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Liver Digest

A weekly update of PLRC happenings

January 23, 2020

PITTSBURGH LIVER RESEARCH CENTER

A partnership of University of Pittsburgh & UPMC

www.livercenter.pitt.edu

Featured Faculty - Dr. Christopher Hughes

In this issue

PLRC Seminar

PLRC Seminar Series

Tue, 1/28/2020

12:00 to 1:00 pm

S123 BST

Suthat Liangpunsakul, MD (click on name to go to bio page)

Professor of Medicine

Professor of Biochemistry and Microbiology

Indiana University School of Medicine

Alterations in circadian machinery and ω-oxidation of fatty acids in the pathogenesis of alcohol-induced liver injury

Pizza will be provided.

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

Senior Vice Chancellor's Research Seminar
Fri, 01/31/2020
12:00 to 1:00 pm
S100A BST

Kari Nejak-Bowen, PhD, MBA

Assistant Professor of Pathology
Enrichment Director, PLRC

Novel Insights into the Role of Beta-Catenin in Biliary Pathophysiology

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

PLRC EAB meeting

The PLRC's first external advisory board meeting will be held on Friday, January 31, 2020 in 1102 Scaife Hall. All PLRC members are welcome and encouraged to attend the following sessions.

January 31, 2020 – 1102 Scaife Hall
8:25-8:30 am – Welcome and Center Overview – Dr. Paul Monga
8:30-8:45 am – PLRC & Center for Liver Diseases – Dr. Ramon Bataller
8:45-9:00 am – PLRC & Pediatric GI – Dr. Andrew Feranchak
9:00-9:15 am – Dean Arthur Levine
9:15-9:30 am – BREAK
9:30-9:45 am – Dr. Steve Shapiro

9:45-11:00 am – Core presentations

- ACTI Core – Donna Stolz
- BRPC – Aatur Singhi & David Geller
- GSBC – Takis Benos & Jianhua Luo
- Clinical – Paul Monga
- Enrichment – Kari Nejak-Bowen
- P&F – Gavin Arteel

11:00-11:30 am – PLRC: The Path Forward – Dr. Paul Monga

PLRC Mini-Retreat

Mon, 02/03/2020 -
10:30 - 4:00
S100A BST

10:30-11:30—P&F presentations (5 minutes presenting and 5 minutes Q&A)

10:30-10:40—Christian Fernandez
10:40-10:50—Sungjin Ko
10:50-11:00—Anita McElroy
11:00-11:10—Zach Freyberg
11:10-11:20—Sadeesh Ramakrishnan
11:20-11:35—Reben Raeman & Jai Behari

11:35-12:00—Lunch

12:00-1:00—P&F presentations (5 minutes presenting and 5 minutes Q&A)

12:00-12:10—Marlies Meisel
12:10-12:20—Amir Borhani group
12:20-12:30—Andres Duarte-Rojo

12:30-12:40—Hossam Abdelsamed

12:40-12:50—Vikrant Rachakonda group

12:50-1:30—Break

1:30-3:00—Grant-writing presentation – Gavin Arteel/Nick Giannoukakis

3:00-3:30—Open discussion & Q&A

3:30-4:00—Concluding remarks & EAB meeting debriefing - Dr. Paul Monga

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Faculty Highlights

PLRC members collaborating on manuscripts are noted in red.

Original Article:

Stahl EC, Delgado ER, Alencastro F, LoPresti ST, Wilkinson PD, Roy N, Haschak MJ, Skillen CD, **Monga SP, Duncan AW, Brown BN**. Inflammation and Ectopic Fat Deposition in the Aging Murine Liver Is Influenced by CCR2. Am J Pathol. 2019 Dec 13. pii: S0002-9440(19)30853-3. doi: 10.1016/j.ajpath.2019.10.016. PubMed PMID: 31843499.

ABSTRACT

Aging is associated with inflammation and metabolic syndrome, which manifests in the liver as nonalcoholic fatty liver disease (NAFLD). NAFLD can range in severity from steatosis to fibrotic steatohepatitis and is a major cause of hepatic morbidity. However, the pathogenesis of NAFLD in naturally aged animals is unclear. Herein, we performed a comprehensive study of lipid content and inflammatory signature of livers in 19-month-old aged female mice. These animals exhibited increased body and liver weight, hepatic triglycerides, and inflammatory gene expression compared with 3-

month-old young controls. The aged mice also had a significant increase in F4/80+ hepatic macrophages, which coexpressed CD11b, suggesting a circulating monocyte origin. A global knockout of the receptor for monocyte chemoattractant protein (CCR2) prevented excess steatosis and inflammation in aging livers but did not reduce the number of CD11b+ macrophages, suggesting changes in macrophage accumulation precede or are independent from chemokine (C-C motif) ligand-CCR2 signaling in the development of age-related NAFLD. RNA sequencing further elucidated complex changes in inflammatory and metabolic gene expression in the aging liver. In conclusion, we report a previously unknown accumulation of CD11b+ macrophages in aged livers with robust inflammatory and metabolic transcriptomic changes. A better understanding of the hallmarks of aging in the liver will be crucial in the development of preventive measures and treatments for end-stage liver disease in elderly patients.

