

# LIVER DIGEST

August 18, 2023

A bi-weekly update of PLRC happenings



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- ASIP "Tissue, Matrix, and Pathobiology" Oct. 22<sup>nd</sup>
- 2nd International Liver Cancer Res. Conf, Heidelberg, Germany
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### • Want Ads :

- Open positions/Jobseekers CVs posted

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

Please continue to 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](http://www.livercenter.pitt.edu)) for up-to-date news, and upcoming seminar and event information. Contact Aaron Bell ([bellaaaro@pitt.edu](mailto:bellaaaro@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



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## FACULTY HIGHLIGHT

### Eric Goetzman, PhD

Associate Professor of Pediatrics along with Ed Prochownik, MD, PhD and Paul Monga, MD

published an article in International Journal of Molecular Sciences entitled, "*A Novel Transgenic Mouse Model Implicates Sirt2 as a Promoter of Hepatocellular Carcinoma*".



Schmidt, A.V.; Monga, S.P.; Prochownik, E.V.; Goetzman, E.S. *Int. J. Mol. Sci.* 2023, 24, 12618. <https://doi.org/10.3390/ijms241612618>

**ABSTRACT:** Hepatocellular carcinoma (HCC) is one of the leading causes of cancer deaths globally. Incidence rates are steadily increasing, creating an unmet need for new therapeutic options. Recently, the inhibition of sirtuin-2 (Sirt2) was proposed as a potential treatment for HCC, despite contradictory findings of its role as both a tumor promoter and suppressor in vitro. Sirt2 functions as a lysine deacetylase enzyme. However, little is known about its biological influence, despite its implication in several age-related diseases. This study evaluated Sirt2's role in HCC in vivo using an inducible c-MYC transgene in Sirt2<sup>+/+</sup> and Sirt2<sup>-/-</sup> mice. Sirt2<sup>-/-</sup> HCC mice had smaller, less proliferative, and more differentiated liver tumors, suggesting that Sirt2 functions as a tumor promoter in this context. Furthermore, Sirt2<sup>-/-</sup> HCCs had significantly less c-MYC oncoprotein and reduction in c-MYC nuclear localization. The RNA-seq showed that only three genes were significantly dysregulated due to loss of Sirt2, suggesting the underlying mechanism is due to Sirt2-mediated changes in the acetylome, and that the therapeutic inhibition of Sirt2 would not perturb the oncogenic transcriptome. The findings of this study suggest that Sirt2 inhibition could be a promising molecular target for slowing HCC growth.

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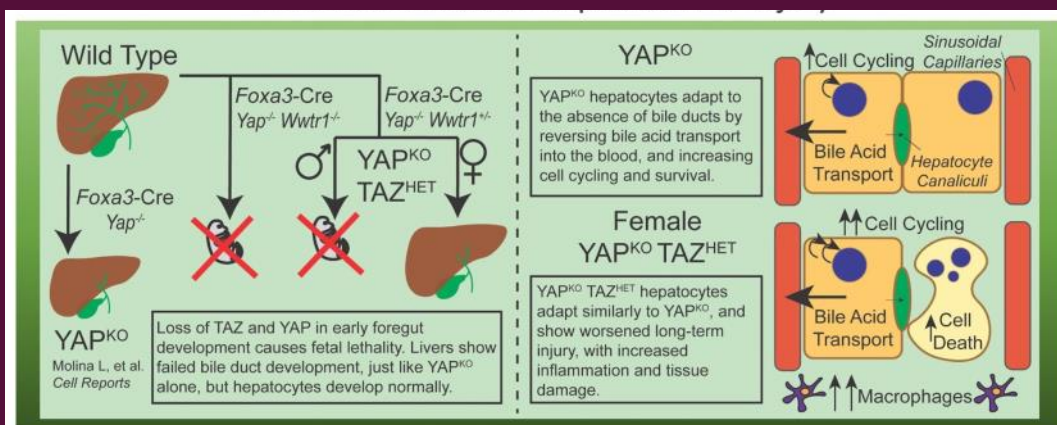


## PLRC HIGHLIGHT

Dr. Laura Molina, PittMed MSTP and first year Pathology Resident at UPMC publishes her first Senior author study along with PLRC members Dr. Paul Monga, MD, PhD, Kari Nejak-Bowen, PhD, MBA, and Xiaochao Ma, PhD. The article is published in Hepatology Communications and is entitled,



**“Loss of TAZ after YAP deletion severely impairs foregut development and worsens cholestatic hepatocellular injury”.**



Gabdulkhakova A, et al. *Hepatology Communications*. 2023.

**HEPATOLOGY COMMUNICATIONS**

**Background:** We previously showed that loss of yes-associated protein 1 (YAP) in early liver development (YAPKO) leads to an Alagille syndrome-like phenotype, with failure of intrahepatic bile duct development, severe cholestasis, and chronic hepatocyte adaptations to reduce liver injury. TAZ, a paralog of YAP, was significantly upregulated in YAPKO hepatocytes and interacted with TEA domain family member (TEAD) transcription factors, suggesting possible compensatory activity.

**Methods:** We deleted both *Yap1* and *Wwtr1* (which encodes TAZ) during early liver development using the *Foxa3* promoter to drive Cre expression, similar to YAPKO mice, resulting in YAP/TAZ double knockout (DKO) and YAPKO with TAZ heterozygosity (YAPKO TAZHET). We evaluated these mice using immunohistochemistry, serum biochemistry, bile acid profiling, and RNA sequencing.

