LIVER DIGEST

December 18, 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

Mo Ebrahimkhani, MD, along with **Samira Kiani, MD**, **Donna Stolz, PhD** and the Imaging Core of the PLRC publish an article in Nature entitled **"Modeling post-implantation human development to yolk sac blood emergence".**

Hislop, J., Song, Q., Keshavarz F., K. *et al.* Modeling post-implantation human development to yolk sac blood emergence. *Nature* (2023). https://doi.org/10.1038/s41586-023-06914-8 **Full text Link**

University PRESS RELEASE: LINK
Eureka News-Release: LINK

ABSTRACT:
Implantation of the human embryo commences a critical developmental stage that comprises profound events including axis formation, gastrulation, and the emergence of hematopoietic system[1,2]. Our mechanistic knowledge of this window of human life remains limited due to restricted access to *in vivo* samples for both technical and ethical reasons[3-5]. Stem cell models of human embryo have emerged to help unlock the mysteries of this stage[6-16]. Here, we present a genetically inducible stem cell-derived embryoid model of early post-implantation human embryogenesis that captures the reciprocal co-development of embryonic tissue and extra-embryonic endoderm and mesoderm niche with early hematopoiesis. This model is produced from induced pluripotent stem cells and shows unanticipated self-organizing cellular programs similar to those that occur in embryogenesis, including the formation of amniotic cavity and bilaminar disc morphologies as well as the generation of an anterior hypoblast pole and posterior domain. The extra-embryonic layer in these embryoids lacks trophoblast and exhibits advanced multilineage yolk sac tissue-like morphogenesis that harbors a process similar to distinct waves of hematopoiesis, including the emergence of erythroid-, megakaryocyte-, myeloid-, and lymphoid-like cells. This model presents an easy-to-use, high-throughput, reproducible, and scalable platform to probe multifaceted aspects of human development and blood formation at the early post-implantation stage. It will provide a tractable human-based model for drug testing, and disease modeling.

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Faculty Highlight



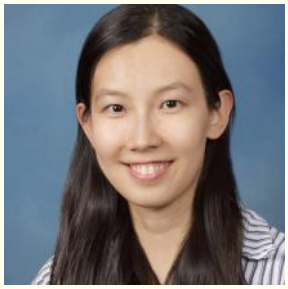

Roberto Mota Avidrez and PLRC members Hamza Yazdani, Paul Monga, and GSBC Core directors Jian-hua Luo and Silvia Liu published an article on an experimental model of Diabetes mellitus in the journal Heliyon, entitled, "**Restoring glucose balance: Conditional HMGB1 knockdown mitigates hyperglycemia in a Streptozotocin induced mouse model**"

Zeyu Liu, Gowtham Annarapu, Hamza O. Yazdani, Qinge Wang, Silvia Liu, Jian-Hua Luo, Yan-Ping Yu, Baoguo Ren, Matthew D. Neal, Satdarshan P. Monga, Roberto Ivan Mota Alvidrez, Heliyon, Volume 10, Issue 1,2024,e23561,ISSN2405-8440,https://doi.org/10.1016/j.heliyon.2023.e23561

Diabetes mellitus (DM) poses a significant global health burden, with hyperglycemia being a primary contributor to complications and high morbidity associated with this disorder. Existing glucose management strategies have shown suboptimal effectiveness, necessitating alternative approaches. In this study, we explored the role of high mobility group box 1 (HMGB1) in hyperglycemia, a protein implicated in initiating inflammation and strongly correlated with DM onset and progression. We hypothesized that HMGB1 knockdown will mitigate hyperglycemia severity and enhance glucose tolerance. To test this hypothesis, we utilized a novel inducible HMGB1 knockout mouse model exhibiting systemic HMGB1 knockdown. Hyperglycemic phenotype was induced using low dose streptozotocin (STZ) injections, followed by longitudinal glucose measurements and oral glucose tolerance tests to evaluate the effect of HMGB1 knockdown on glucose metabolism. Our findings showed a substantial reduction in glucose levels and enhanced glucose tolerance in HMGB1 knockdown mice. Additionally, we performed RNA sequencing analyses, which identified potential alternations in genes and molecular pathways within the liver and skeletal muscle tissue that may account for the in vivo phenotypic changes observed in hyperglycemic mice following HMGB1 knockdown. In conclusion, our present study delivers the first direct evidence of a causal relationship between systemic HMGB1 knockdown and hyperglycemia in vivo, an association that had remained unexamined prior to this research. This discovery positions HMGB1 knockdown as a potentially efficacious therapeutic target for addressing hyperglycemia and, by extension, the DM epidemic. Furthermore, we have revealed potential underlying mechanisms, establishing the essential groundwork for subsequent in-depth mechanistic investigations focused on further elucidating and harnessing the promising therapeutic potential of HMGB1 in DM management.

