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Liver Digest

A weekly update of PLRC happenings

February 27, 2020

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

www.livercenter.pitt.edu

Featured Faculty - Dr. Alessandro Furlan

REMINDER: Please acknowledge support from the PLRC (NIH/NIDDK P30DK120531) in your publications and presentations.

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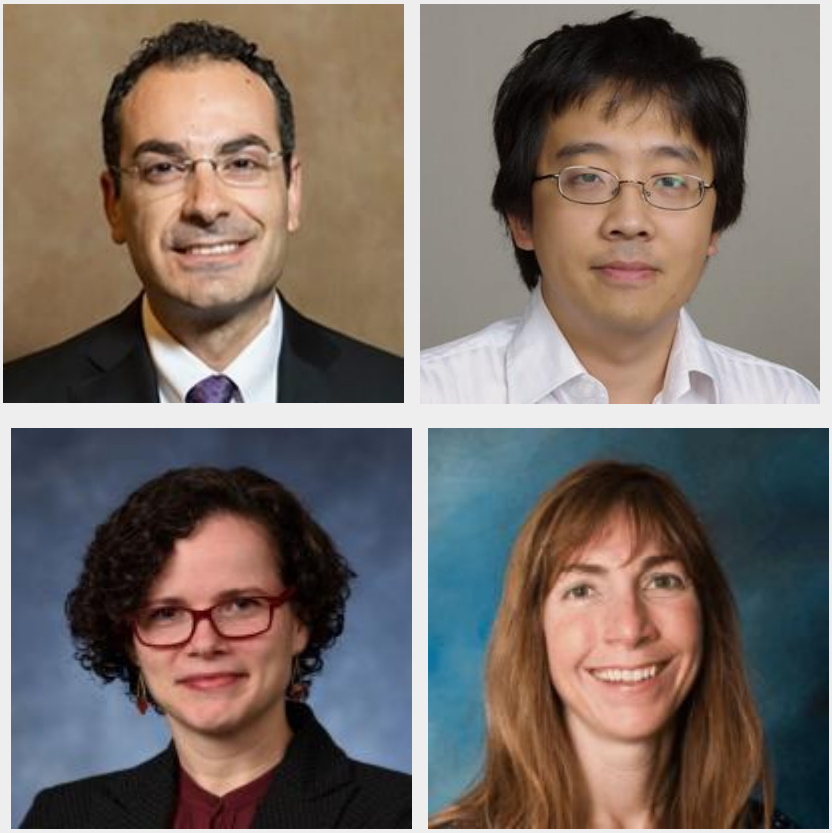
2020-2021 PLRC P&F Awardees

Congratulations to the 2020-2021 PLRC Pilot and Feasibility awardees! Please go to the **Grants page** for more information on their projects.



Pictured left to right: Drs. Andres Duarte-Rojo, Akshata Moghe, Samer Tohme, Bokai Zhu, Carla Ng, and Stacy Wendell

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Upcoming Seminar

Transplantation Grand Rounds

Friday, February 28, 2020

8:00am

LHAS Auditorium, located in Montefiore University Hospital, Seventh Floor.

Dr. Angus Thomson

Distinguished Professor of Surgery
Professor of Immunology and Professor of Clinical & Translational Science
University of Pittsburgh

Regulatory cell therapy in organ transplantation: news from the front

Light breakfast will be provided.

The full schedule of Enrichment activities is posted on **https://www.livercenter.pitt.edu/events**

Faculty Highlights

PLRC members collaborating on manuscripts are noted in red.

Original Article:

Yi Z, Deng M, **Scott MJ**, Fu G, Loughran PA, Lei Z, Li S, Sun P, Yang C, Li W, Xu H, Huang F, **Billiar TR**. IRG1/Itaconate Activates Nrf2 in Hepatocytes to Protect Against Liver Ischemia-Reperfusion Injury. Hepatology. 2020 Jan 30;10.1002/hep.31147. doi: 10.1002/hep.31147. PMID: 31997373.

ABSTRACT
Itaconate, a metabolite of the tricarboxylic acid cycle, plays anti-inflammatory roles in macrophages during endotoxemia. The mechanisms underlying its anti-inflammatory roles have been shown to be mediated by the modulation of oxidative stress, an important mechanism of hepatic ischemia-reperfusion (I/R) injury. However, the role of itaconate in liver I/R injury is unknown. Here we found

that deletion of immune-responsive gene 1 (IRG1), encoding for the enzyme producing itaconate, exacerbated liver injury and systemic inflammation. Furthermore, bone marrow adoptive transfer experiments indicated that deletion of IRG1 in both hematopoietic and non-hematopoietic compartments contributes to the protection mediated by IRG1 after I/R. Interestingly, the expression of IRG1 was up-regulated in hepatocytes after I/R and hypoxia/reoxygenation (H/R)-induced oxidative stress. Modulation of the IRG1 expression levels in hepatocytes regulated hepatocyte cell death. Importantly, addition of 4-octyl itaconate (4-OI) significantly improved liver injury and hepatocyte cell death after I/R. Furthermore, our data indicated that nuclear factor erythroid 2–related factor 2 (Nrf2) is required for the protective effect of IRG1 on mouse and human hepatocytes against oxidative stress–induced injury. Our studies are the first to document the important role of IRG1 in the acute setting of sterile injury induced by I/R. Specifically, we provide evidence that the IRG1/itaconate pathway activates Nrf2-mediated antioxidative response in hepatocytes to protect liver from I/R injury. Conclusion: Our data expand on the importance of IRG1/itaconate in non-immune cells and identify itaconate as a potential therapeutic strategy for this unfavorable postsurgical complication.

