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Liver Digest

A weekly update of PLRC happenings

January 30, 2020

PITTSBURGH LIVER RESEARCH CENTER

A partnership of University of Pittsburgh & UPMC

www.livercenter.pitt.edu

Featured Faculty - Dr. Christopher Hughes

In this issue

Liver 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"

Department of Developmental Biology Seminar

Wed, 02/05/2020

2:00 to 3:00 pm

Rangos Research Center, 3rd floor, rooms B & C

Mo Ebrahimkhani, MD
Associate Professor of Pathology

"Synthetic Developmental Biology: Build and Control Multicellular Systems"

Hosted by Dr. Donghun Shin
Light refreshments provided.

Aging Institute Seminar
Thurs., 3/12/2020
4:00-5:00 pm
S100A BST

Joseph S. Takahashi, PhD
Professor and Chair, Department of Neuroscience
Investigator, Howard Hughes Medical Institute
Lloyd B. Sands, Distinguished Chair in Neuroscience
Peter O'Donnell Jr. Brain Institute
University of Texas Southwestern Medical Center

"Circadian Clocks and the Importance of Timing in Aging and Longevity"
Although trained as a neuroscientist, Dr. Takahashi's recent work has shifted to understanding the interplay among circadian clock, metabolism and aging in the metabolic tissues including liver.

Informal reception to follow at 5:00-6:00 p.m.

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

8:15-8:30 am – Welcome and overview (Dr. Paul Monga)

8:30-8:45 am – PLRC and Center of Liver Diseases (Dr. Ramon Bataller)

8:45:9:00 am – PLRC and Pediatric GI and Hepatology (Dr. Andrew Feranchak)

9:00-9:15 am – University of Pittsburgh (Dr. Levine, Dean and Senior VC)

9:15-9:30 am – Break

9:30-9:45 am – UPMC (Dr. Shapiro, Executive Vice President, CMO, CSO, UPMC)

9:45-11:00 am – Core Presentations

- 9:45-9:55-ACTIC (Dr. Donna Stolz)
- 9:55-10:05-BRPC (Drs. David Geller and Aatur Singhi)
- 10:05-10:15-GSBC (Drs. Jianhua Luo and Takis Benos)
- 10:15-10:25-Clinical Component (Dr. Paul Monga)
- 10:25-10:35-Enrichment Program (Dr. Kari Nejak-Bowen)
- 10:35-10:45-P&F Program (Dr. Gavin Arteel)

10:45-11:00 am – Break

11:00-11:30 am – Path Forward (Dr. Paul Monga, Dr. Drew Feranchak)

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)** The currently funded P&F awardees will provide brief presentations on their projects.
10:30-10:40	Christian Fernandez, PhD • Asparaginase hepatotoxicity is lipolysis-dependent
10:40-10:50	Sungjin Ko, DVM, PhD • Elucidating the therapeutic effect of Sox9 and/or YAP inhibition in intrahepatic cholangiocarcinoma
10:50-11:00	Anita McElroy, MD, PhD • Hepatocyte tropism in RVFV pathogenesis
11:00-11:10	Zach Freyberg, MD, PhD • Dynamic GPCR & Wnt modulation of hepatic zonation
11:10-11:20	Sadeesh Ramakrishnan, DVM, PhD • Role of Zonal Dysregulation of Hypoxia Signaling
11:20-11:35	Reben Raeman, PhD & Jai Behari, MD, PhD • Role of gut-liver axis in NASH pathogenesis
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, PhD • Role of gut microbial-induced Nlrp3 inflammasome in spontaneous

	liver disease
12:10-12:20	Amir Borhani, MD, and group • Application of deep learning for non-invasive assessment of liver fibrosis in patients with NAFLD
12:20-12:30	Andres Duarte-Rojo, MD, DSc • EL-FIT: a virtual tool to promote physical activity in advanced liver disease
12:30-12:40	Hossam Abdelsamed, PhD • Epigenetic effector programs of Allo-reactive memory CD8 T cells in liver transplant patients
12:40-12:50	Vikrant Rachakonda, MD, and group • Ultrasound Radiomics in Acute Alcoholic Hepatitis
1:00-1:30	**Break**
1:30-3:00	**Grant-writing workshop** Gavin Arteel, PhD • A Guide to the Secrets of Study Sections Nick Giannoukakis, PhD • How to write successful F and K awards: Insights from an Insider
3:00-3:30	**Open discussion & Q&A**
3:30-4:00	**Wrap-up and Closing Remarks** Paul Monga, MD • PLRC's commitment to trainees and junior faculty

Post-doc Opportunity

PLRC member Dr. Samira Kiani has an opening in her lab for a post-doc. Please see the detailed announcement at the following link: **Kiani Post-Doc**.

