Liver Digest

A weekly update of PLRC happenings

May 30, 2019

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

www.livercenter.pitt.edu

Featured Faculty - Dr. Obaid Shaikh

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Upcoming Seminar

The PLRC's regular seminar series and SIG roundtables are on hiatus until the fall. We will continue to update you on liver-related seminars and events over the summer.

Starzl Transplant Institute Conference Series Internal Grand Rounds

Friday, May 31, 2019
8:00 – 9:00 a.m.
LHAS Auditorium, 7th Floor, Montefiore Hospital

Patrick J. McKiernan, MD
Director, Pediatric Hepatology Program, Children's Hospital of Pittsburgh of UPMC
Visiting Professor of Pediatrics, University of Pittsburgh

"Pediatric Liver Transplant Current Trends and Long-Term Outcomes"

Sponsored by
Thomas E. Starzl Transplantation Institute
University of Pittsburgh School of Medicine
Department of Surgery, Division of Transplantation
Center for Continuing Education in the Health Sciences

PLRC Pilot and Feasibility Award Winners Announced

The PLRC Pilot and Feasibility awards committee has completed its review of the applications for the upcoming grant cycle (2019-2020). The level of application was very high this year, and all who submitted proposals are to be commended. The following projects have been selected for funding for 2019-2020.

Congratulations to:

Individual Awards

Hossam Abdelsamed, PhD - Epigenetic effector programs of Allo-reactive memory CD8 T cells in liver transplant patients

Andres Duarte-Rojo, MD, DSc - EL-FIT: a virtual tool to promote

physical activity in advanced liver disease

Christian Fernandez, PhD - Asparaginase hepatotoxicity is lipolysis-dependent

Zachary Freyberg, MD, PhD - Dynamic GPCR & Wnt modulation of hepatic zonation

Sungjin Ko, DVM, PhD - Elucidating the therapeutic effect of Sox9 and/or YAP inhibition in intrahepatic cholangiocarcinoma

Anita McElroy, MD, PhD - Hepatocyte tropism in Rift Valley fever pathogenesis

Marlies Meisel, PhD - Role of gut microbial-induced Nlrp3 inflammasome in spontaneous liver disease

Sadeesh Ramakrishnan, PhD - Role of Zonal Dysregulation of Hypoxia Signaling in Nonalcoholic Fatty Liver Disease

Physician-Basic Scientist Team Award

Reben Raeman, PhD, and Jaideep Behari, MD, PhD - Mechanisms underlying loss of intestinal epithelial barrier function in nonalcoholic steatohepatitis

Multidisciplinary Team Awards

Amir Borhani, MD - Application of deep learning for non-invasive assessment of liver fibrosis in patients with NAFLD

Vikrant Rachakonda, MD - Novel Ultrasound Radomics Approaches to Outcome Prediction in Acute Alcoholic Hepatitis

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Faculty Highlights

Original Article:

Yovchev, M. I., Lee, E. J., Rodriguez-Silva, W. , **Locker, J. and Oertel, M.** (2019), Biliary Obstruction Promotes Multilineage Differentiation of Hepatic Stem Cells. Hepatol Commun. doi:10.1002/hep4.1367.

ABSTRACT

Because of their high regenerative potential, stem cells are an ideal resource for development of therapies that replace injured tissue mass and restore function in patients with end-stage liver diseases. Using a rat model of bile duct ligation (BDL) and biliary fibrosis, we investigated cell engraftment, liver repopulation, and ectopic tissue formation after intrasplenic transplantation of epithelial stem/progenitor cells. Fetal liver cells were infused into the spleens of Fisher 344 rats with progressing biliary fibrosis induced by common BDL or rats without BDL. Cell delivery was well tolerated. After migration to the liver, donor-derived stem/progenitor cells engrafted, differentiated into hepatocytes and cholangiocytes, and formed large cell clusters at 2 months in BDL rats but not controls. Substantial numbers of donor cells were also detected at the splenic injection site where they generated hepatic and nonhepatic tissue. Transplanted cells differentiated into phenotypes other than hepato/cholangiocytic cells only in rats that underwent BDL. Quantitative reverse-transcription polymerase chain reaction analyses demonstrated marked up-regulation of tissue-specific genes of nonhepatic endodermal lineages (e.g., caudal type homeobox 2 [Cdx2], pancreatic and duodenal homeobox 1 [Pdx1], keratin 13 [CK-13]), confirmed by immunohistochemistry. Conclusion: BDL and its induced fibrosis promote liver repopulation by ectopically transplanted fetal liver-derived cells. These cell fractions contain multipotent stem cells that colonize the spleen of BDL rats and differentiate into multiple gastrointestinal tissues, including liver, pancreas, intestine, and esophagus. The splenic microenvironment, therefore, represents an ideal niche to assess the differentiation of these stem cells, while BDL provides a stimulus that induces their differentiation.

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

Review Article:

Banrida Wahlang, Jian Jin, **Juliane I. Beier**, Josiah E. Hardesty, Erica F. Daly, Regina D. Schnegelberger, K. Cameron Falkner, Russell A. Prough, Irina A Kirpich, Matthew C. Cave. Mechanisms of Environmental Contributions to Fatty Liver Disease. Curr Envir Health Rpt

(2019). https://doi.org/10.1007/s40572-019-00232-w.

ABSTRACT
PURPOSE: Fatty liver disease (FLD) affects over 25% of the global population and may lead to liver-related mortality due to cirrhosis and liver cancer. FLD caused by occupational and environmental chemical exposures is termed "toxicant-associated steatohepatitis" (TASH). The current review addresses the scientific progress made in the mechanistic understanding of TASH since its initial description in 2010.

RECENT FINDINGS: Recently discovered modes of actions for volatile organic compounds and persistent organic pollutants include the following: (i) the endocrine-, metabolism-, and signaling-disrupting chemical hypotheses; (ii) chemical-nutrient interactions and the "two-hit" hypothesis. These key hypotheses were then reviewed in the context of the steatosis adverse outcome pathway (AOP) proposed by the US Environmental Protection Agency. The conceptual understanding of the contribution of environmental exposures to FLD has progressed significantly. However, because this is a new research area, more studies including mechanistic human data are required to address current knowledge gaps.

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

Funding Opportunity

Methods to Improve Reproducibility of Human iPSC Derivation, Growth and Differentiation (SBIR) (R44 Clinical Trial Not Allowed)

(RFA-GM-19-001)
National Institute of General Medical Sciences
National Center for Advancing Translational Sciences
National Cancer Institute
National Heart, Lung, and Blood Institute
National Institute on Alcohol Abuse and Alcoholism
National Institute of Allergy and Infectious Diseases
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute of Biomedical Imaging and Bioengineering

National Institute on Drug Abuse
National Institute of Dental and Craniofacial Research
National Institute of Diabetes and Digestive and Kidney Diseases
National Institute of Environmental Health Sciences

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