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Liver Digest

A weekly update of PLRC happenings

May 16, 2019



www.livercenter.pitt.edu

Featured Faculty - Dr. Courtney Sparacino-Watkins

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Upcoming Seminars

Starzl Transplant Institute Conference Series Internal Grand Rounds

Friday, May 17, 2019

8:00 - 9:00 a.m.

LHAS Auditorium, 7th Floor, Montefiore Hospital

James E. Squires, MD, MS

Assistant Professor of Pediatrics

Director, Transplant Hepatology Fellowship

"Liver Transplant for Pediatric Metabolic Disorders: A Clinician's Perspective"

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 & Feasibility Semifinalist Presentations

Monday, May 20, 2019

10:00-12:00

Eye & Ear Institute 5th Floor Boardroom

All members of the PLRC are invited to come and support the P&F semifinalists as they present their proposals. You are welcome to attend some or all of the presentations. The schedule is as follows:

Time	Name	Proposal title
10:00 – 10:15	McElroy, Anita	Hepatocyte tropism in RVFV pathogenesis
10:15 – 10:20	Abdelsamed, Hossam	Epigenetics of memory T cells in liver transplants
10:20 – 10:25	Fernandez, Christian	Asparaginase hepatotoxicity is lipolysis-dependent
10:25 – 10:30	Freyberg, Zachary	Dynamic GPCR & Wnt modulation of hepatic zonation
10:30 – 10:45	Ramakrishnan, Sadeesh	Role of Zonal Dysregulation of Hypoxia Signaling
10:45 – 11:00	Ko, Sungjin	Elucidating the therapeutic effect of Sox9 and/or
11:00 – 11:15	Meisel, Marlies	Microbiota and Nlrp3 inflammasome in liver disease
11:15 – 11:25	Raeman, Reben & Behari, Jaideep	Role of gut-liver axis in NASH pathogenesis
11:25	<i>Pizza lunch arrives</i>	
11:30 – 11:45	Borhani, Amir et al.	Application of deep learning for non-invasive assessment of
11:45 – 12:00	Rachakonda, Vikrant et al.	Ultrasound Radiomics in Acute Alcoholic Hepatitis

Faculty Highlights

PLRC Members presenting at American Transplant Congress

Please see the attached documents for a complete listing of the basic science and clinical abstract and lecture presentations for the ATC this June in Boston. Thanks to Casey Zell and Joy Merusi for making these tables available to the PLRC.

Original Article highlighted in Commentary:

Dr. Wolfram Goessling has published a commentary on the manuscript from Dr. Monga's team in Cell Metabolism: Goessling, Wolfram. "Position is Destiny: Metabolism and Cell Identity." Cell Metabolism. Volume 29, Issue 5, 7 May 2019,

Pages 1017-1019.

ABSTRACT

CTNNB1, encoding β -catenin, is frequently mutated in hepatocellular carcinoma, the most rapidly growing solid cancer in the US, and activating mutations in this gene are associated with increased expression of glutamine synthetase. A new report by Adebayo Michael et al. (2019) identifies mTOR as a direct target of WNT/ β -catenin signaling through increased production of glutamine, which is required for the carcinogenic effects of WNT/ β -catenin activity in the liver.

For full text of the commentary, please [click here](#).

To access the original article by Dr. Monga's team, please [click here](#).

Original Article:

Bhushan B, Banerjee S, Paranjpe S, Koral K, **Mars WM**, Stoops JW, Orr A, Bowen WC, **Locker J**, **Michalopoulos GK**. Pharmacologic Inhibition of Epidermal Growth Factor Receptor Suppresses Non-alcoholic Fatty Liver Disease in Murine Fast-food Diet Model. *Hepatology*. 2019 May 7. doi: 10.1002/hep.30696. [Epub ahead of print]

