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Liver Digest

A weekly update of PLRC happenings

May 9, 2019

PITTSBURGH LIVER RESEARCH CENTER

A partnership of University of Pittsburgh & UPMC

www.livercenter.pitt.edu

Featured Faculty - Dr. Courtney Sparacino-Watkins

In this issue

Next Week's Seminar

Liver Seminar

Wednesday, May 15, 2019

12:00 -1:00 p.m.

1104 Scaife Hall

Rajanikanth Vadigepalli, PhD

Professor and Vice Chair of Research
Department of Pathology, Anatomy and Cell Biology
Jefferson University

"Seeing, Sampling, Simulating: A Convergent Approach to Study Tissue Injury and Regeneration"

This activity has been approved for AMA PRA Category 1 Credit(s)™
Pizza will be provided.

PLRC Conversation on HCC:
Local Opportunities for Translation and Innovation

June 18, 2019
4:00-8:00 p.m.
LHAS Auditorium, 7th floor Montefiore
Dinner and drinks will be served
RSVP to Ann Vinski (vinskiam@upmc.edu) by June 4

Because we will be ordering catering for this event, we need all RSVPs no later than June 4, 2019. Thank you!

Session 1: Surveillance and Diagnosis

- Surveillance of HCC: Role of Hepatologist – Andres Duarte-Rojo
- Role of Imaging in HCC Diagnosis – Amir Borhani
- Role of Pathologist in HCC Diagnosis and Classification – Michael Nalesnik

Session 2: Current State of Therapies

- Non-transplant Surgical Management of HCC – David Geller
- Liver transplantation for HCC – Abhi Humar
- Medical Management of HCC – Nathan Bahary
- Role of Interventional Radiologist in HCC Management – Paula Novelli

Session 3: Fundamental Research in HCC

- Lymphocyte specific protein-1 as a biomarker for HCC – George Michalopoulos

- Beta-catenin mutations and precision medicine in HCC – Paul Monga
- Therapies for HCC based on novel fusion genes in HCC – Jianhua Luo

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Faculty Highlights

Original Article:

Chang CH, Bryce CL, Shneider BL, Yabes JG, Ren Y, Zenarosa GL, Tomko H, Donnell DM, **Squires RH**, Roberts MS. Accuracy of the Pediatric End-stage Liver Disease Score in Estimating Pretransplant Mortality Among Pediatric Liver Transplant Candidates. JAMA Pediatr. 2018 Nov 1;172(11):1070-1077. doi: 10.1001/jamapediatrics.2018.2541. PubMed PMID: 30242345; PubMed Central PMCID: PMC6248160.

ABSTRACT

IMPORTANCE: Fair allocation of livers between pediatric and adult recipients is critically dependent on the accuracy of mortality estimates afforded by the Pediatric End-stage Liver Disease (PELD) and Model for End-stage Liver Disease, respectively. Widespread reliance on exceptions for pediatric recipients suggests that the 2 systems may not be comparable.

OBJECTIVE: To evaluate the accuracy of the PELD score in estimating 90-day pretransplant mortality among pediatric patients on the United Network for Organ Sharing (UNOS) waiting list.

DESIGN, SETTING, AND PARTICIPANTS: Patients who were listed from February 27, 2002, to March 31, 2014, for primary liver transplant were included in this retrospective analysis and were followed up for at least 2 years through June 17, 2016. The study analyzed 2 cohorts

using the UNOS Standard Transplant Analysis and Research data files. The full cohort comprised 4298 patients (<18 years of age) who had chronic liver disease (excluding cancer). The reduced cohort (n=2421) excluded patients receiving living donor transplantation or PELD exception points.

MAIN OUTCOMES AND MEASURES: Observed and expected 90-day pretransplant mortality rates evaluated at 10-point interval PELD levels.

RESULTS: Among the 4298 patients in the full cohort (mean [SD] age, 2.5 [4.2] years; 2251 [52.4%] female; 2201 [51.2%] white), PELD scores and mortality were concordant (C statistic, 0.8387 [95% CI, 0.8191-0.8584] for the full cohort and 0.8123 [95% CI, 0.7919-0.8327] for the reduced cohort). However, the estimated 90-day mortality using the PELD score underestimated the actual probability of death by as much as 17%.

CONCLUSIONS AND RELEVANCE: With use of the PELD score, the ranking of risk among children was preserved, but direct comparisons between adult and pediatric candidates were not accurate. Children with chronic liver disease who are in need of transplant may be at a disadvantage compared with adults in a similar situation.

