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Liver Digest

A weekly update of PLRC happenings

August 15, 2019

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

www.livercenter.pitt.edu

Featured Faculty - Dr. Michael Nalesnik

In this issue

Acknowledging PLRC P30 Grant

Please remember to acknowledge the PLRC P30 grant support in your own work, as appropriate. Suggested text: "This research was supported by the [ ] shared resource of the NIH/NIDDK P30DK120531."

The NIH Policy for Communicating and Acknowledging Federal Funding is available here: **https://grants.nih.gov/grants/acknow.htm**

PLRC Meet & Greet - September 12

Please save the date for the **PLRC's Meet and Greet!**
September 12, 2019
4:30-7:30 p.m.
Ballroom A - University Club
123 University Place
Pittsburgh, PA 15260

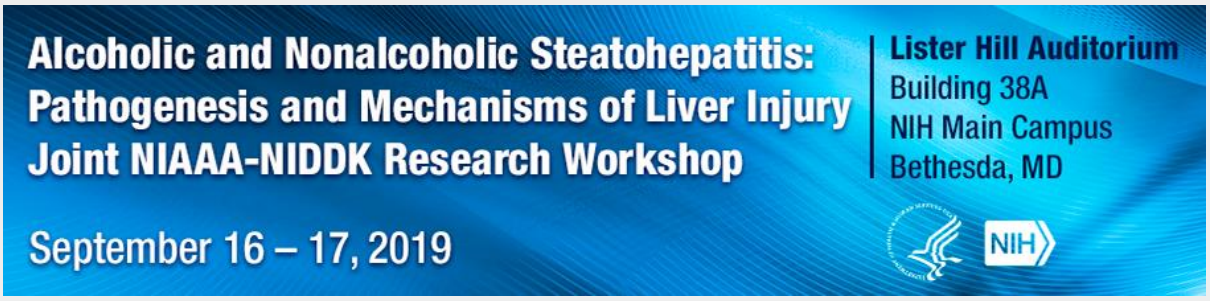
Invitations containing program details and requesting RSVPs will be forthcoming.

Upcoming Liver Meetings

Alcoholic and Nonalcoholic Steatohepatitis: Pathogenesis and Mechanisms of Liver Injury Joint NIAAA-NIDDK Research Workshop

September 16-17, 2019
NIH Main Campus
Bathesda, Maryland

Workshop program and registration are **available here**.



AASLD Emerging Topic Conference: The Genomics Revolution

September 20-21, 2019

Westin Crystal City

Arlington, Virginia

Information and registration are **available here**.

EMERGING TOPIC CONFERENCE

The Genomics Revolution

September 20–21 | Arlington, VA

AASLD The Liver Meeting® 2019

November 8-12, 2019

Boston, Massachusetts

The official site of The Liver Meeting® 2019 is **available here.**

Mayo Clinic Hepato-Pancreatico-Biliary Cancer Symposium

November 15-16, 2019

Wynn Las Vegas

Las Vegas, Nevada

Course brochure is **available here**.

Faculty Highlights

PLRC members collaborating on manuscripts are noted in red.

Original Article:

Zhang Y, Mohsen AW, Kochersperger C, Solo K, Schmidt AV, **Vockley J, Goetzman ES**. An acyl-CoA dehydrogenase microplate activity assay using recombinant porcine electron transfer flavoprotein. Anal Biochem. 2019 Jun 10;581:113332. doi: 10.1016/j.ab.2019.06.003. [Epub ahead of print] PubMed PMID: 31194945.

ABSTRACT

Acyl-CoA dehydrogenases (ACADs) play key roles in the mitochondrial catabolism of fatty acids and branched-chain amino acids. All nine characterized ACAD enzymes use electron transfer flavoprotein (ETF) as their redox partner. The gold standard for measuring ACAD activity is the anaerobic ETF fluorescence reduction assay, which follows the decrease of pig ETF fluorescence as it accepts electrons from an ACAD in vitro. Although first described 35 years ago, the assay has not been widely used due to the need to maintain an anaerobic assay environment and to purify ETF from pig liver mitochondria. Here, we present a method for

expressing recombinant pig ETF in E coli and purifying it to homogeneity. The recombinant protein is virtually pure after one chromatography step, bears higher intrinsic fluorescence than the native enzyme, and provides enhanced activity in the ETF fluorescence reduction assay. Finally, we present a simplified protocol for removing molecular oxygen that allows adaption of the assay to a 96-well plate format. The availability of recombinant pig ETF and the microplate version of the ACAD activity assay will allow wide application of the assay for both basic research and clinical diagnostics.