Faculty Highlight

Dr. Silvia Liu and **Dr. Sungjin Ko**, active members of the PLRC and both former P&F grant recipients were awarded a Discovery Grant by the ICI (**Innovation in Cancer Informatics**) for their joint project on Discovery and Validation of Cancer Therapeutic Targets Through the Single-Cell Long-Read RNA-seq Analysis. This project stems from their P&F work. **CONGRATULATIONS!**


Silvia Liu, PhD


Sungjin Ko, DMV, PhD

The innovation of single-cell long-read RNA-seq technology has advanced our capacity to characterize the transcriptome at the isoform and single-cell levels, surmounting substantial challenges in detecting and analyzing molecular alteration in cancer cells. Our goal is to devise computational methodologies to expedite the individual single-cell-level identification of concealed oncogenic modifications such as alternative splicing variants, novel isoforms, and mutation profiles based on this state-of-the-art technique. By annotating known and novel isoforms, quantifying isoform expressions, and profiling mutation isoforms with single-cell precision, and subsequently validating the functional implications of discovered candidates, we aim to facilitate the discovery of novel targets for cancer therapy and innovative diagnostic approaches. Furthermore, the resultant bioinformatics tools and our findings will be disseminated to the medical scientific community, potentially contributing to the development of effective diagnostic and therapeutic regimens in the clinic.

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Faculty Highlight

Brandon Lehrich, an MD-PhD trainee in the Medical Scientist Training Program along with his mentor Dr. Paul Monga authored a review article in Journal of Hepatology entitled, **"Battle of the Biopsies: Role of tissue and liquid biopsy in hepatocellular carcinoma".**

Lehrich BM, Zhang J, Monga SP, Dhanasekaran R. Battle of the Biopsies: Role of tissue and liquid biopsy in hepatocellular carcinoma. J Hepatol. 2023 Dec 15:S0168-8278(23)05307-2. doi: 10.1016/j.jhep.2023.11.030. Epub ahead of print. PMID: 38104635.

Hepatocellular carcinoma (HCC) diagnosis and management have undergone significant improvements in recent years. With the introduction of immunotherapy-based combination therapy, there has been a notable expansion in treatment options for patients with unresectable HCC. Simultaneously, innovative molecular tests for early detection and management of HCC are emerging. This progress prompts a key question: as liquid biopsy techniques rise in prominence, will they replace traditional tissue biopsies, or will both techniques remain relevant? Given the ongoing challenges of early HCC detection, including issues with ultrasound sensitivity, accessibility, and patient adherence to surveillance, the evolution of diagnostic techniques is more relevant than ever. Furthermore, the accurate stratification of HCC is limited by the absence of reliable biomarkers which can predict response to therapies. While the advantages of molecular diagnostics are evident, their potential has not yet been fully harnessed, largely because tissue biopsies are not routinely performed for HCC. Liquid biopsies, analyzing components such as circulating tumor cells, DNA, and extracellular vesicles, provide a promising alternative, though they still face challenges in sensitivity, cost, and accessibility. The early results from multianalyte liquid biopsy panels are promising and suggest they could play a transformative role in HCC detection and management, however, comprehensive clinical validation is still ongoing. In this review, we explore the challenges and potential of both tissue and liquid biopsy, highlighting that these diagnostic methods, while distinct in their approaches, are set to jointly reshape the future of HCC management.

Seasons Greetings

Dear Members and Friends of the Pittsburgh Liver Research Center,

As another year draws to a close and we take time to celebrate in this festive season and spend time with family and friends, we hope each of you will take time to reflect and cherish these special moments that are so often missed through the hustle and bustle of our regular work schedules.

The PLRC has grown and evolved with the times in our membership base, funding, collaborative science, and our Cores. We would like to take this opportunity to thank all of our members and especially the Core Directors and Administrators for their efforts to make the PLRC the best it can be.

We sincerely wish you all a very happy and safe holiday season and health, happiness and prosperity in the New Year!

All the Best,

Paul Monga and the PLRC administration

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PLRC Seminars

Jan 16th @ 12:00 pm – 1:00 pm in S120 BST

Lindsey Kennedy, PhD

Assistant Research Professor, Medicine
Indiana University School of Medicine

Seminar Title: Multifunctional Roles for Endothelin Signaling in Models of Cholangitis

Jan 23rd @ 12:00 pm – 1:00 pm in S120 BST

Wen Xie**, MD, PhD**

Chair & Endowed Professor Dept of Pharmaceutical Sciences, and Professor of Pharmacology & Chemical Biology at the School of Medicine

Seminar Title: TBD

Jan 30th @ 12:00 pm – 1:00 pm in S120 BST

Robert Schwartz, MD, PhD

Associate Professor of Medicine, Physiology, Biophysics, Systems Biology, & Biomedical Engineering
Cornell University, NY

Seminar Title: **Leveraging Bioengineered and Primary Tissues to Study Human Liver Diseases**

NOTICE!

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

Please submit by the standard dates

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

NOFOs:

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

AASLD Bridge Award in Liver Diseases
Jan 15th deadline URL/Link

Diabetes: JDRF Grant Opportunities
URL/LINK

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

Or click below for recent weeks:

Week of: Dec 15: Dec 8: Dec 1:

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

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ANNOUNCEMENTS

- Communityliveralliance.org
- 5th Annual UPMC Annual Update in Medical Hepatology (2024) February 3, 2024 8:00AM-3:00PM @ The University Club, Pitt Campus. In-person or Virtual option Agenda: Registration
- PLRC External Advisory Board Meeting 2/6/24 9AM-4PM @ 1104 Scaife Hall Conference Center
- The FASEB Liver Meeting is now the Summer Liver Academy Meeting (SLAM). June 16-20, 2024 @ Cape Coral, FL
- THE LIVER SINUSOID MEETING April 24-26, 2024 @ Chicago, IL Program: Registration

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