Liver Digest

A weekly update of PLRC happenings

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PITTSBURGH LIVER RESEARCH CENTER

A partnership of University of Pittsburgh & UPMC

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Featured Faculty - Dr. Vikrant Rachakonda

In this issue

PLRC's Liver Digest Email List

If you would like to have students, trainees, or members of your lab added to the PLRC newsletter email distribution list, please send their names and emails to Ann Vinski (**vinskiam@upmc.edu**). Thank you!

Faculty Highlights

Review Article:

Thomson AW, Metes DM, Ezzelarab MB, Raïch-Regué D. Regulatory dendritic cells for human organ transplantation. Transplant Rev (Orlando). Transplant Rev (Orlando). 2019 Jul;33(3):130-136. doi: 10.1016/j.trre.2019.05.001. Epub 2019 May 13. Review. PubMed PMID: 31130302.

ABSTRACT

Current immunosuppressive (IS) regimens used to prevent organ allograft rejection have well-recognized side effects, that include enhanced risk of infection and certain types of cancer, metabolic disorders, cardiovascular disease, renal complications and failure to control chronic allograft rejection. The life-long dependency of patients on these IS agents reflects their inability to induce donor-specific tolerance. Extensive studies in rodent and non-human primate models have demonstrated the ability of adoptively-transferred regulatory immune cells (either regulatory myeloid cells or regulatory T cells) to promote transplant tolerance. Consequently, there is considerable interest in the potential of regulatory immune cell therapy to allow safe minimization/complete withdrawal of immunosuppression and the promotion of organ transplant tolerance in the clinic. Here, we review the properties of regulatory dendritic cells (DCreg) with a focus on the approaches being taken to generate human DCreg for clinical testing. We also document the early phase clinical trials that are underway to assess DCreg therapy in clinical organ transplantation as well as in autoimmune disorders.

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

Original Article:

Hofmann CE, Harmatz P, **Vockley J**, Högler W, Nakayama H, Bishop N, Martos-Moreno GÁ, Moseley S, Fujita KP, Liese J, Rockman-Greenberg C; ENB-010-10 Study Group. Efficacy and Safety of Asfotase Alfa in Infants and Young Children With Hypophosphatasia: A Phase 2 Open-Label Study. J Clin Endocrinol Metab. 2019 Jul 1;104(7):2735-2747. doi: 10.1210/jc.2018-02335. PubMed PMID: 30811537.

ABSTRACT

--CONTEXT: Long-term data on enzyme replacement treatment of hypophosphatasia (HPP) are limited.

--OBJECTIVE: To evaluate efficacy and safety of asfotase alfa in patients aged ≤5 years with HPP followed for up to 6 years.

--DESIGN: Phase 2 open-label study (July 2010 to September 2016).

--SETTING: Twenty-two sites; 12 countries.

--PARTICIPANTS: Sixty-nine patients [median (range) age: 16.0 (0.02 to 72) months] with severe HPP and sign/symptom onset before age 6 months.

--INTERVENTION: Asfotase alfa 2 mg/kg three times/week or 1 mg/kg six times/week subcutaneously.

--MAIN OUTCOME MEASURES: Primary efficacy measure: Radiographic Global Impression of Change (RGI-C) score [-3 (severe worsening) to +3 (complete/near-complete healing)]. Additional outcome measures: respiratory status, growth, and safety. Post hoc analysis: characteristics of radiographic responders vs nonresponders at Year 1 (RGI-C: ≥+2 vs <+2).

--RESULTS: During median (minimum, maximum) 2.3 (0.02, 5.8) years of treatment, RGI-C scores improved significantly at Month 6 [+2.0 (-1.7, +3.0)], Year 1 [+2.0 (-2.3, +3.0)], and Last Assessment [+2.3 (-2.7, +3.0); P < 0.0001 all]. Of 24 patients requiring respiratory support at Baseline, 11 (46%) no longer needed support. Height/weight z scores generally increased. Nine patients died (13%). All patients experienced at least one adverse event; pyrexia was most common. Compared with responders [n = 50 (72%)], nonresponders [n = 19 (28%)] had more severe disease at Baseline and a higher rate of neutralizing antibodies (NAbs) at Last Assessment.

