J, Raeman R, Oertel M. *Cells*. 2024; 13(7):649. https://doi.org/10.3390/cells13070649

Background/Aim: Activin A is involved in the pathogenesis of human liver diseases, but its therapeutic targeting is not fully explored. Here, we tested the effect of novel, highly specific small-molecule-based activin A antagonists (NUCC-474/555) in improving liver regeneration following partial hepatectomy and halting fibrosis progression in models of chronic liver diseases (CLDs).

Methods: Cell toxicity of antagonists was determined in rat hepatocytes and Huh-7 cells using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide assay. Hepatocytes and hepatic stellate cells (HSCs) were treated with activin A and NUCC-555 and analyzed by reverse transcription–polymerase chain reaction and immuno-histochemistry. Partial hepatectomized Fisher (F)344 rats were treated with NUCC-555, and bromodeoxyuridine (BrdU) incorporation was determined at 18/24/36/120/240 h. NUCC-555 was administered into thioacetamide- or carbon tetra-chloride-treated F344 rats or C57BL/6 mice, and the fibrosis progression was studied.

Results: NUCC-474 showed higher cytotoxicity in cultured hepatic cells; therefore, NUCC-555 was used in subsequent studies. Activin A-stimulated overexpression of cell cycle-/senescence-related genes (e.g., p15INK4b, DEC1, Glb1) was near-completely reversed by NUCC-555 in hepatocytes. Activin A-mediated HSC activation was blocked by NUCC-555. In partial hepatectomized rats, antagonizing activin A signaling resulted in a 1.9-fold and 2.3-fold increase in BrdU+ cells at 18 and 24 h, respectively. Administration of NUCC-555 in rats and mice with progressing fibrosis signifi-cantly reduced collagen accumulation (7.9-fold), HSC activation indicated by reduced alpha smooth muscle actin+ and vimentin+ cells, and serum aminotransferase activity.

Conclusions: Our studies demonstrate that activin A antagonist NUCC-555 promotes liver regeneration and halts fibro-sis progression in CLD models, suggesting that blocking activin A signaling may represent a new approach to treating people with CLD.

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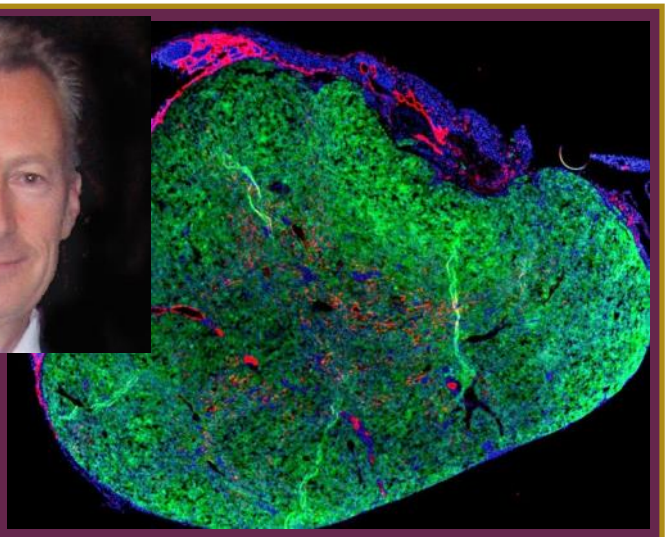
Faculty Highlight

PLRC researcher **Dr. Eric Lagasse** and his company LyGenesis have launched a Phase II clinical trial in which healthy donor hepatocytes are transplanted into lymph nodes of patients with liver failure. The News Article was published in Science: 'Mini liver' will grow in person's own lymph node in bold new trial. The first patient was treated March 25th and is doing well so far. The procedure has worked in mice, dogs and pigs thus far, and is being used primarily as a stop-gap measure to bridge patients until a transplantable liver becomes available.



Researchers injected a mouse's lymph node with liver cells (green), converting the organ into a 'mini liver'. Credit: Lagasse

Faculty Highlight

PLRC Researcher and Co director of the Genomics and Systems Biology Core, **Dr. Silvia Liu** co-authored a publication in FASEB Journal entitled, " ***Proteome characterization of liver -kidney comorbidity after microbial sepsis".***

Gui Y, Yu Y, Wang W, Wang Y, Lu H, Mozdzierz S, Eskander K, Lin YH, Li H, Tian XJ, Liu S, Zhou D. Proteome characterization of liver-kidney comorbidity after microbial sepsis. FASEB J. 2024 Apr 15;38(7):e23597. doi: 10.1096/fj.202302520R. PMID: 38581235.

Abstract:

Sepsis is a life-threatening condition that occurs when the body responds to an infection but subsequently triggers widespread inflammation and impaired blood flow. These pathologic responses can rapidly cause multiple organ dysfunction or failure either one by one or simultaneously. The fundamental common mechanisms involved in sepsis-induced multiple organ dysfunction remain unclear. Here, employing quantitative global and phosphoproteomics, we examine the liver's temporal proteome and phosphoproteome changes after moderate sepsis induced by cecum ligation and puncture. In total, 4593 global proteins and 1186 phosphoproteins according to 3275 phosphosites were identified. To characterize the liver–kidney comorbidity after sepsis, we developed a mathematical model and performed cross-analyses of liver and kidney proteome data obtained from the same set of mice. Beyond immune response, we showed the commonly disturbed pathways and key regulators of the liver–kidney comorbidity are linked to energy metabolism and consumption. Our data provide open resources to understand the communication between the liver and kidney as they work to fight infection and maintain homeostasis.

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Faculty Highlight

COMMUNITY LIVER ALLIANCE™
GLOBAL AWARENESS. LOCAL IMPACT.