ABSTRACT

EGFR is a critical regulator of hepatocyte proliferation and liver regeneration. Our recent work indicated EGFR can also regulate lipid metabolism during liver regeneration after partial-hepatectomy. Based on these findings, we investigated role of EGFR in a mouse model of NAFLD utilizing a pharmacological inhibition strategy. C57BL6/J mice were fed chow-diet, or fast-food diet with/without EGFR inhibitor (Canertinib) for 2-months. EGFR inhibition completely prevented development of steatosis and liver injury in this model. In order to study if EGFR inhibition can reverse NAFLD progression, mice were fed fast-food diet for 5-months, with/without Canertinib-treatment for the last 5-weeks of the study. EGFR-inhibition remarkably decreased steatosis, liver injury, fibrosis and improved glucose tolerance. Microarray analysis revealed ~40% of genes altered by fast-food diet were differentially expressed after EGFR-inhibition, and thus, are potentially regulated by EGFR. Several genes and enzymes related to lipid metabolism (particularly fatty-acid synthesis and lipolysis), which were disrupted by fast-food diet, were found to be modulated by EGFR. Several crucial transcription factors that play a central role in regulating these lipid metabolism genes during NAFLD, including PPAR γ , SREBF1, ChREBP and HNF4 α , were also found to be modulated by EGFR. In fact, ChIP-analysis revealed PPAR γ binding to several crucial lipid metabolisms genes (Fasn, Scd1 and Plin2) was drastically

reduced by EGFR inhibition. Further upstream, EGFR-inhibition suppressed AKT signaling, which is known to control these transcription factors, including PPAR γ and SREBF1, in NAFLD models. Lastly, the effect of EGFR in FFD-induced fatty-liver phenotype was not shared by receptor-tyrosine-kinase MET, as investigated using MET-KO mice. In-conclusion, our study revealed a role of EGFR in NAFLD and the potential of EGFR-inhibition as a treatment strategy for NAFLD.

For full text, please [click here](#).

Original Article:

López-Pelayo H, Miquel L, Altamirano J, **Bataller R**, Caballeria J, Ortega L, Lligoña A, Gual A. Treatment retention in a specialized alcohol programme after an episode of alcoholic hepatitis: Impact on alcohol relapse. *J Psychosom Res.* 2019 Jan;116:75-82. doi: 10.1016/j.jpsychores.2018.11.020. Epub 2018 Nov 28. PubMed PMID: 30654998.

ABSTRACT

AIMS: Alcoholic hepatitis (AH) is a life-threatening complication of alcohol use disorder (AUD). Alcohol abstinence is the main predictor of the long-term prognosis of AH. It is unknown whether AUD treatment retention (TR) after an AH episode impacts alcohol relapse and mortality or what baseline factors influence TR.

METHODS: Design: case-control study; Study population: hospitalized patients (1999-2012) with an episode of biopsy-proven AH were included (n=120); Assessment: demographic and clinical data, the High-Risk Alcoholism Relapse (HRAR) scale, mortality and alcohol relapse were assessed through clinical records and telephone or personal interviews; Follow-up period: short-term and long-term TRs were assessed at 12 and 24 months, respectively.

RESULTS: The overall short-term and long-term TRs were 37% and 27.8%, respectively. The severity of liver disease at baseline predicted both short-term and long-term TR (OR 3.7 and 3.3, respectively), whereas HRAR >3 and a history of psychiatric disorders predicted long-term TR (OR 2.9 and 2.6, respectively). Moreover, HRAR >3 (OR 3.0) and previous treatment for AUD (OR 2.9) increased the risk of relapse in the short term. Importantly, receiving alcohol therapy in a centre different from the hospital where the patient was admitted was associated with increased risk of alcohol relapse over the long term (OR 5.4).

CONCLUSION: Experiencing an alcohol-related life-threatening complication is insufficient motivation to seek treatment for AUD. AUD treatment after an episode of AH is suboptimal, with a low TR rate, high risk of alcohol relapse and poor impact of treatment on alcohol relapse.

For full text, please [click here](#).

Original Article:

Tohme S, Yazdani HO, Sud V, Loughran P, Huang H, **Zamora R**, Simmons RL, **Vodovotz Y**, Tsung A. Computational Analysis Supports IL-17A as a Central Driver of Neutrophil Extracellular Trap-Mediated Injury in Liver Ischemia Reperfusion. *J Immunol*. 2019 Jan 1;202(1):268-277. doi: 10.4049/jimmunol.1800454. Epub 2018 Nov 30. PubMed PMID: 30504418; PubMed Central PMCID: PMC6310076.