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

Webinar Presentation:

Dr. Jianhua Luo

Long-Read Sequencing of Human Transcription Provides Insights into Metastatic Cancer

February 25, 2020 | 1 - 2 pm EST

To register, please follow this

link: https://www.labpulse.com/index.aspx?sec=eba&sub=eml&pag=dis&itemId=800736

This webinar will discuss a study that used long-read transcriptome sequencing to explore the distribution of isoforms in colon cancer samples and their metastasis counterparts.

The complexity of mammalian gene expression involves the combinatorial use of exons during RNA splicing. The selective splicing process generates a plethora of isoforms per gene and accounts for what is arguably the largest source of variation in transcriptome diversity and adaptability. However, the quantification of the diversity of mammalian transcriptome is impeded by the lack of accurate, quantitative, and affordable long-read isoform sequencing.

Accurate analyses of the distribution of isoforms, fusion gene isoforms, and point mutation isoforms remains a huge challenge for human malignancies. In this webinar, Jianhua Luo of the University of Pittsburgh will discuss a study that used the ability to capture transcripts from user-defined sets of genes together with synthetic long-read sequencing of full-length mRNA to characterize the long-read transcriptomes from three pairs of colon cancers and their metastasis counterparts.

Dr. Luo will share how the study demonstrated a unique pattern of RNA isoform redistribution and enrichment for specific mutated isoforms and fusions in metastatic cancer cells in comparison with their primary cancer counterparts. The isoform switching and mutation-enriched isoforms are predicted to have subtle effects on protein structure, which may differentially impact protein signal transduction and response to drug treatment.

The results demonstrate that the use of probe capture and long-read

sequencing provides focus and granularity that was previously inaccessible in transcriptome analysis. Full-length transcriptome analysis may be essential for our understanding of gene expression regulation in human cancers.

Clinical Observations:

Lin FP, Ferrando AA, Dennis RA, **Dunn MA**, Kim WR, **Duarte-Rojo A**. Exercise-Induced Hyperammonemia Does Not Precipitate Overt Hepatic Encephalopathy. Hepatology. 2020 Jan 30;10.1002/hep.31148. doi: 10.1002/hep.31148. PMID: 31997375.

ABSTRACT

Moderate-to-vigorous exercise increases blood ammonia concentrations, potentially contributing to the development of hepatic encephalopathy (HE). Patients with end-stage liver disease (ESLD) often suffer from frailty or physical deconditioning as a result of sarcopenia, fluid overload/ascites, obesity and concomitant diseases. Exercise is therefore recommended for ESLD patients to reverse or halt progression of frailty/sarcopenia, as these conditions contribute to increased mortality.

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

Original Article:

Bennewitz MF, Tutuncuoglu E, Gudapati S, Brzoska T, Watkins SC, **Monga SP, Pradhan-Sundd T, Sundd P**. P-selectin-deficient mice to study pathophysiology of sickle cell disease. Blood Adv. 2020 Jan 28;4(2):266-273. doi: 10.1182/bloodadvances.2019000603. PMID: 31968076; PMCID: PMC6988409.

ABSTRACT

P-selectin-deficient SCD mice are protected from lung vaso-occlusion.P-selectin-deficient SCD mice will be useful in assessing the benefits of anti-P-selectin therapy in diverse complications of SCD.

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

Invited Commentary:

Henkel SAF, **McKiernan PJ**. Bye Bye Benzoate: What Next for Hyperammonemia in Liver Disease? J Pediatr Gastroenterol Nutr. 2020 Feb;70(2):158. doi: 10.1097/MPG.0000000000002571. PMID: 31978006.

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

Original Article:

Kevin Melody, Chandra N. Roy, Christopher Kline, Mackenzie L. Cottrell, Dwayne Evans, Kathleen Shutt, Pleuni S. Pennings, Brandon F. Keele, **Moses Bility**, Angela D.M. Kashuba, Zandrea Ambrose. Long-acting rilpivirine (RPV LA) pre-exposure prophylaxis does not inhibit vaginal transmission of RPV-resistant HIV-1 nor select for high frequency drug resistance in humanized mice [published online ahead of print, 2020 Jan 22]. J Virol. 2020;JVI.01912-19. doi:10.1128/JVI.01912-19.

