View this email in your browser

Liver Digest

A weekly update of PLRC happenings

February 13, 2020

PITTSBURGH LIVER RESEARCH CENTER

A partnership of University of Pittsburgh & UPMC

www.livercenter.pitt.edu

Featured Faculty - Dr. David Geller

REMINDER: Please acknowledge support from the PLRC (NIH/NIDDK P30DK120531) in your publications and presentations.

In this issue

Next Week's Seminar

PLRC Seminar Series

Tues., 2/18/2020

12:00 to 1:00 pm

S123 BST

David Mangelsdorf, PhD

Alfred G. Gilman Distinguished Chair in Pharmacology
Raymond and Ellen Willie Distinguished Chair in Molecular Neuropharmacology in Honor of Harold B. Crasilneck, Ph.D.
Departments of Pharmacology and Biochemistry
UT Southwestern Medical Center

Role of FGF19 and 21 on Hepatic Lipid Metabolism

Pizza will be provided.
This activity has been approved for AMA PRA Category 1 credit.
#6242-Liver Center Seminars.

The full schedule of Enrichment activities is posted on **https://www.livercenter.pitt.edu/events**

Faculty Highlights

PLRC members collaborating on manuscripts are noted in red.

Original Article:Artru F, Bou Saleh M, Maggiotto F, Lassailly G, Ningarhari M, Demaret J, Ntandja-Wandji LC, Pais de Barros JP, Labreuche J, Drumez E, Helou DG, Dharancy S, Gantier E, Périanin A, Chollet-Martin S, **Bataller R**, Mathurin P, Dubuquoy L, Louvet A. IL-33/ST2 pathway regulates neutrophil migration and predicts outcome in patients with severe alcoholic hepatitis. J Hepatol. 2020 Jan 15;S0168-8278(20)30008-8. doi: 10.1016/j.jhep.2019.12.017. [Epub ahead of print]. PMID: 31953139.

Background and aims: Severe alcoholic hepatitis (SAH) is associated with a high risk of infection. The interleukin-33 (IL33)/ST2 pathway is involved in sepsis control but data in alcohol-related liver disease (ALD) are lacking. We aimed to characterize the role of IL-33/ST2 in the neutrophils (PMNs) of patients with ALD and SAH.

Methods: Serum and circulating neutrophils were collected from patients with SAH, alcoholic cirrhosis (Cirrh) and healthy controls (Ctrl). We quantified the IL-33/ST2 pathway and CXCR2 at baseline and after exposure to IL-33. We also determined the migration capacity of PMN.

Results: The decoy receptor of IL-33 (sST2) was increased in SAH vs. Cirrh and Ctrl, demonstrating the defect in this pathway during

ALD. The sST2 level was associated with response to treatment, 2-month survival, infection-free survival and probability of infection in SAH. Endotoxemia was weakly correlated with sST2. GRK2, a negative regulator of CXCR2, was overexpressed in SAH and Cirrh PMNs and was decreased by IL-33. CXCR2 levels on PMNs were lower in SAH vs. Cirrh and Ctrl. Treatment with IL-33 partially restored CXCR2 expression in SAH and Cirrh. PMN migration upon IL-8 was lower in SAH and Cirrh vs. Ctrl. Treatment with IL-33 partially restored migration in SAH and Cirrh. Interestingly, the migration capacity of PMNs and the response to IL-33 were enhanced in responders to corticosteroids (Lille<0.45) compared to non-responders.

Conclusion: The IL33/ST2 pathway is defective in SAH and predicts outcome. This defect is associated with decreased CXCR2 expression on the surface of PMNs and lower migration capacity, which can be corrected by IL-33, especially in patients responding to steroids. These results suggest a therapeutic potential in SAH and its infectious complications.