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

Original Article:

Li Y, Pu S, Liu Q, Li R, Zhang J, Wu T, Chen L, Li H, Yang X, Zou M, Xiao J, **Xie W***, He J*. An integrin-based nanoparticle that targets activated hepatic stellate cells and alleviates liver fibrosis. J Control Release. 2019 Apr 17. [Epub ahead of print] PMID: 31004666 (*, co-corresponding authors)

ABSTRACT

Activation of hepatic stellate cells (HSCs) contributes to the development of liver fibrosis. Because of a relatively small population of HSCs in the liver and the lack of specific membrane targeting proteins, HSC-targeted therapy remains a major clinical challenge. Here we first showed that a hallmark of activated HSC (aHSC) is their increased expression of integrin αvβ3. Thus we established sterically stable liposomes that contain the cyclic peptides (cRGDyK) with a high affinity to αvβ3 to achieve aHSC-specific delivery. Our results showed that the cRGDyK-guided liposomes were preferentially internalized by activated HSCs in vitro and in vivo, and the internalization was abolished by excess free cRGDyK or knockdown of αvβ3. In contrast, quiescent HSCs, hepatocytes, Kupffer cells, sinusoidal endothelial cells, or biliary cells showed minimal uptake of the cRGDyK-guided liposomes. When loaded with the hedgehog inhibitor vismodegib, the cRGDyK-guided liposomes inhibited hedgehog pathway signaling specifically in activated HSCs. Moreover, treatment of mice with vismodegib-loaded cRGDyK-liposomes markedly inhibited the fibrogenic phenotype in bile duct ligation- or thioacetamide-treated mice. We conclude that the cRGDyK-guided liposomes can specifically target the activated HSCs, but not quiescent HSCs. This nanoparticle system showed great promise to deliver therapeutic agents to aHSC to treat liver fibrosis.

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

Original Article:

Xie Y, Xu M, Deng M , Li Z, Wang P, Ren S, Guo Y, **Ma X**, Fan J, **Billiar TR**, **Xie W**. Activation of pregnane X receptor sensitizes mice to hemorrhagic shock induced liver injury. Hepatology 2019 Apr 30. [Epub ahead of print] PMID: 31038762.

ABSTRACT

Hemorrhagic shock (HS) is a life-threatening condition associated with tissue hypoperfusion, and often leads to injury of multiple organs including the liver. Pregnane X receptor (PXR) is a species-specific xenobiotic receptor that regulates the expression of drug-metabolizing enzymes (DMEs) such as the cytochrome P450 3A (CYP3A). Many clinical drugs, including those often prescribed to trauma patients, are known to activate PXR and induce CYP3A. The goal of this study is to determine whether PXR plays a role in the regulation of DMEs in the setting of HS, and whether activation of PXR is beneficial or detrimental to HS-induced hepatic injury. PXR transgenic, knockout, and humanized mice were subject to HS, and the liver injury was assessed histologically and biochemically. The expression and/or activity of PXR and CYP3A were manipulated genetically or pharmacologically in order to determine their effects on HS-induced liver injury. Our results showed that genetic or pharmacological activation of PXR sensitized wild-type and hPXR/CYP3A4 humanized mice to HS-induced hepatic injury, whereas knockout of PXR protected mice from HS-induced liver injury. Mechanistically, the sensitizing effect of PXR activation was accounted for by PXR-responsive induction of CYP3A and increased oxidative stress in the liver. The sensitizing effect of PXR was attenuated by ablation or pharmacological inhibition of CYP3A, treatment with the antioxidant N-acetylcysteine amide (NACA), or treatment with a PXR antagonist. CONCLUSIONS: We have uncovered a novel function of PXR in HS-induced hepatic injury. Our results suggest that the unavoidable use of PXR-activating drugs in trauma patients has the potential to exacerbate HS-induced hepatic injury, which can be mitigated by the co-administration of anti-oxidative agents, CYP3A inhibitors, or PXR antagonists.

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

Original Article:

Seminotti B, Leipnitz G, Karunanidhi A, Kochersperger C, Roginskaya VY, Basu S, Wang Y, Wipf P, Van Houten B, Mohsen AW, **Vockley J.**Mitochondrial energetics is impaired in very long-chain acyl-CoA dehydrogenase deficiency and can be rescued by treatment with mitochondria-targeted electron scavengers. Hum Mol Genet. 2018 Nov 16. doi: 10.1093/hmg/ddy403. [Epub ahead of print] PubMed PMID: 30445591.