ABSTRACT
As a long-acting formulation of the non-nucleoside reverse transcriptase inhibitor rilpivirine (RPV LA) has been proposed for use as pre-exposure prophylaxis (PrEP) and the prevalence of transmitted RPV-resistant viruses can be relatively high, we evaluated the efficacy of RPV LA to inhibit vaginal transmission of RPV-resistant HIV-1 in humanized mice. Vaginal challenges of

wildtype (WT), Y181C, and Y181V HIV-1 were performed in mice left untreated or after RPV PrEP. Plasma viremia was measured for 7-10 weeks and single-genome sequencing was performed on plasma HIV-1 RNA in mice infected during PrEP. RPV LA significantly prevented vaginal transmission of WT HIV-1 and Y181C HIV-1, which is 3-fold resistant to RPV. However, it did not prevent transmission of Y181V HIV-1, which has 30-fold RPV resistance in the viruses used for this study. RPV LA did delay WT HIV-1 dissemination in infected animals until genital and plasma RPV concentrations waned. Animals that became infected despite RPV LA PrEP did not acquire new RPV-resistant mutations above frequencies in untreated mice or untreated people living with HIV-1 and the mutations detected conferred low-level resistance. These data suggest that high, sustained concentrations of RPV were required to inhibit vaginal transmission of HIV-1 with little or no resistance to RPV but could not inhibit virus with high resistance. HIV-1 did not develop high-level or high frequency RPV resistance in the majority of mice infected after RPV LA treatment. However, the impact of low frequency RPV resistance on virologic outcome during subsequent antiretroviral therapy is still unclear.

IMPORTANCE The antiretroviral drug rilpivirine was developed into a long-acting formulation (RPV LA) to improve adherence for pre-exposure prophylaxis (PrEP) to prevent HIV-1 transmission. A concern is that RPV LA will not inhibit transmission of drug-resistant HIV-1 and may select for drug-resistant virus. In female humanized mice, we found that RPV LA inhibited vaginal transmission of WT or 3-fold RPV-resistant HIV-1 but not virus with 30-fold RPV resistance. In animals that became infected despite RPV LA PrEP, WT HIV-1 dissemination was delayed until genital and plasma RPV concentrations waned. RPV resistance was detected at similar low frequencies in untreated and PrEP-treated mice that became infected. These results indicate the importance of maintaining RPV

at a sustained threshold after virus exposure to prevent dissemination of HIV-1 after vaginal infection and low frequency resistance mutations conferred low-level resistance, suggesting that RPV resistance is difficult to develop after HIV-1 infection during RPV LA PrEP.

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

Original Article:
Raphael BP, Mitchell PD, Gura KM, Potemkin AK, **Squires RH**, Puder M, Duggan CP. Growth in Infants and Children With Intestinal Failure-associated Liver Disease Treated With Intravenous Fish Oil. J Pediatr Gastroenterol Nutr. 2020 Feb;70(2):261-268. doi: 10.1097/MPG.0000000000002551. PMID: 31978030.

ABSTRACT
Background: Infants with intestinal failure (IF) and IF-associated liver disease (IFALD) are at risk for poor somatic growth because of increased metabolic demands, inadequate intake, intestinal malabsorption, chronic liver disease and other comorbidities. There are limited data on the nutritional adequacy of intravenous fish oil lipid emulsion (FOLE) compared with standard soybean oil lipid emulsion (SOLE) in the setting of intestinal failure.

Aims: To describe growth patterns in a large cohort of infants with IFALD treated with FOLE.

Methods: We compared growth data from infants enrolled in a single-center, prospective FOLE study to published norms, as well as to a multicenter, historical cohort of infants with IF treated with SOLE.

Results: One hundred thirty-eight infants with IFALD were treated with FOLE and 108 with SOLE. Compared with normative growth curves from WHO and published preterm data, infants in both groups from 6 to 11 months postmenstrual age exhibited declines in mean weight- and length-for-age z scores. At 24 months postmenstrual age compared with WHO growth data, infants treated with FOLE had a mean (95% confidence interval [CI]) weight-for-age z-score of 0.13 (-0.18 to 0.45) and length-for-age z-score of 0.07 (-0.33 to 0.47). In comparison, at 24 months postmenstrual age, infants treated with SOLE had a mean weight for age z-score of -0.93 (-1.20 to -0.67) and mean length for age z-score of -2.33 (-2.75 to -1.91). Independent predictors of higher weight, length and head circumference z-scores included older postmenstrual age at baseline, fewer central line-associated blood stream infections, resolution of cholestasis, type of intravenous fat emulsion (FOLE vs SOLE) and female sex.

Conclusions: Infants with IFALD treated with FOLE showed comparable somatic growth to those treated with SOLE in early infancy, and improved somatic growth up to 24 months of age, supporting its wider use in this patient population.

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

Funding Opportunity

Clinical Pilot and Feasibility Awards

Cystic Fibrosis Foundation (CFF)

Cystic Fibrosis Foundation Therapeutics, Inc. (CFFT)

Our mailing address is:
Pittsburgh Liver Research Center
200 Lothrop St. | Pittsburgh, PA 15261