Interested candidates should contact Dr. Samira Kiani (**samira.kiani@pitt.edu**) with their CV, cover letter, and contact information of at least 2 referees included in the email.

Faculty Highlights

PLRC members collaborating on manuscripts are noted in red.

Review Article:

Pandelakis M, Delgado E, **Ebrahimkhani MR**. "CRISPR-Based Synthetic Transcription Factors In Vivo: The Future of Therapeutic Cellular Programming. Cell Systems Volume 10, Issue 1, 22 January 2020, Pages 1-14.

ABSTRACT

Pinpoint control over endogenous gene expression in vivo has long been a fevered dream for clinicians and researchers alike. With the recent repurposing of programmable, RNA-guided DNA endonucleases from the CRISPR bacterial immune system, this dream is becoming a powerful reality. Engineered CRISPR/Cas9-based transcriptional regulators and epigenome editors have enabled researchers to perturb endogenous gene expression in vivo, allowing for the therapeutic reprogramming of cell and tissue behavior. For this technology to be of maximal use, a variety of technological hurdles still need to be addressed. Better understanding of the design principle controlling gene expression together with technologies that enable spatiotemporal control of

transcriptional engineering are fundamental for rational design, improved efficacy, and ultimately safe translation to humans. In this review, we will discuss recent advances and integrative strategies that can help pave the path toward a new class of transcriptional therapeutics.

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

Original Article:
Cheng J, Klei LR, Hubel NE, Zhang M, Schairer R, Maurer LM, Klei HB, Kang H, Concel VJ, Delekta PC, Dang EV, Mintz MA, Baens M, Cyster JG, Parameswaran N, Thome M, **Lucas PC**, McAllister-Lucas LM. GRK2 suppresses lymphomagenesis by inhibiting the MALT1 proto-oncoprotein. J Clin Invest. 2020 Jan 21. pii: 97040. doi: 10.1172/JCI97040. [Epub ahead of print] PubMed PMID: 31961340.

ABSTRACT
Antigen receptor-dependent (AgR-dependent) stimulation of the NF-κB transcription factor in lymphocytes is a required event during adaptive immune response, but dysregulated activation of this signaling pathway can lead to lymphoma. AgR stimulation promotes assembly of the CARMA1-BCL10-MALT1 complex, wherein MALT1 acts as (a) a scaffold to recruit components of the canonical NF-κB machinery, and (b) a protease to cleave and inactivate specific substrates, including negative regulators of NF-κB. In multiple lymphoma subtypes, malignant B cells hijack AgR signaling pathways to promote their own growth and survival, and inhibiting MALT1 reduces the viability and growth of these tumors. As such, MALT1 has emerged as a potential pharmaceutical target. Here, we identified G protein-coupled receptor kinase 2 (GRK2) as a new MALT1-interacting protein. We demonstrated that GRK2 binds the death domain of MALT1 and inhibits MALT1 scaffolding and proteolytic activities. We found that

lower GRK2 levels in activated B cell-type diffuse large B cell lymphoma (ABC-DLBCL) are associated with reduced survival, and that GRK2 knockdown enhances ABC-DLBCL tumor growth in vitro and in vivo. Together, our findings suggest that GRK2 can function as a tumor suppressor by inhibiting MALT1 and provide a roadmap for developing new strategies to inhibit MALT1-dependent lymphomagenesis.

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

Original Article:
Wei H, Zapata RC, Lopez-Valencia M, Aslanoglou D, Farino ZJ, Benner V, Osborn O, **Freyberg Z**, McCarthy MJ. Dopamine D(2) receptor signaling modulates pancreatic beta cell circadian rhythms. Psychoneuroendocrinology. 2019 Dec 23;113:104551. doi: 10.1016/j.psyneuen.2019.104551. PubMed PMID: 31884319.

ABSTRACT
Antipsychotic drugs (APD) have clinically important, adverse effects on metabolism that limit their therapeutic utility. Pancreatic beta cells produce dopamine and express the D2 dopamine receptor (D2R). As D2R antagonists, APDs alter glucose-stimulated insulin secretion, indicating that dopamine likely plays a role in APD-induced metabolic dysfunction. Insulin secretion from beta cells is also modulated by the circadian clock. Disturbed circadian rhythms cause metabolic disturbances similar to those observed in APD-treated subjects. Given the importance of dopamine and circadian rhythms for beta cells, we hypothesized that the beta cell dopamine system and circadian clock interact and dually regulate insulin secretion, and that circadian manipulations may alter the metabolic impact of APDs. We measured circadian rhythms, insulin release, and the impact of dopamine upon these processes in beta cells using bioluminescent reporters. We then assessed the impact of circadian timing on weight gain and metabolic

outcomes in mice treated with the APD sulpiride at the onset of light or dark. We found that molecular components of the dopamine system were rhythmically expressed in beta cells. D2R stimulation by endogenous dopamine or the agonist bromocriptine reduced circadian rhythm amplitude, and altered the temporal profile of insulin secretion. Sulpiride caused greater weight gain and hyperinsulinemia in mice when given in the dark phase compared to the light phase. D2R-acting drugs affect circadian-dopamine interactions and modulate beta cell metabolic function. These findings identify circadian timing as a novel and important mechanism underlying APD-induced metabolic dysfunction, offering new possibilities for therapeutic interventions.