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

Meeting Summary:
Avila MA, Dufour JF, Gerbes AL, Zoulim F, **Bataller R**, Burra P, Cortez-Pinto H, Gao B, Gilmore I, Mathurin P, Moreno C, Poznyak V, Schnabl B, Szabo G, Thiele M, Thursz MR. Recent advances in alcohol-related liver disease (ALD): summary of a Gut round table meeting. Gut. 2019 Dec 26. pii: gutjnl-2019-319720. doi: 10.1136/gutjnl-2019-319720. Review. PubMed PMID: 31879281.

ABSTRACT
Alcohol-related liver disease (ALD), which includes a range of disorders of different severity and is one of the most prevalent types of liver disease worldwide, has recently regained increased attention. Among other reasons, the realisation that any alcohol

intake, regardless of type of beverage represents a health risk, and the new therapeutic strategies tested in recently published or undergoing clinical trials spur scientific interest in this area.In April 2019, Gut convened a round table panel of experts during the European Association for the Study of the Liver International Liver Congress in Vienna to discuss critical and up-to-date issues and clinical trial data regarding ALD, its epidemiology, diagnosis, management, pathomechanisms, possible future treatments and prevention. This paper summarises the discussion and its conclusions.

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

Original Article:

Buschur KL, **Chikina M, Benos PV**. Causal network perturbations for instance-specific analysis of single cell and disease samples. Bioinformatics. 2019 Dec 24. pii: btz949. doi: 10.1093/bioinformatics/btz949. PubMed PMID: 31873725.

ABSTRACT

MOTIVATION: Complex diseases involve perturbation in multiple pathways and a major challenge in clinical genomics is characterizing pathway perturbations in individual samples. This can lead to patient-specific identification of the underlying mechanism of disease thereby improving diagnosis and personalizing treatment. Existing methods rely on external databases to quantify pathway activity scores. This ignores the data dependencies and that pathways are incomplete or condition-specific.

RESULTS: ssNPA is a new approach for subtyping samples based on deregulation of their gene networks. ssNPA learns a causal graph directly from control data. Sample-specific network neighborhood

deregulation is quantified via the error incurred in predicting the expression of each gene from its Markov blanket. We evaluate the performance of ssNPA on liver development single-cell RNAseq data, where the correct cell timing is recovered; and two TCGA datasets, where ssNPA patient clusters have significant survival differences. In all analyses ssNPA consistently outperforms alternative methods, highlighting the advantage of network-based approaches.

AVAILABILITY: **http://www.benoslab.pitt.edu/Software/ssnpa/**

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

Original Article:
Yang X, Cheng X, Tang Y, Qiu X, Wang Y, Kang H, Wu J, Wang Z, Liu Y, Chen F, Xiao X, Mackman N, **Billiar TR**, Han J, Lu B. Bacterial Endotoxin Activates the Coagulation Cascade through Gasdermin D-Dependent Phosphatidylserine Exposure. Immunity. 2019 Dec 17;51(6):983-996.e6. doi: 10.1016/j.immuni.2019.11.005. Epub 2019 Dec 10. PubMed PMID: 31836429.

ABSTRACT
Excessive activation of the coagulation system leads to life-threatening disseminated intravascular coagulation (DIC). Here, we examined the mechanisms underlying the activation of coagulation by lipopolysaccharide (LPS), the major cell-wall component of Gram-negative bacteria. We found that caspase-11, a cytosolic LPS receptor, activated the coagulation cascade. Caspase-11 enhanced the activation of tissue factor (TF), an initiator of coagulation, through triggering the formation of gasdermin D (GSDMD) pores and subsequent phosphatidylserine exposure, in a manner independent of cell death. GSDMD pores mediated calcium influx, which induced phosphatidylserine exposure through transmembrane protein 16F, a

calcium-dependent phospholipid scramblase. Deletion of Casp11, ablation of Gsdmd, or neutralization of phosphatidylserine or TF prevented LPS-induced DIC. In septic patients, plasma concentrations of interleukin (IL)-1α and IL-1β, biomarkers of GSDMD activation, correlated with phosphatidylserine exposure in peripheral leukocytes and DIC scores. Our findings mechanistically link immune recognition of LPS to coagulation, with implications for the treatment of DIC.

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

Funding Opportunities

Mechanisms of Disparities in Chronic Liver Diseases and Cancer (R21- Clinical Trial Not Allowed)

(PAR-20-081)

National Institute on Minority Health and Health Disparities

Mechanisms of Disparities in Chronic Liver Diseases and Cancer (R01- Clinical Trial Not Allowed)

(PAR-20-088)

National Institute on Minority Health and Health Disparities

Medications Development for the Treatment of Alcohol Use Disorder (AUD) or Alcohol-Related Organ Damage (AROD), or the Combination of AUD and AROD (U01 Clinical Trial Optional)

(RFA-AA-20-007)

National Institute on Alcohol Abuse and Alcoholism

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