ABSTRACT

Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency is the most common defect of mitochondrial long-chain fatty acid β-oxidation (FAO). Patients present with heterogeneous clinical phenotypes affecting heart, liver, and skeletal muscle predominantly. The full pathophysiology of the disease is unclear and patient response to current therapeutic regimens is incomplete. To identify additional cellular alterations and explore more effective therapies, mitochondrial bioenergetics and redox homeostasis were assessed in VLCAD deficient fibroblasts, and several protective compounds were evaluated. The results revealed cellular and tissue changes, including decreased respiratory chain function, increased reactive oxygen species (ROS) production, and altered mitochondrial function and signaling pathways in a variety of VLCAD deficient fibroblasts. The mitochondrially enriched electron and free radical scavengers JP4-039 and XJB-5-131 improved respiratory chain function and decreased ROS production significantly, suggesting that they are viable candidate compounds to further develop to treat VLCAD deficient patients.

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

Book Chapter:

Ko S., **Shin D.** (2019) Chemical Screening Using a Zebrafish Model for

Liver Progenitor Cell-Driven Liver Regeneration. In: Tanimizu N. (eds) Hepatic Stem Cells. Methods in Molecular Biology, vol 1905. Humana Press, New York, NY.

ABSTRACT
Following massive hepatocyte ablation in zebrafish, biliary epithelial cells can extensively give rise to hepatocytes through liver progenitor cells (LPCs). The zebrafish liver injury model is an important system to elucidate the molecular mechanisms underlying LPC-driven liver regeneration. Here, we describe a chemical screening method using the zebrafish model for identifying small molecules that can modulate LPC-driven liver regeneration.

For full text of this chapter, please **click here**.

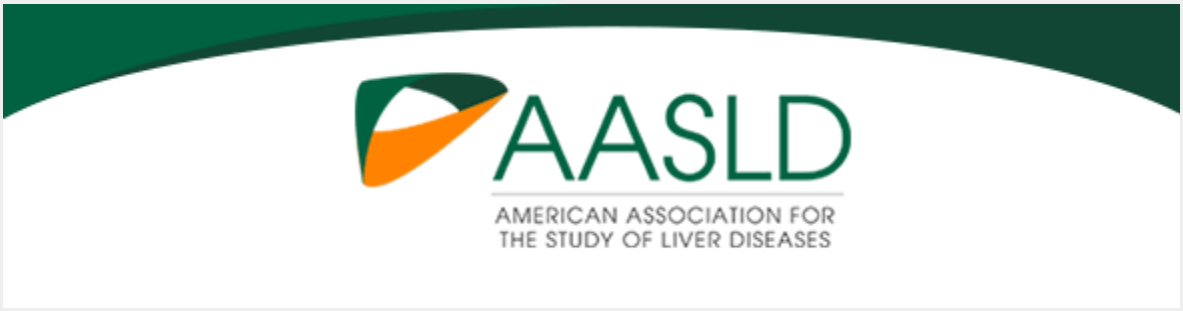
Funding Opportunity

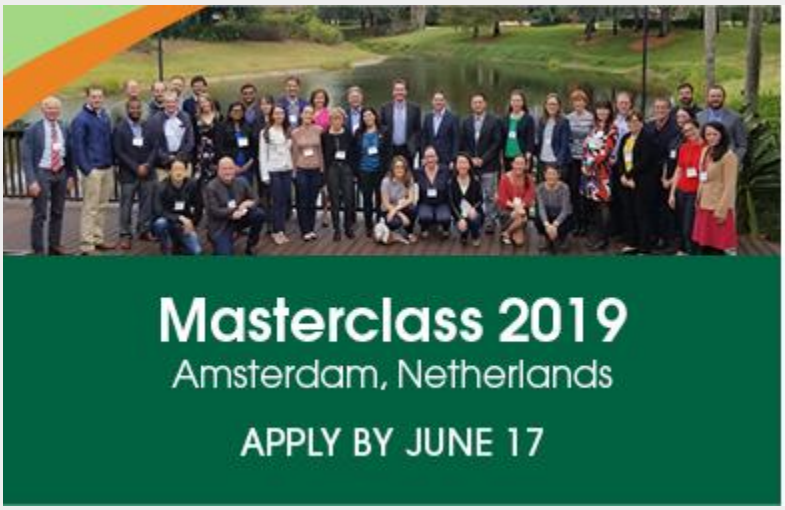
Imaging, Biomarkers and Digital Pathomics for the Early Detection of Premetastatic Aggressive Cancer (R01 Clinical Trial Optional)

(PAR-19-264)

National Cancer Institute

AASLD Master Class





The **2019 AASLD/EASL Masterclass**, a two-day intensive training session in Amsterdam, is an excellent opportunity for early-career investigators (MD, PhD or equivalent) to network with world leaders in hepatology.

AASLD will provide complimentary registration, travel and accommodation expenses for up to 10 candidates to attend. **View the eligibility requirements** and apply or encourage a young investigator to apply. Applications are due to AASLD on Monday, June 17 by 11:59 PM ET.

APPLY NOW

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