10th Annual You Make a Difference Awards

WE ARE PLEASED TO ANNOUNCE THIS YEAR'S AWARD RECIPIENTS

Awardees are recognized for their outstanding accomplishments going above and beyond supporting, advocating, and educating our community about the Community Liver Alliance mission.

2024 Awardees:

Aaron W. Bell, PhD: Administrator, Pittsburgh Liver Research Center, University of Pittsburgh

Rachel Beckstrom: Global Lead; People, Culture & Engagement, BNY Melon

Sara Booz: Living Liver Transplant Donor

Nadia Jonassaint, MD, MHS: Interim Chief Div. Gastroenterology, Hepatology & Nutrition, Associate Dean of Clinical Affairs, Vice chair, Diversity, Equity and Inclusion, Associate Professor of Medicine, UPMC Center for Liver Diseases

Nebeeha Moyh Ud Din, MD: Transplant Hepatologist, Allegheny Center for Digestive Health, Allegheny Health Network

Jen Skertich "BOARD SPOTLIGHT AWARD" Security Program Advisor, FedEx Express-Americas & Aviation Security

"I thank CLA for recognizing Dr. Aaron Bell and awarding him the "You Make a Difference" award. This award is given to those who have worked tirelessly to promote 'all things liver' in our beautiful city, region and nationally. Having known and worked with Aaron for 25 years, I can think of no better person to receive such recognition. I am personally grateful to Aaron for his role as the Administrator of the Pittsburgh Liver Research Center, one of the 17 NIDDK funded Digestive Diseases Research Core Centers and only 1 of 3 with liver focus. Administering these kinds of centers is a full time task with so many moving parts and Aaron has worked tirelessly and diligently to ensure its optimal functions and delivery of its many services. And as a result of his organization and administration, this center which is composed of more than 80 members from around 15 departments at the University of Pittsburgh and UPMC, was just renewed for funding for another 5 years. I am grateful to Aaron for his service and to CLA for their support and friendship" : Paul Monga

Faculty Highlight

The Department of Pathology Hosted its Inaugural "*George K. Michalopoulos Endowed Lecture*". **Dr. Jeff Albrecht, MD**, Professor of Medicine, Division of Gastroenterology, Hepatology, and Nutrition at the University of Minnesota, was the Speaker and the title of his talk was "***Cyclin D1 at the nexus of cell cycle control and metabolism in the liver***".

He was Hosted by **Dr Kari Nejak-Bowen** (Photo-Left), and **Dr. George Michalopoulos** (Photo-right) who presented him with a commemorative engraved crystal sculpture .

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PLRC Seminars

Apr 30th @ 12:00 pm – 1:00 pm in 1104 Scaife

"Maud Menten Lecture"

Ulysses G. J. Balis, MD

Professor of Pathology
Director of Division of Informatics
University of Michigan

Seminar Title: **Reflections of a Tinkerer: Pathology and Lab Medicine as the Ideal Playground for Invention**

Apr 30th @ 2:00 pm – 1:00 pm in 1104 Scaife

Sarah Taylor, MD

Associate Professor
Department of Pediatrics
Division of Gastroenterology, Hepatology and Nutrition
University of Colorado School of Medicine

Seminar Title: Identifying immune-metabolic targets to modulate hepatic macrophage function and improve patient outcomes in biliary atresia

May 21th @ 12:00 pm – 1:00 pm in S120 BST

Scott W. Biggins, MD
Professor & Chief of Hepatology
Department of Medicine
Division of Gastroenterology, Hepatology and Nutrition
University of Pittsburgh Medical Center

Seminar Title: TBD

May 28th @ 12:00 pm – 1:00 pm in S120 BST

Hao Zhu, MD
Professor of Pediatrics
Nancy B. and Jake L. Hamon Distinguished Chair in Therapeutic Oncology Research
Department of Internal Medicine
Children's Medical Research Institute
UT Southwestern Medical Center

Seminar Title: Somatic mosaicism in regeneration, disease resilience, and cancer

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

NOT-DK-24-013: PAR-24-077: "Addressing Health and Health Care Disparities among Sexual and Gender Minority (SGM) Populations (R01 - Clinical Trials Optional)." For details, see https://grants.nih.gov/grants/guide/notice-files/NOT-DK-24-013.html

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

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: **Apr 5:** **Apr12:** **Apr19:**

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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ANNOUNCEMENTS & Meetings

- Communityliveralliance.org
- You make a difference Awards Luncheon 4/19/24: Carnegie Science Center
- 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
- University of Pittsburgh Department of Pathology Research Day & Retreat- May 29, 2024 Abstract Deadline 4/29/24 (SUBMIT Abstract HERE) Retreat INFO & Registration
- 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
- Annual DDRCC Meeting Sept 22-24, 2024 Yale Liver Center, New Haven, CT
- NIDDK Central Repository Policy Notice : NOT-DK-24-003, The purpose of this Notice is to rescind NIDDK Data Sharing Policy (July 2013) and NIDDK Repository Usage Policy (March 2015) and introduce NIDDK Central Repository Resource Archival and Sharing Policy that aligns with timelines and requirements and expectations of the NIH Data Management and Sharing Policy and NIDDK Data Management and Sharing Guidance
- Changes Coming to Applications and Peer Review in January 2025: NOT-OD-24-084 Webinar slides

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ANNOUNCEMENT

PLRC 2024 P&F awardee Dr. Jishnu Das to give Senior Vice Chancellor's Research Seminar on May 10th from 12:00PM-1:00PM. *"From Bench to Bedside: Using Machine Learning to study the immune system"*

Virtual Presentation: Registration Required (Register Here): More Info

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
* 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