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

Original Article:

Zhang Q, Li X, Cui K, Liu C, Wu M, **Prochownik EV**, Li Y. The MAP3K13-TRIM25-FBXW7α axis affects c-Myc protein stability and tumor development. Cell Death Differ. 2019 Jun 11. doi: 10.1038/s41418-019-0363-0. [Epub ahead of print] PubMed PMID: 31186535.

ABSTRACT

c-Myc (Myc) is a master transcription factor that is often deregulated and highly expressed by at least 50% of cancers. In many cases, Myc protein levels correlate with resistance to therapy and poor prognosis. However, effective direct inhibition of Myc by pharmacologic approaches has remained unachievable. Here, we identify MAP3K13 as a positive regulator of Myc to promote tumor development. Our findings show that MAP3K13 upregulation is predictive of poor outcomes in patients with hepatocellular carcinoma (HCC). Mechanistically, MAP3K13 phosphorylates the E3 ubiquitin ligase TRIM25 at Ser12 to decrease its polyubiquitination and proteasomal degradation. This newly stabilized TRIM25 then directly ubiquitinates Lys412 of FBXW7α, a core subunit of the SKP1-Cullin-F-box (SCF) ubiquitin ligase complex involved in Myc ubiquitination, thereby stabilizing Myc. Together, these results reveal a novel regulatory pathway that supervises Myc protein stability via the MAP3K13-TRIM25-FBXW7α signaling axis. In addition, they provide a potential therapeutic target in Myc over-expressing human cancers.

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

Book Chapter:

Taylor DL, Gough A, Schurdak ME, **Vernetti L**, Chennubhotla CS, Lefever D, Pei F, Faeder JR, Lezon TR, Stern AM, **Bahar I**. Harnessing Human Microphysiology Systems

as Key Experimental Models for Quantitative Systems Pharmacology. Handb Exp Pharmacol. 2019 Jun 15. doi: 10.1007/164_2019_239. PubMed PMID: 31201557.

ABSTRACT
Two technologies that have emerged in the last decade offer a new paradigm for modern pharmacology, as well as drug discovery and development. Quantitative systems pharmacology (QSP) is a complementary approach to traditional, target-centric pharmacology and drug discovery and is based on an iterative application of computational and systems biology methods with multiscale experimental methods, both of which include models of ADME-Tox and disease. QSP has emerged as a new approach due to the low efficiency of success in developing therapeutics based on the existing target-centric paradigm. Likewise, human microphysiology systems (MPS) are experimental models complementary to existing animal models and are based on the use of human primary cells, adult stem cells, and/or induced pluripotent stem cells (iPSCs) to mimic human tissues and organ functions/structures involved in disease and ADME-Tox. Human MPS experimental models have been developed to address the relatively low concordance of human disease and ADME-Tox with engineered, experimental animal models of disease. The integration of the QSP paradigm with the use of human MPS has the potential to enhance the process of drug discovery and development.

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

Meeting Report:

Squires JE, Logan B, Lorts A, Haskell H, Sisaithong K, Pillari T, Szolna J, Dodd D, Gonzalez-Peralta RP, Hsu E, Kelly B, Kosmach-Park B, Lobritto S, Ng VL, Perito E, Rasmussen S, Romero R, Shemesh E, Karolak H, **Mazariegos GV.** A learning health network for pediatric liver transplantation: Inaugural meeting report from the Starzl Network for Excellence in Pediatric Transplantation. Pediatr Transplant. 2019 Jul 22:e13528. doi: 10.1111/petr.13528. PubMed PMID: 31328841.

