PITTSBURGH LIVER RESEARCH CENTER
A partnership of University of Pittsburgh & UPMC

# PLRC - Weekly Update

December 13, 2018

In this email:



## Upcoming Seminars

### PLRC Seminar Series

Tuesday, January 15, 2019
12:00-1:00 p.m.
S123 BST

**Samira Kiani, MD**
Assistant Professor
School of Biological and Health Systems Engineering
Ira A. Fulton Schools of Engineering
Arizona State University

**Title TBA**

*This activity has been approved for AMA PRA Category 1 Credit. #6242 Liver Center Seminars.*

*Pizza will be provided.*

## PLRC Seminar Series

Tuesday, January 29, 2019
12:00-1:00 p.m.
S123 BST

**Yanqiao Zhang, MD**
Professor of Integrative Medical Sciences
Northeast Ohio Medical University

**"NAFLD: Novel Pathogenic Mechanisms and Potential Therapeutics"**

*This activity has been approved for AMA PRA Category 1 Credit. #6242 Liver Center Seminars.*

*Pizza will be provided.*
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**Registration URL: https://attendee.gotowebinar.com/register/6607572696840938499**

For those viewing thru the webinar, please follow the directions below:

- Please Register for the live Webinar ASAP
- After registering, you will receive the confirmation email
- You will be prompt to download the CitrixOnline application and install on your PC or Laptop
- Please contact your local PC Support if you need help installing the application
- Feel free to email Ishtiaque Ahmed (**ahmedi@upmc.edu**) if you have any questions

NOTE Webinar attendees -- use Telephone/Speakerphone and dial-in instead of using desktop/laptop speakers for better audio quality.

Telephone/Speakerphone Audio option is shown right at the Click to Join Webinar prompt.

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## Liver Seminar

Wednesday, January 30, 2019
12:00-1:00 p.m.
1104 Scaife

**Chandrashekhar R. Gandhi, Ph.D., FAASLD**
Professor of Integrative Medical Sciences
Northeast Ohio Medical University

**"NAFLD: Novel Pathogenic Mechanisms and Potential Therapeutics"**

### PLRC SIG - Tumorigenesis

Tuesday, February 5, 2019
12:00-1:00 p.m.
S123 BST

**Dr. Sarangarajan Ranganathan - Histology and Molecular Classification of Hepatoblastoma**

**Dr. Edward Prochownik - Predicting Hepatoblastoma Phenotypes**

*Pizza will be provided.*

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For a complete list of upcoming PLRC events, please visit our website: **www.livercenter.pitt.edu/events**

## Funding Opportunities

**AGA-Moti L. & Kamla Rustgi International Travel Awards**
American Gastroenterological Association (AGA)
AGA Research Foundation

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**AGA Fellow Abstract Award**
American Gastroenterological Association (AGA)
AGA Research Foundation

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**AGA Student Abstract Award**
American Gastroenterological Association (AGA)
AGA Research Foundation

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**AGA Research Scholar Award**
American Gastroenterological Association (AGA)
AGA Research Foundation

# Recent Faculty Publications

**James E. Squires, Patrick McKiernan, Robert H. Squires**. Acute Liver Failure: An Update. Clinics in Liver Disease, 2018-11-01, Volume 22, Issue 4, Pages 773-805. PMID: 30266162

ABSTRACT

Pediatric acute liver failure (PALF) is a dynamic, life-threatening condition of disparate etiology. Management of PALF is dependent on intensive collaborative clinical care and support. Proper recognition and treatment of common complications of liver failure are critical to optimizing outcomes. In parallel, investigations to identify underlying cause and the implementation of timely, appropriate treatment can be life-saving. Predicting patient outcome in the era of liver transplantation has been unfulfilling and better predictive models must be developed for proper stewardship of the limited resource of organ availability.

For full text, please **click here**.

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Piekos SC, Chen L, Wang P, Shi J, Yaqoob S, Zhu HJ, **Ma X**, Zhong XB. Consequences of Phenytoin Exposure on Hepatic Cytochrome P450 Expression during Postnatal Liver Maturation in Mice. Drug Metab Dispos. 2018 Aug;46(8):1241-1250. doi: 10.1124/dmd.118.080861. Epub 2018 Jun 8. PubMed PMID: 29884652; PubMed Central PMCID: PMC6053591.

ABSTRACT

The induction of cytochrome P450 (P450) enzymes in response to drug treatment is a significant contributing factor to drug-drug interactions, which may reduce therapeutic efficacy and/or cause toxicity. Since most studies on P450 induction are performed in adults, enzyme induction at neonatal, infant, and adolescent ages is not well understood. Previous work defined the postnatal ontogeny of drug-metabolizing P450s in human and mouse livers; however, there are limited data on the ontogeny of the induction potential of each enzyme in response to drug treatment. Induction of P450s at the neonatal age may also cause permanent alterations in P450 expression in adults. The goal of this study was to investigate the short- and long-term effects of phenytoin treatment on mRNA and protein expressions and enzyme activities of CYP2B10, 2C29, 3A11, and 3A16 at different ages during postnatal liver maturation in mice. Induction of mRNA immediately following phenytoin treatment appeared to depend on basal expression of the enzyme at a specific age. While neonatal mice showed the greatest fold changes in CYP2B10, 2C29, and 3A11 mRNA expression following treatment, the levels of induced protein expression and enzymatic activity were much lower than that of induced levels in adults. The expression of fetal CYP3A16 was repressed by phenytoin treatment. Neonatal treatment with phenytoin did not

permanently induce enzyme expression in adulthood. Taken together, our data suggest that inducibility of drug-metabolizing P450s is much lower in neonatal mice than it is in adults and neonatal induction by phenytoin is not permanent.