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

Original Article:

Borhani AA, Dewan R, **Furlan A**, Seiser N, Zureikat AH, **Singhi AD**, Boone B, **Bahary N**, Hogg ME, Lotze M, Iii HJZ, Tublin ME. Assessment of Response to Neoadjuvant Therapy Using CT Texture Analysis in Patients With Resectable and Borderline Resectable Pancreatic Ductal Adenocarcinoma. AJR Am J Roentgenol. 2019 Dec 4:1-8. doi: 10.2214/AJR.19.21152. PubMed PMID: 31799875.

ABSTRACT

OBJECTIVE. The goal of this study was to assess the correlation between CT-derived texture features of pancreatic ductal adenocarcinoma (PDAC) and histologic and biochemical markers of response to neoadjuvant treatment as well as disease-free survival in patients with potentially resectable PDAC. SUBJECTS AND METHODS. Thirty-nine patients completed this prospective study protocol between November 2013 and December 2016. All patients received neoadjuvant chemotherapy, underwent surgical resection, and had

histologic grading of tumor response. Similar CT protocol was used for all patients. Pancreatic (late arterial) phase of pre- and posttreatment CT scans were evaluated. Histogram analysis and spatial-band-pass filtration were used to extract textural features. Correlation between textural parameters, histologic response, biochemical response, and genetic mutations was assessed using Mann-Whitney test, chi-square analysis, and multivariate logistic regression. Association with disease-free survival was assessed using Kaplan-Meier method and Cox model. RESULTS. Pretreatment mean positive pixel (MPP) at fine- and medium-level filtration, pretreatment kurtosis at medium-level filtration, changes in kurtosis, and pretreatment tumor SD were statistically different between patients with no or poor histologic response and favorable histologic response ($p < 0.05$). Changes in skewness and kurtosis at medium-level filtration significantly correlated with biochemical response ($p < 0.01$). On the basis of multivariate analysis, patients with higher MPP at pretreatment CT were more likely to have favorable histologic response (odds ratio, 1.06; 95% CI, 1.002-1.12). The Cox model for association between textural features and disease-free survival was statistically significant ($p = 0.001$). CONCLUSION. Textural features extracted from baseline pancreatic phase CT imaging of patients with potentially resectable PDAC and longitudinal changes in tumor heterogeneity can be used as biomarkers for predicting histologic response to neoadjuvant chemotherapy and disease-free survival.

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

Original Article:

Lang AL, Goldsmith WT, Schnegelberger RD, **Arteel GE, Beier JI**. Vinyl Chloride and High-Fat Diet as a Model of Environment and Obesity Interaction. J Vis Exp. 2020 Jan 12;(155):10.3791/60351. doi:

10.3791/60351. PMID: 31984951.

ABSTRACT

Vinyl chloride (VC), an abundant environmental contaminant, causes steatohepatitis at high levels, but is considered safe at lower levels. Although several studies have investigated the role of VC as a direct hepatotoxicant, the concept that VC modifies sensitivity of the liver to other factors, such as nonalcoholic fatty liver disease (NAFLD) caused by high-fat diet (HFD) is novel. This protocol describes an exposure paradigm to evaluate the effects of chronic, low-level exposure to VC. Mice are acclimated to low-fat or high-fat diet one week prior to the beginning of the inhalation exposure and remain on these diets throughout the experiment. Mice are exposed to VC (sub-OSHA level: <1 ppm) or room air in inhalation chambers for 6 hours/day, 5 days/week, for up to 12 weeks. Animals are monitored weekly for body weight gain and food consumption. This model of VC exposure causes no overt liver injury with VC inhalation alone. However, the combination of VC and HFD significantly enhances liver disease. A technical advantage of this co-exposure model is the whole-body exposure, without restraint. Moreover, the conditions more closely resemble a very common human situation of a combined exposure to VC with underlying nonalcoholic fatty liver disease and therefore support the novel hypothesis that VC is an environmental risk factor for the development of liver damage as a complication of obesity (i.e., NAFLD). This work challenges the paradigm that the current exposure limits of VC (occupational and environmental) are safe. The use of this model can shed new light and concern on the risks of VC exposure. This model of toxicant-induced liver injury can be used for other volatile organic compounds and to study other interactions that may impact the liver and other organ systems.

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

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