ABSTRACT

Hepatic ischemia reperfusion (I/R) is a clinically relevant model of acute sterile inflammation leading to a reverberating, self-sustaining inflammatory response with resultant necrosis. We hypothesized that computerized dynamic network analysis (DyNA) of 20 inflammatory mediators could help dissect the sequence of post-I/R mediator interactions that induce injury. Although the majority of measured inflammatory mediators become elevated in the first 24 h, we predicted that only a few would be secreted early in the process and serve as organizational centers of downstream intermediator complexity. In support of this hypothesis, DyNA inferred a central organizing role for IL-17A during the first 3 h of reperfusion. After that, DyNA revealed connections among almost all the inflammatory mediators, representing an ongoing cytokine storm. Blocking IL-17A immediately after reperfusion disassembled the inflammatory networks and protected the liver from injury. Disassembly of the networks was not achieved if IL-17A blockage was delayed two or more hours postreperfusion. Network disassembly was accompanied by decrease in neutrophil infiltration and neutrophil extracellular trap (NET) formation. By contrast, administration of recombinant IL-17A increased neutrophil infiltration, NET formation, and liver necrosis. The administration of DNase, a NET inhibitor, significantly reduced hepatic damage despite prior administration of IL-17A, and DNase also disassembled the inflammatory networks. In vitro, IL-17A was a potent promoter of NET formation. Therefore, computational analysis identified IL-17A's early, central organizing role in the rapid evolution of a network of inflammatory mediators that induce

neutrophil infiltration and NET formation responsible for hepatic damage after liver I/R.

For full text, please [click here](#).

Original Article:

Chapin CA, Horslen SP, **Squires JE**, Lin H, Blondet N, Mohammad S, Alonso EM. Corticosteroid Therapy for Indeterminate Pediatric Acute Liver Failure and Aplastic Anemia with Acute Hepatitis. *J Pediatr*. 2019 Feb 12. pii: S0022-3476(18)31816-X. doi: 10.1016/j.jpeds.2018.12.042. [Epub ahead of print] PubMed PMID: 30770193.

ABSTRACT

OBJECTIVE: To examine the characteristics and outcomes of a multicenter patient cohort with indeterminate pediatric acute liver failure (IND-PALF) and with aplastic anemia with acute hepatitis treated with corticosteroids.

STUDY DESIGN: Retrospective study of patients age 1-17 years with IND-PALF and aplastic anemia with acute hepatitis who presented between 2009 and 2018 to 1 of 4 institutions and were treated with corticosteroids for presumed immune dysregulation.

RESULTS: Of 28 patients with IND-PALF (median of 4.0 years of age [range 1-16] and 71% male) 71% (n = 20) were treated with 0.5-4 mg/kg/day of intravenous methylprednisolone, and 8 patients received 10 mg/kg/day followed by a taper. By 21 days postcorticosteroid initiation, 14 patients (50%) underwent liver transplantation, 13 patients (46%) recovered with their native liver, and 1 patient (4%) died. Patients who recovered with their native liver received a median of 139 days (range 19-749) of corticosteroid therapy, with a median of 12 days (range 1-240) to international normalized ratio ≤ 1.2 . Patients with aplastic anemia with acute hepatitis (n = 6; median of 9.5 years of age [range 1-12], 83% male), received 1-2 mg/kg/day of methylprednisolone for a median of 100 days (range 63-183), and all recovered with their native liver. One patient with IND-PALF and 2 patients with aplastic anemia with acute hepatitis developed a serious infection within 90 days postcorticosteroid initiation.

CONCLUSIONS: Many patients with IND-PALF or aplastic anemia with acute hepatitis that were treated with corticosteroids improved, but survival with native liver

may not be different from historical reports. A randomized controlled trial exploring the benefits and risks of steroid therapy is needed before it is adopted broadly.

For full text, please [click here](#).

