LIVER DIGEST

November 22, 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)

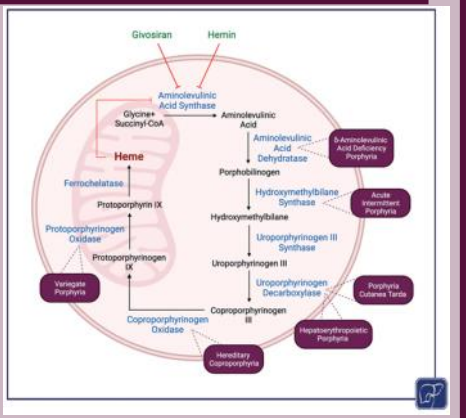
Please share your relevant accolades (grants, publications, awards and other news worthy items) with us, as it relates to the PLRC mission, so we can share with all of our members.

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



Kari Nejak-Bowen, MBA, PhD, published a review article on Porphyrias in Semiars in Liver Disease.

Balogun O, Nejak-Bowen K. The Hepatic Porphyrias: Revealing the Complexities of a Rare Disease. Semin Liver Dis. 2023 Nov 16. doi: 10.1055/s-0043-1776760. Epub ahead of print. PMID: 37973028.

The porphyrias are a group of metabolic disorders that are caused by defects in heme biosynthesis pathway enzymes. The result is accumulation of heme precursors, which can cause neurovisceral and/or cutaneous photosensitivity. Liver is commonly either a source or target of excess porphyrins, and porphyria-associated hepatic dysfunction ranges from minor abnormalities to liver failure. In this review, the first of a three-part series, we describe the defects commonly found in each of the eight enzymes involved in heme biosynthesis. We also discuss the pathophysiology of the hepatic porphyrias in detail, covering epidemiology, histopathology, diagnosis, and complications. Cellular consequences of porphyrin accumulation are discussed, with an emphasis on oxidative stress, protein aggregation, hepatocellular cancer, and endothelial dysfunction. Finally, we review current therapies to treat and manage symptoms of hepatic porphyria.

Faculty Highlight

George Michalopoulos, MD, PhD. Authored a commentary in Hepatology entitled "Hepatocytes of mice and men: Different regenerative signals? "

Michalopoulos GK. Hepatology. 2023 Nov16.doi:10.1097/HEP.0000000000000693. Epub ahead of print. PMID: 37972957.

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Faculty Highlight

Dr. Wen Xie, PhD authors review in Pharmacology & Therapeutics entitled "Sulfoconjugation of protein peptides and glycoproteins in physiology and diseases".

Xu P, Cai X, Guan X, Xie W. . Pharmacol Ther. 2023 Nov;251:108540.doi:10.1016/j.pharmthera.2023.108540. Epub 2023 Sep 28. PMID: 37777160.

ABSTRACT:

Protein sulfoconjugation, or sulfation, represents a critical post-translational modification (PTM) process that involves the attachment of sulfate groups to various positions of substrates within the protein peptides or glycoproteins. This process plays a dynamic and complex role in many physiological and pathological processes. Here, we summarize the importance of sulfation in the fields of oncology, virology, drug-induced liver injury (DILI), inflammatory bowel disease (IBD), and atherosclerosis. In oncology, sulfation is involved in tumor initiation, progression, and migration. In virology, sulfation influences viral entry, replication, and host immune response. In DILI, sulfation is associated with the incidence of DILI, where altered sulfation affects drug metabolism and toxicity. In IBD, dysregulation of sulfation compromises mucosal barrier and immune response. In atherosclerosis, sulfation influences the development of atherosclerosis by modulating the accumulation of lipoprotein, and the inflammation, proliferation, and migration of smooth muscle cells. The current review underscores the importance of further research to unravel the underlying mechanisms and therapeutic potential of targeting sulfoconjugation in various diseases. A better understanding of sulfation could facilitate the emergence of innovative diagnostic or therapeutic strategies.

Faculty Highlight

Dr. Andy Duncan, PhD, published a review in Seminars in Liver Disease entitled, "The Ploidy State as a Determinant of Hepatocyte Proliferation."

Wilson SR, Duncan AW. Semin Liver Dis. 2023 Nov 15. doi: 10.1055/a-2211-2144. Epub ahead of print. PMID: 37967885.