For full text, please **click here**.

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Tandon P, Ismond KP, Riess K, Duarte-Rojo A, Al-Judaibi B, **Dunn MA**, Holman J, Howes N, Haykowsky MJF, Josbeno DA, McNeely M. Exercise in cirrhosis: Translating evidence and experience to practice. Journal of Hepatology. 2018; 69(5):1164-1177. PubMed [journal] PMID: 29964066.

ABSTRACT

Physical inactivity, sarcopenia, and frailty are highly prevalent, independent predictors of morbidity and mortality in patients with cirrhosis. Across a range of chronic diseases, exercise training is a key recommendation supported by guidelines and, for some conditions, even by governmental funding of exercise programmes. Consistent with the broader chronic disease literature, the evidence for a benefit of exercise in cirrhosis is promising. Several small trials have reported significant improvements in muscle health (mass, strength, functional capacity), quality of life, fatigue, and reductions in the hepatic venous pressure gradient, without adverse events. With strong emerging evidence surrounding the substantial risks of sarcopenia/frailty and our first-hand experiences with liver pre-transplant exercise programmes, we contend that routine patient care in cirrhosis should include an exercise prescription. Some clinicians may lack the resources and necessary background to translate the existing evidence into a practicable intervention. Our team, comprised of physiotherapists, exercise physiologists, hepatologists, transplant specialists, and knowledge translation experts from six North American centres, has distilled the essential background information, tools, and practices into a set of information ready for immediate implementation into clinics ranging from a family practice setting to specialty cirrhosis clinics. Augmenting the rationale and evidence are supplementary materials including video and downloadable materials for both patients and the physician. Supporting the exercising patient is a section regarding information about nutrition, providing practical tips suitable for all patients with cirrhosis.

For full text, please **click here**.

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Gu L, Zhu Y, Lin X, Li Y, Cui K, **Prochownik EV**, Li Y. Amplification of Glyceronephosphate O-Acyltransferase and Recruitment of USP30 Stabilize DRP1 to Promote Hepatocarcinogenesis. Cancer Res. 2018 Oct 15;78(20):5808-5819. doi: 10.1158/0008-5472.CAN-18-0340. Epub 2018 Aug 24. PubMed PMID: 30143522.

ABSTRACT

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death worldwide, and the underlying pathophysiology of HCC is highly complex. In this study, we report that, in a bioinformatic screen of 2,783 genes encoding metabolic enzymes, GNPAT, which encodes the enzyme glyceronephosphate O-

acyltransferase, is amplified, upregulated, and highly correlated with poor clinical outcome in human patients with HCC. High GNPAT expression in HCC was due to its amplification and transcriptional activation by the c-Myc/KDM1A complex. GNPAT compensated the oncogenic phenotypes in c-Myc-depleted HCC cells. Mechanistically, GNPAT recruited the enzyme USP30, which deubiquitylated and stabilized dynamin-related protein 1 (DRP1), thereby facilitating regulation of mitochondrial morphology, lipid metabolism, and hepatocarcinogenesis. Inhibition of GNPAT and DRP1 dramatically attenuated lipid metabolism and hepatocarcinogenesis. Furthermore, DRP1 mediated the oncogenic phenotypes driven by GNPAT. Taken together, these results indicate that GNPAT and USP30-mediated stabilization of DRP1 play a critical role in the development of HCC.Significance: This study identifies and establishes the role of the enzyme GNPAT in liver cancer progression, which may serve as a potential therapeutic target for liver cancer.

To access full article, please **click here**.

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Zhu J, Wang P, Li F, Lu J, Shehu AI, **Xie W**, McMahon D, **Ma X**. CYP1A1 and 1B1-mediated metabolic pathways of dolutegravir, an HIV integrase inhibitor. Biochem Pharmacol. 2018 Oct 17;158:174-184. doi: 10.1016/j.bcp.2018.10.012. PubMed PMID: 30342022.

ABSTRACT
Dolutegravir (DTG), a potent integrase inhibitor, is part of a recommended initial regimen for the treatment of human immunodeficiency virus (HIV). Prior reports demonstrated that the clearance of DTG was higher in current smokers than non-smokers, but the mechanism remains unclear. Using a metabolomic approach, M4 (an aldehyde) was identified as a novel metabolite of DTG. In addition, the formation of M4 was found to be mediated by cytochrome P450 (CYP) 1A1 and 1B1, the enzymes that can be highly induced by cigarette smoking. CYP1A1 and 1B1 were also identified as the major enzymes contributing to the formation of M1 (an N-dealkylated metabolite of DTG) and M5 (an aldehyde). Furthermore, the production of M1 and M4 was significantly increased in the lung of mice treated with 2,3,7,8-tetrachlorodibenzo-p-dioxin, an inducer of CYP1A1 and 1B1. In summary, the current study uncovered the CYP1A1 and 1B1-mediated metabolic pathways of DTG. These data suggest that persons with HIV infection receiving DTG should be cautious to cigarettes, and drugs, or exposure to environmental chemicals that induce CYP1A1 and 1B1.

For full text, please **click here**.

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