Funding Opportunity

Gilead Research Scholars

Liver Disease Program - The Americas

http://researchscholars.gilead.com/en/liver_disease_portal/program-overview



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STI CLINICAL SCIENCE PRESENTATIONS – AMERICAN TRANSPLANT CONGRESS 2019

ORAL PRESENTATIONS

PRESENTER	TITLE	SESSION DATE AND TIME
Kevin Louis	Circulating T Follicular Helper Proliferation and Memory B Cell Activation Correlate with Donor Specific Allo-antibody Occurrence and Antibody-mediated Rejection after Kidney Transplantation	Concurrent Session: Biomarkers, Immune Monitoring and Outcomes I June 2, 2019; 2:54 PM Publication #56
Angus Thomson	Preliminary Mechanistic Studies of Regulatory Dendritic Cell (DCreg) Cell Infusion in Living Donor Liver Transplant Recipients	Concurrent Session: Tolerance: Clinical Studies June 2, 2019; 3:30 PM Publication #87
Mary Amanda Dew	Impact of Race and Substance Use on Listing Decisions for Kidney Transplant	Concurrent Session: Kidney Psychosocial II: Substances and Access & Barriers June 4, 2019; 2:30 PM Publication #438
Abhinav Humar	Adult Living Donor vs. Deceased Donor Liver Transplant (LDLT vs. DDLT) at a Single US Center - Time to Change Our Paradigm for Liver Transplant	Concurrent Session: Liver: Living Donors and Partial Grafts June 4, 2019; 3:42 PM Publication #458
Rajil Mehta	Impact of Early Borderline Histological Changes on Subsequent Events in Renal Transplant Recipients	Concurrent Session: Kidney: Acute Cellular Rejection June 4, 2019; 3:42 PM Publication #430
Christine Haugen (Presenter) UPMC Co-Authors: Andres Duarte-Rojo Michael Dunn	Frailty and BMI in Liver Transplant (LT) Candidates: 9-center Functional Assessment in Liver Transplantation Study	Concurrent Session: Liver: Recipient Selection June 4, 2019; 4:42 PM Publication #565
Camila Macedo	Monitoring Circulating T Follicular Helper Cells Polarization, Activation and Function Distinguishes Asymptomatic Donor-Specific Anti-HLA Antibody Positive Kidney Transplant Recipients from Those Undergoing Antibody-Mediated Rejection	Concurrent Session: Biomarkers, Immune Monitoring and Outcomes V June 4, 2019; 4:54 PM Publication #580
James Fleming (Presenter) UPMC Co-Author: Naudia Jonassaint	Results from the LIVE-C Free Trial	Concurrent Session: Non-organ specific: viral hepatitis June 4, 2019; 5:42 PM Publication #591

POSTER PRESENTATIONS

PRESENTER	TITLE	SESSION DATE AND TIME
Andres Duarte-Rojo	A Randomized Pilot Trial of Home-Based Physical Activity Plus Dietary Intervention to Improve Physical Function in Patients with Advanced Liver Disease	Poster Session A: Liver: Recipient Selection June 1, 2019; 5:30 PM – 7:30 PM Publication/Poster #315
Michele Molinari	The Impact of KDPI on Post Transplant Kidney Function: Intercept versus Slope. A Single Center Study	Poster Session A: Kidney Deceased Donor Allocation June 1, 2019; 5:30 PM – 7:30 PM Publication/Poster #212
Tejaswini Narayanan Presenter UPMC Co-author: Rakesh Sindhi	Hepatoblastoma Tumors Requiring Liver Transplantation Manifest Dysregulated Ciliary, Autophagy and Cell Cycling Pathways in Systems Biology Analysis	Poster Session A: Biomarkers, Immune Monitoring, and Outcomes June 1, 2019; 5:30 PM - 7:30 PM Publication/Poster # 176
Neslihan Celik	Management of Orphan Ducts After Pediatric Living Donor Liver Transplantation	Poster Session B: Liver: Living Donors and Partial Grafts June 2, 2019; 6:00 PM – 7:00 PM Publication/Poster #351
Raman Venkataramanan	Drug Metabolizing Capacity of the Liver in Liver Donors Recovers Fully by One Month Post Donation	Poster Session B: Liver: Living Donors and Partial Grafts June 2, 2019; 6:00 PM – 7:00 PM Publication/Poster #356
Swaytha Ganesh	Donor Exclusions and Shifting Trends in Living Liver Donor Evaluations: A Single Center Experience	Poster Session B: Liver: Living Donors and Partial Grafts June 2, 2019; 6:00 PM – 7:00 PM Publication/Poster #352
Rajil Mehta	Outcomes of Phenotypes in Early Subclinical Inflammation (SCI) Determined by Presence of Interstitial Inflammation with or without Concomitant Tubulitis	Poster Session C: Kidney: Acute Cellular Rejection June 3, 2019; 6:00 PM - 7:00 PM Publication/Poster #161
Larissa Myaskovsky Presenter UPMC Co-author: Mary Amanda Dew	Social Determinants of Health-Related Quality of Life in Patients Evaluated for Kidney Transplant	Poster Session C: Kidney Psychosocial June 3, 2019; 6:00 PM – 7:00 PM Publication/Poster #105
Itunu Owoyemi	Impact of T-cell Mediated Allograft Rejection and Antibody Mediated Rejection within the First Year after Kidney Transplantation	Poster Session C: Kidney Acute Cellular Rejection June 3, 2019; 6:00 PM - 7:00 PM Publication/Poster #173
Parmjeet Randhawa	Tandem Mass Tags Based Liquid Chromatography/Mass Spectrometry Analysis of Quantitative Proteomic Changes in Renal Allograft Biopsies with Polyomavirus BK Nephropathy	Poster Session C: Kidney Polyoma June 3, 2019; 6:00 PM - 7:00 PM Publication/Poster #255
Srijan Tandukar	Impact of T-cell Mediated Allograft Inflammation within First-Year after Kidney Transplantation: An Analysis of Paired Biopsies from a Single Center Study	Poster Session C: Kidney Acute Cellular Rejection June 3, 2019; 6:00 PM - 7:00 PM Publication/Poster #168