ABSTRACT
Learning Health Networks (LHN) improve the well-being of populations by aligning clinical care specialists, technology experts, patients and patient advocates, and other thought leaders for continuous improvement and seamless care delivery. A novel LHN focused on pediatric transplantation, the Starzl Network for Excellence in Pediatric Transplantation (SNEPT), convened its inaugural meeting in September 2018. Clinical care team representatives, patients, and patient families/advocates partnered to take part in educational sessions, pain point

exercises, and project identification workshops. Participants discussed the global impact of transplant from both a population and individual perspective, identifying challenges and opportunities where the Starzl Network could work to improve outcomes at scale across a variety of transplant-related conditions.

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

Original Article:

Humar A, Ganesh S, Jorgensen D, Tevar A, Ganoza A, Molinari M, **Hughes C**. Adult Living Donor Versus Deceased Donor Liver Transplant (LDLT Versus DDLT) at a Single Center: Time to Change Our Paradigm for Liver Transplant. Ann Surg. 2019 Jul 10. doi: 10.1097/SLA.0000000000003463. PubMed PMID: 31305283.

ABSTRACT

OBJECTIVE: The aim of this study was to compare outcomes between living donor liver transplant (LDLT) and deceased donor liver transplant (DDLT) at a single center to demonstrate the advantages of LDLT and provide justification for the increased utilization and application of this procedure.

SUMMARY OF BACKGROUND DATA: LDLT comprises a very small percentage of all liver transplants performed in the United States, this despite its advantages and a shortage of the availability of deceased donor organs.

METHODS: A retrospective review of all adult LDLT (n = 245) and DDLT (n = 592) performed at a single center over 10 years (2009-2019), comparing survival outcomes by Kaplan-Meier analysis and comparing other measures of outcome such as recovery times, complications, costs, and resource utilization.

RESULTS: Patient survival outcomes were superior in LDLT recipients (3-year 86% vs 80%, P = 0.03). Other outcomes demonstrated shorter length of hospital stay (11 vs 13 days, P = 0.03), less likelihood of intraoperative blood transfusion (52% vs 78%, P < 0.01), and less likelihood of need for posttransplant dialysis (1.6% vs 7.4%, P < 0.01). Early reoperation and biliary/vascular complication rates were similar. Hospital costs related to the transplant were 29.5% lower for LDLT. Complications in living donors were acceptable with no early or late deaths, 3-month reoperation rate of 3.1%, and overall complication rate of 19.5%. Given its advantages, we have expanded LDLT-in 2018, LDLT comprised 53.6% of our transplants (national average 4.8%), and our transplant rate increased from 44.8 (rate per 100-person years) in 2015 to 87.5 in 2018.

CONCLUSIONS: LDLT offers advantages over DDLT including superior outcomes and less resource utilization. The time has come to change the paradigm of how LDLT is utilized in this country.

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

Funding Opportunities

SBIR/STTR Commercialization Readiness Pilot (CRP) Program Technical Assistance and Late Stage Development (SB1, R44) Clinical Trial Not Allowed

(PAR-19-333)
National Institute on Aging
National Eye 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 on Deafness and Other Communication Disorders
National Institute of Dental and Craniofacial Research
National Institute of Diabetes and Digestive and Kidney Diseases
National Institute of General Medical Sciences
National Institute of Mental Health
National Institute of Neurological Disorders and Stroke

SBIR/STTR Commercialization Readiness Pilot (CRP) Program Technical Assistance (SB1, R44) Clinical Trial Not Allowed

(PAR-19-334)
National Institute on Aging
National Center for Advancing Translational Sciences
National Cancer Institute
National Eye Institute
National Human Genome Research Institute
National Heart, Lung, and Blood Institute
National Institute on Aging
National Institute on Alcohol Abuse and Alcoholism
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute of Biomedical Imaging and Bioengineering
National Institute on Deafness and Other Communication Disorders
National Institute of Dental and Craniofacial Research

National Institute of Diabetes and Digestive and Kidney Diseases
National Institute of Environmental Health Sciences
National Institute of General Medical Sciences
National Institute of Mental Health
National Institute of Neurological Disorders and Stroke

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