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

Original Article:
Chen HW, Ferrando A, White MG, Dennis RA, Xie J, Pauly M, Park S, Bartter T, **Dunn MA**, Ruiz-Margain A, Kim WR, **Duarte-Rojo A**. Home-Based Physical Activity and Diet Intervention to Improve Physical Function in Advanced Liver Disease: A Randomized Pilot Trial. Dig Dis Sci. 2020 Jan 6;10.1007/s10620-019-06034-2. doi: 10.1007/s10620-019-06034-2. PMID: 31907774.

ABSTRACT
Introduction: A decline in physical function is highly prevalent

and a poor prognostic factor in cirrhosis. We assessed the benefits of a home-based physical activity program (HB-PAP) in patients with cirrhosis with a randomized pilot trial.

Methods: All participants received a personal activity tracker to monitor daily activities and were given 12 g/day of an essential amino acid supplement. The HB-PAP intervention consisted of biweekly counseling sessions to increase physical activity for 12 weeks. Six-minute walk test (6MWT) and cardiopulmonary exercise testing (CPET) assessed changes in aerobic fitness. Different anthropometric measuring tools were used for skeletal muscle and adiposity assessment.

Results: Seventeen patients (60% male; 29% nonalcoholic steatohepatitis/cryptogenic, 29% hepatitis C, 24% alcohol, 18% other) were randomized, 9 to HB-PAP group. There were no significant differences in MELD-sodium between HB-PAP and controls at baseline or after the 12-week intervention. By the end of study, there was a significant between-group difference in daily step count favoring the active group (2627 [992-4262], p = 0.001), with less sedentary patients in the active group (33-17% vs. 25-43%, p = 0.003). The 6MWT improved in the HB-PAP group (423 ± 26 m vs. 482 ± 35 m), while the controls had a nonsignificant drop (418 ± 26 m vs. 327 ± 74 m) with a significant between-group difference. CPET did not change. Other than an improvement in psoas muscle index, there were no differences in anthropometry, or in quality of life.

Conclusions: HB-PAP maintained physical performance and improved aerobic fitness according to 6MWT but not CPET, supporting the use of personal activity trackers to monitor/guide home-based prehabilitation programs in cirrhosis.

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

Original Article:

van Rijt WJ, Jager EA, Allersma DP, Aktuğlu Zeybek AÇ, Bhattacharya K, Debray FG, Ellaway CJ, Gautschi M, Geraghty MT, Gil-Ortega D, Larson AA, Moore F, Morava E, Morris AA, Oishi K, Schiff M, Scholl-Bürgi S, Tchan MC, **Vockley J**, Witters P, Wortmann SB, van Spronsen F, Van Hove JLK, Derks TGJ. Efficacy and safety of D,L-3-hydroxybutyrate (D,L-3-HB) treatment in multiple acyl-CoA dehydrogenase deficiency. Genet Med. 2020 Jan 6;10.1038/s41436-019-0739-z. doi: 10.1038/s41436-019-0739-z. PMID: 31904027.

ABSTRACT

Purpose: Multiple acyl-CoA dehydrogenase deficiency (MADD) is a life-threatening, ultrarare inborn error of metabolism. Case reports described successful D,L-3-hydroxybutyrate (D,L-3-HB) treatment in severely affected MADD patients, but systematic data on efficacy and safety is lacking.

Methods: A systematic literature review and an international, retrospective cohort study on clinical presentation, D,L-3-HB treatment method, and outcome in MADD(-like) patients.

Results: Our study summarizes 23 MADD(-like) patients, including 14 new cases. Median age at clinical onset was two months (interquartile range [IQR]: 8 months). Median age at starting D,L-3-HB was seven months (IQR: 4.5 years). D,L-3-HB doses ranged between 100 and 2600 mg/kg/day. Clinical improvement was reported in 16 patients (70%) for cardiomyopathy, leukodystrophy, liver symptoms, muscle symptoms, and/or respiratory failure. D,L-3-HB appeared not effective for neuropathy. Survival appeared longer upon D,L-3-HB compared with historical controls. Median time until first clinical improvement was one month, and ranged up to six

months. Reported side effects included abdominal pain, constipation, dehydration, diarrhea, and vomiting/nausea. Median D,L-3-HB treatment duration was two years (IQR: 6 years). D,L-3-HB treatment was discontinued in 12 patients (52%).