ABSTRACT:

The liver's unique chromosomal variations, including polyploidy and aneuploidy, influence hepatocyte identity and function. Among the most well-studied mammalian polyploid cells, hepatocytes exhibit a dynamic interplay between diploid and polyploid states. The ploidy state is dynamic as hepatocytes move through the "ploidy conveyor," undergoing ploidy reversal and re-polyploidization during proliferation. Both diploid and polyploid hepatocytes actively contribute to proliferation, with diploids demonstrating an enhanced proliferative capacity. This enhanced potential positions diploid hepatocytes as primary drivers of liver proliferation in multiple contexts, including homeostasis, regeneration and repopulation, compensatory proliferation following injury, and oncogenic proliferation. This review discusses the influence of ploidy variations on cellular activity. It presents a model for ploidy-associated hepatocyte proliferation, offering a deeper understanding of liver health and disease with the potential to uncover novel treatment approaches.

Faculty Highlight

Dr. Tirthadipa Pradhan-Sundd, PhD published an article in Haematologica entitled "Impaired hemoglobin clearance by sinusoidal endothelium promotes vaso-occlusion and liver injury in sickle cell disease"

Kaminski TW, Katoch O, Li Z, Hanway CB, Dubey RK, Alagbe A, Brzoska T, Zhang H, Sundd P, Kato GJ, Novelli EM, Pradhan-Sundd T. Impaired hemoglobin clearance by sinusoidal endothelium promotes vaso-occlusion and liver injury in sickle cell disease. Haematologica. 2023 Nov 9. doi: 10.3324/haematol.2023.283792. Epub ahead of print. PMID: 37941440.

Abstract

Sickle cell disease (SCD) is a monogenic disorder that affects 100,000 African Americans and millions of people worldwide. Intra-erythrocytic polymerization of sickle hemoglobin (HbS) promotes erythrocyte sickling, impaired rheology, ischemia and hemolysis, leading to the development of progressive liver injury in SCD. Liver resident macrophages and monocytes are known to enable the clearance of HbS, however, the role of liver sinusoidal endothelial cells (LSECs) in HbS clearance and liver injury in SCD remains unknown. Using real-time intravital (in vivo) imaging in the mice liver as well as flow cytometric analysis and confocal imaging of primary human LSECs, we show for the first time that liver injury in SCD is associated with accumulation of HbS and iron in the LSECs, leading to LSEC senescence. Hb uptake by LSECs was mediated by micropinocytosis. Hepatic monocytes were observed to attenuate LSECsenescence by accelerating HbS clearance in the liver of SCD mice, however, this protection was impaired in P-selectin-deficient SCD mice secondary to reduced monocyte recruitment in the liver. These findings are the first to suggest that LSECs contribute to HbS clearance and HbS induced LSEC-senescence promotes progressive liver injury in SCD mice. Our results provide a novel insight into the pathogenesis of hemolysis induced chronic liver injury in SCD caused by LSEC senescence. Identifying the regulators of LSEC mediated HbS clearance may lead to new therapies to prevent the progression of liver injury in SCD.

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PLRC Seminars

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

Enis Kostallari, PhD
Assistant Professor of Biochemistry and Molecular Biology
Mayo Clinic, Rochester

Seminar Title: Fibrogenic extracellular vesicles during liver fibrosis amplification

Dec 5th @ 12:00 pm – 1:00 pm in S120 BST

Liya Pi, PhD
Assistant Professor
Dept. of Pathology
Tulane University

Seminar Title: "Regeneration or Fibrosis" A Balancing Act for Liver Repair"

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

Alice O. Silvia Kamphorst, PhD
Assistant Professor
Icahn School of Medicine
Moune Sinai, New York

Seminar Title: "Re-priming of PD-1+ CD8 T cells for effective immunotherapy"

NOTICE!