**Results:** DKO mice were embryonic lethal, but their livers were similar to YAPKO, suggesting an extrahepatic cause of death. Male YAPKO TAZHET mice were also embryonic lethal, with insufficient samples to determine the cause. However, YAPKO TAZHET females survived and were phenotypically similar to YAPKO mice, with increased bile acid hydrophilicity and similar global gene expression adaptations but worsened the hepatocellular injury. TAZ heterozygosity in YAPKO impacted the expression of canonical YAP targets *Ctgf* and *Cyr61*, and we found changes in pathways regulating cell division and inflammatory signaling correlating with an increase in hepatocyte cell death, cell cycling, and macrophage recruitment.

**Conclusions:** YAP loss (with or without TAZ loss) aborts biliary development. YAP and TAZ play a codependent critical role in foregut endoderm development outside the liver, but they are not essential for hepatocyte development. TAZ heterozygosity in YAPKO livers increased cell cycling and inflammatory signaling in the setting of chronic injury, highlighting genes that are especially sensitive to TAZ regulation.

# LIVER DIGEST

## August 18, 2023



### PLRC SEMINARS

NOTE: *Members are highly encouraged to physically attend to support our external and internal speakers.*

\* Aug 22<sup>nd</sup> @ 12:00-1:00PM in S120 BST \*\*In-Person\*\*



Speaker: Dr. Paul Monga

**"State of the PLRC Address" & "Pittsburgh Liver Institute; Overview of Structure and function."**

**MEMBER ATTENDANCE and feedback REQUESTED.**

\* Aug 29<sup>th</sup> @ 12:00-1:00PM in S120 BST



**Irina Bochkis, PhD**  
Associate Professor of Pharmacology

University of Virginia

Email: [imb3q@virginia.edu](mailto:imb3q@virginia.edu)  
Website: <http://pharm.virginia.edu/bochkis>

**Seminar Title: Pioneer factor Foxa2 and chromatin landscape in the liver**

\* Sept 12<sup>th</sup> @ 12:00-1:00PM in S120 BST



Feng Li, PhD

Associate Professor

Dept of Pharmacology and Chemical Biology  
Baylor College of Medicine

**Seminar Title: Mechanistic Studies of Antidepressant Duloxetine Hepatotoxicity**

### ANNOUNCEMENT

**PLRC Pilot & Feasibility Grants  
2024 Application Cycle NOW OPEN!**

PLRC Members should encourage qualified senior Post-Docs (ready to transition to independence) and junior faculty to begin to prepare now, and apply.

Letters of Intent Due: September 1<sup>st</sup>, 2023

Full application Due: October 13<sup>th</sup>, 2023

More details on the PLRC P&F [Website](#)

**\*\*NEW\*\* CLA/PLRC Award**

The Community Liver Alliance and the PLRC joint award will prioritize funding studies of liver diseases in underserved communities, healthcare disparity, pathogenesis of sexually dimorphic diseases or other topics or candidates with DEI focus.

### FUNDING OPPORTUNITIES

**Human Liver Tissue and Hepatocytes Resource-Related Research Project (R24 Clinical Trial Not Allowed)**

**[RFA-DK-23-012 NIH/NIDDK](#)**

The purpose of this Notice of Funding Opportunity (NOFO) is to support a Human Liver Tissue and Hepatocytes Research Resource (HLTHRR) program to enable the continued availability of human liver tissue and hepatocytes to biomedical researchers. The research resource is expected to facilitate the procurement and preservation of human liver tissue and hepatocytes as well as the distribution of these materials to qualified biomedical researchers

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.**

### FUNDING OPPORTUNITIES

**To see all NIH Grants sorted by week, please visit [NIH Guide: 2023](#)**

**Or click below for recent weeks:**

**Week of: [Aug 4:](#) [Aug 11:](#) [Aug 18:](#)**

**[Click here](#) for all current **NIDDK** Funding opportunities**

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## ANNOUNCEMENTS

- [Communityliveralliance.org](https://communityliveralliance.org)  
**DeLIVERing HOPE campaign: Liver Disease Awareness**
- Pittsburgh Liver Institute/PLRC Reception at The AASLD LIVER MEETING in Boston. Saturday **November 11<sup>th</sup>**, 7:30pm-9:30pm @ Sheraton Hotel Boston **"Save the Date"**
- PLRC Annual Retreat 2023 **October 17<sup>th</sup>** at University Club. Agenda TBD. Keynote Speaker: Rebecca Wells, Univ. of Pennsylvania. **"SAVE the DATE"**
- PLRC Pilot & Feasibility Grant Program Open NOW! **More details and info available on Website**  
LOI due **September 1, 2023**, Applications Due **October 13, 2023** **Link to RFA**
- FIRST INTERNATIONAL CONFERENCE OF LIVER PATHOBIOLOGY: FROM BENCH TO BEDSIDE. CRETE, GREECE  
**OCTOBER 11-16, 2023** **CONFERENCE SCHEDULE** / **SPEAKERS** / **REGISTRATION**
- **AASLD "THE LIVER MEETING"** **Nov. 10-14, 2023** @ Boston, MA. Meeting Registration open Now!
- **ASIP "Tissue, Matrix, and Pathobiology: Joint Meeting of ASMB, HCS and ASIP"** **Oct. 22-25, 2023** @ Salt Lake City Utah. **Meeting Registration Site**
- 2nd INTERNATIONAL LIVER CANCER RESEARCH CONFERENCE 2023 "Novel Directions in Liver Cancer Research" **Oct. 11-13, 2023** @ Heidelberg, Germany **Detail-Flyer** **Conference Program**

## 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](mailto: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](mailto:hcblair@pitt.edu)

## JOB SEEKERS:

- **Research Assistant Professor**, Pathology Dept, UPMC Hillman Cancer Ctr. With experience in Bioinformatics, proteomics, genomics, molecular biology. [liz45@pitt.edu](mailto:liz45@pitt.edu) **link to CV**