CLINICAL SCIENCE PRESENTATIONS

Ghady Haidar	A Pilot Study of Organ Donor Registration among Persons Living with HIV (PLWH)	Poster Session D: Non-Organ Specific: Public Policy & Allocation June 4, 2019; 6:00 PM - 7:00 PM Publication/Poster #230
Michele Molinari	Policy Changes in Liver Graft Allocation for Hepatocellular Carcinoma in the USA: Improved Survival for African American Recipients	Poster Session D: Liver: Hepatocellular Carcinoma and Other Malignancies June 4, 2019; 6:00 PM - 7:00 PM Publication/Poster #118

INVITED PRESENTATIONS

PRESENTER	TITLE	SESSION DATE AND TIME
Ghady Haidar	Managing Infections in Transplant Candidates: MDROs- Treatment and Does It Affect Candidacy?	June 1, 2019; 1:20 PM – 1:40 PM
Abhinav Humar	TID is a Team Sport!: The Cutting Edge Surgeons Perspective of Managing Post-Transplant Infections	June 1, 2019; 3:45 PM – 4:05 PM
Martin Oberbarnscheidt	Innate Immune System for Clinicians	June 1, 2019; 4:30 PM – 4:50 PM
David Rothstein	B Cell Biomarkers for Transplantation	June 1, 2019; 5:00 PM – 5:20 PM
Fernanda Silveira	Cases in Transplant Infections - Stump the Expert	June 1, 2019; 5:10 PM – 5:15 PM
George Mazariegos	Surgical Management - Can I Do Surgery to Prevent Future Transplant?	June 2, 2019; 7:20 AM – 7:40 AM
Rajil Mehta	Borderline Rejection After Kidney Transplantation – Is it Borderline?	June 2, 2019; 11:15 AM – 11:35 AM
Abhinav Humar	Time to Change Paradigm for Liver Transplant	June 3, 2019; 11:35 AM – 11:55 AM
Parmjeet Randhawa	Histologic Assessment of Donor Kidney Biopsies: Are they Helpful or Do They Merely Increase the Discard Rate?	June 3, 2019; 11:45 AM – 12:05 PM
Marian Michaels	14 Years of DTAC; US Perspective	June 4, 2019; 7:00 AM – 7:20 AM
Fernanda Silveira	Does This Patient Need Antifungal Prophylaxis?	June 4, 2019; 7:45 AM - 8:00 AM
Diana Metes	Human Circulating T Follicular Helper Cells in Transplantation	June 5, 2019; 7:00 AM – 8:15 AM