Conclusion: The strength of the current study is the international pooling of data demonstrating that D,L-3-HB treatment can be effective and safe in MADD(-like) patients.

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

Original Article:

Hughes CB, Humar A. Liver transplantation: current and future. Abdom Radiol (NY). 2020 Jan 17;10.1007/s00261-019-02357-w. doi: 10.1007/s00261-019-02357-w. PMID: 31953588.

ABSTRACT

Purpose: The aim of this paper is to summarize the allocation challenges facing the field of liver transplantation while providing examples of the expansion of indications for the procedure.

Methods: UNOS allocation policy was reviewed as well as the recent literature describing expanded criteria for recipient candidate selection.

Results: Liver allocation policy changes for deceased-donor organs remain gridlocked in legal and bureaucratic red tape. Meanwhile, the indications for liver transplantation are being expanded to include acute alcoholic hepatitis, intrahepatic cholangiocarcinoma, and colorectal metastasis, previously viewed as absolute contraindications, but under strict selection criteria.

Conclusions: Attempting to meet the demand for livers, transplant centers are increasingly turning to living donor liver transplantation, protocols such as HCV-positive to HCV-negative transplants, and machine perfusion of marginal organs.

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

Review Article:

Wang Y, Fang Z, Hong M, Yang D, **Xie W**. Long-noncoding RNAs (lncRNAs) in drug metabolism and disposition, implications in cancer chemo-resistance. Acta Pharm Sin B. 2020 Jan;10(1):105-112. doi: 10.1016/j.apsb.2019.09.011. Epub 2019 Oct 19. PMID: 31993309; PMCID: PMC6976993.

ABSTRACT

Drug metabolism is an orchestrated process in which drugs are metabolized and disposed through a series of specialized enzymes and transporters. Alterations in the expression and/or activity of these enzymes and transporters can affect the bioavailability (pharmacokinetics, or PK) and therapeutic efficacy (pharmacodynamics, or PD) of drugs. Recent studies have suggested that the long non-coding RNAs (lncRNAs) are highly relevant to drug metabolism and drug resistance, including chemo-resistance in cancers, through the regulation of drug metabolism and disposition related genes. This review summarizes the regulation of enzymes, transporters, or regulatory proteins involved in drug metabolism by lncRNAs, with a particular emphasis on drug metabolism and chemo-resistance in cancer patients. The perspective strategies to integrate multi-dimensional pharmacogenomics data for future in-depth analysis of drug metabolism related lncRNAs are also proposed. Understanding the role of lncRNAs in drug metabolism will

not only facilitate the identification of novel regulatory mechanisms, but also enable the discovery of lncRNA-based biomarkers and drug targets to personalize and improve the therapeutic outcome of patients, including cancer patients.

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

Funding Opportunities

Developmental Centers for AIDS Research (P30 Clinical Trial Not Allowed)

(PAR-20-107)

National Institute of Allergy and Infectious Diseases

John E. Fogarty International Center

National Cancer Institute

National Heart, Lung, and Blood Institute

National Institute on Aging

Eunice Kennedy Shriver National Institute of Child Health and Human Development

National Institute on Drug Abuse

National Institute of Dental and Craniofacial Research

National Institute of Diabetes and Digestive and Kidney Diseases

National Institute of Mental Health

National Institute on Minority Health and Health Disparities

National Institute of Nursing Research

Centers for AIDS Research (P30 Clinical Trial Not Allowed)

(PAR-20-106)

National Institute of Allergy and Infectious Diseases

John E. Fogarty International Center

National Cancer Institute
National Heart, Lung, and Blood Institute
National Institute on Aging
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institute on Drug Abuse
National Institute of Dental and Craniofacial Research
National Institute of Diabetes and Digestive and Kidney Diseases
National Institute of Mental Health
National Institute on Minority Health and Health Disparities
National Institute of Nursing Research

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