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

Please submit by the standard dates

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

NOFOs:

NOFO RFA-DK-25-003 Silvio O. Conte Digestive Diseases Research Core Centers (P30 Clinical Trial Optional) Plan for Enhancing Diverse Perspectives (PEDP), DMS. Etc changes in effect January 2024

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

Or click below for recent weeks:

Week of: Nov 10: Nov 17: Nov 24:

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

AASLD "Research & Career Development Awards"
Multiple Awards:
Deadline December 4th, 2023
More info on website

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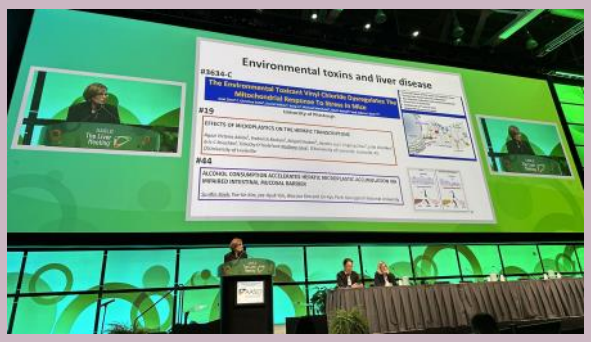
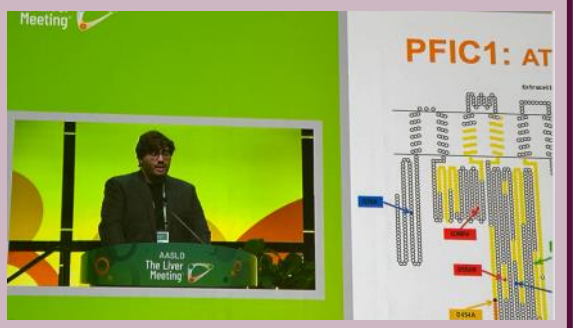
PLI/ Pitt GI Reception Highlights

Meeting Snapshots





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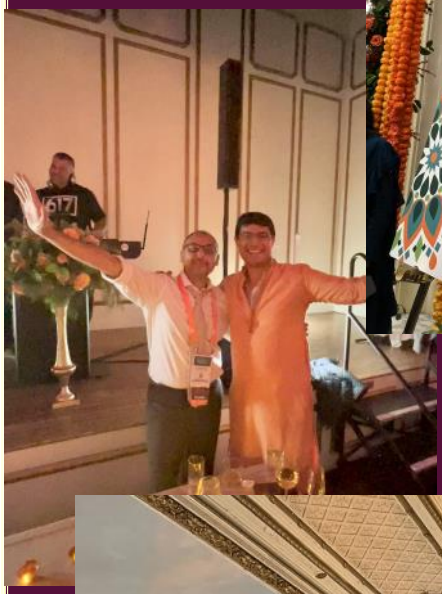
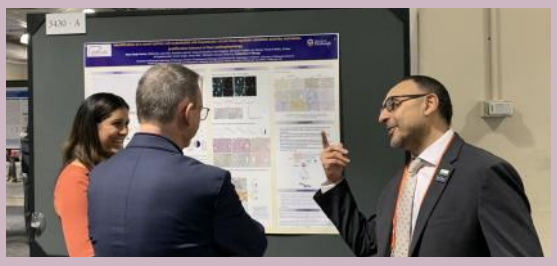
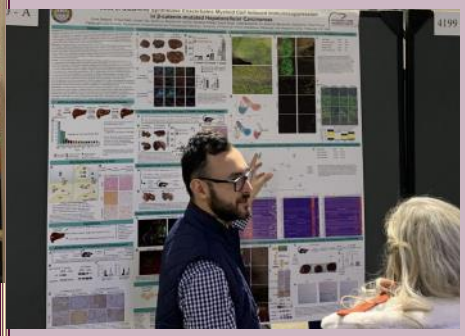
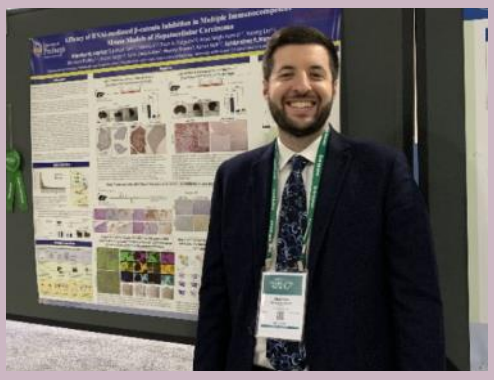
AASLD Member Reception Highlights



AASLD Poster Session Highlights







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ANNOUNCEMENTS

- **Communityliveralliance.org**

CLA 10yr ANNIVERSARY Celebration

November 30th 6:00—8:00PM @ Grand Concourse (100 West Station Square Dr, Pittsburgh, PA 15219) RSVP @ CommunityLiverAlliance.org

$50/person Click Here for more info and to register

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, Molecular Biology, metabolism, signal transduction.

Email: kpant@umn.edu Link to CV