SESSION CO-CHAIR/MODERATOR

CO-CHAIR	SESSION TITLE	SESSION DATE AND TIME
Mary Amanda Dew	From Policy to Postop: Opioid and Benzodiazepine Use Across the Transplant Process	June 3, 2019; 11:15 AM - 12:45 PM
Swaytha Ganesh	1000 LDLTS in the US: Pipedream or Near Future	June 3, 2019; 11:15 AM – 12:45 PM

CLINICAL SCIENCE PRESENTATIONS

Parmjeet Randhawa	What Do I Do Now: Challenging Cases in Post Renal Transplant	June 4, 2019; 7:00 AM – 8:15 AM
Ghady Haidar	Novel Insights in Kidney Infections	June 4, 2019; 2:30 PM – 4:00 PM

STI BASIC SCIENCE PRESENTATIONS – AMERICAN TRANSPLANT CONGRESS 2019

ORAL PRESENTATIONS

PRESENTER	TITLE	SESSION DATE AND TIME
Daqiang Zhao	Role of Innate Allorecognition Pathways in Mouse Renal Allograft Rejection	Session: Plenary Session I June 2, 2019; 8:30 AM Publication #1
Kazuki Sasaki	Granulocyte - Colony Stimulating Factor (G-CSF) and Granulocyte - Macrophage Colony Stimulating Factor (GM-CSF) Administration Augments the Incidence of Peripheral Blood Suppressive Regulatory T Cells in Nonhuman Primates	Concurrent Session: Immunosuppression Preclinical Studies June 3, 2019; 2:30 PM Publication #260
Helong Dai	mTORC2 Restricts mTORC1 Metabolic Function in Dendritic Cells to Limit Their Allostimulatory Activity	Concurrent Session: Antigen Presentation and Allorecognition June 3, 2019; 2:42 PM Publication #247
Khodor Abou Daya	Tertiary Lymphoid Organs in Renal Chronic Allograft Rejection	Concurrent Session: Antigen Presentation and Allorecognition June 3, 2019; 3:30 PM Publication #251
Zhixing Song	B Cell IL-4 Signaling Induces the IL-10 Secreting TIM-1+ Bregs and Suppresses T Cell Inflammatory Cytokines	Concurrent Session: Tolerance / Immune Deviation June 3, 2019; 4:30 PM Publication #372
Zhongqiang Zhang	Local IL-33 Regulates Heart Transplant Infiltrating Myeloid Cells Metabolism and Differentiation to Protect against Chronic Rejection	Concurrent Session: Innate Immunity; Chemokines, Cytokines, Complement June 4, 2019; 3:06 PM Publication #483
Khodor Abou Daya	Tissue Resident Memory T Cells in Murine Renal Transplantation	Concurrent Session: Acute Rejection: Basic June 4, 2019; 3:18 PM Publication #491
Jason Ossart	Treg Suppressor Function within Allografts is Required for Tolerance	Concurrent Session: Late Breaking Oral Abstract June 4, 2019; 4:54 PM Publication #628

POSTER PRESENTATIONS

PRESENTER	TITLE	SESSION DATE AND TIME
Angelica Perez-Gutierrez	Phenotypic and Functional Analysis of Non-Activated and Allo-Activated Eomesodermin+ CD8+ T Cells in Humans and Nonhuman Primates	Poster Session D: Lymphocyte Biology: Signaling, Co-Stimulation, Regulation June 4, 2019; 6:00 PM - 7:00 PM Publication/Poster #149

BASIC SCIENCE PRESENTATIONS

INVITED PRESENTATIONS

PRESENTER	TITLE	SESSION DATE AND TIME
David Rothstein	B Cell Biomarkers for Transplantation	June 1, 2019; 5:00 PM – 5:20 PM
Angus Thomson	Dendritic Cell Intervention	June 4, 2019; 11:15 AM - 11:35 AM

AWARDS

RECIPIENT	AWARD RECEIVED
Khodor Abou-Daya	ATC Young Investigator Award 2019
Zhongqiang Zhang	ATC Young Investigator Award 2019
Daqiang Zhao	ATC Young Investigator Award 2019

BASIC SCIENCE PRESENTATIONS