--CONCLUSIONS: Most infants/young children given asfotase alfa showed early radiographic and clinical improvement sustained up to 6 years; radiographic nonresponders had more severe disease and more frequent NAbs at Last

Assessment.

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

Review Article:
Parikh S, Karaa A, Goldstein A, Bertini ES, Chinnery PF, Christodoulou J, Cohen BH, Davis RL, Falk MJ, Fratter C, Horvath R, Koenig MK, Mancuso M, McCormack S, McCormick EM, McFarland R, Nesbitt V, Schiff M, Steele H, Stockler S, Sue C, Tarnopolsky M, Thorburn DR, **Vockley J**, Rahman S. Diagnosis of 'possible' mitochondrial disease: an existential crisis. J Med Genet. 2019 Mar;56(3):123-130. doi: 10.1136/jmedgenet-2018-105800. Epub 2019 Jan 25. PubMed PMID: 30683676.

ABSTRACT
Primary genetic mitochondrial diseases are often difficult to diagnose, and the term 'possible' mitochondrial disease is used frequently by clinicians when such a diagnosis is suspected. There are now many known phenocopies of mitochondrial disease. Advances in genomic testing have shown that some patients with a clinical phenotype and biochemical abnormalities suggesting mitochondrial disease may have other genetic disorders. In instances when a genetic diagnosis cannot be confirmed, a diagnosis of 'possible' mitochondrial disease may result in harm to patients and their families, creating anxiety, delaying appropriate diagnosis and leading to inappropriate management or care. A categorisation of 'diagnosis uncertain', together with a specific description of the metabolic or genetic abnormalities identified, is preferred when a mitochondrial disease cannot be genetically confirmed.

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

Original Article:
Seymour CW, Kennedy JN, Wang S, Chang CH, Elliott CF, Xu Z, Berry S, Clermont G, Cooper G, Gomez H, Huang DT, Kellum JA, Mi Q, Opal SM, Talisa V, van der Poll T, Visweswaran S, **Vodovotz Y**, Weiss JC, Yealy DM, Yende S, Angus DC. Derivation, Validation, and Potential Treatment Implications of Novel Clinical Phenotypes for Sepsis. JAMA. 2019 May 19. doi: 10.1001/jama.2019.5791. [Epub ahead of print] PubMed PMID: 31104070.

ABSTRACT
IMPORTANCE: Sepsis is a heterogeneous syndrome. Identification of distinct

clinical phenotypes may allow more precise therapy and improve care.

OBJECTIVE: To derive sepsis phenotypes from clinical data, determine their reproducibility and correlation with host-response biomarkers and clinical outcomes, and assess the potential causal relationship with results from randomized clinical trials (RCTs).

DESIGN, SETTINGS, AND PARTICIPANTS: Retrospective analysis of data sets using statistical, machine learning, and simulation tools. Phenotypes were derived among 20 189 total patients (16 552 unique patients) who met Sepsis-3 criteria within 6 hours of hospital presentation at 12 Pennsylvania hospitals (2010-2012) using consensus k means clustering applied to 29 variables. Reproducibility and correlation with biological parameters and clinical outcomes were assessed in a second database (2013-2014; n = 43 086 total patients and n = 31 160 unique patients), in a prospective cohort study of sepsis due to pneumonia (n = 583), and in 3 sepsis RCTs (n = 4737).

EXPOSURES: All clinical and laboratory variables in the electronic health record.

MAIN OUTCOMES AND MEASURES: Derived phenotype (α, β, γ, and δ) frequency, host-response biomarkers, 28-day and 365-day mortality, and RCT simulation outputs.

RESULTS: The derivation cohort included 20 189 patients with sepsis (mean age, 64 [SD, 17] years; 10 022 [50%] male; mean maximum 24-hour Sequential Organ Failure Assessment [SOFA] score, 3.9 [SD, 2.4]). The validation cohort included 43 086 patients (mean age, 67 [SD, 17] years; 21 993 [51%] male; mean maximum 24-hour SOFA score, 3.6 [SD, 2.0]). Of the 4 derived phenotypes, the α phenotype was the most common (n = 6625; 33%) and included patients with the lowest administration of a vasopressor; in the β phenotype (n = 5512; 27%), patients were older and had more chronic illness and renal dysfunction; in the γ phenotype (n = 5385; 27%), patients had more inflammation and pulmonary dysfunction; and in the δ phenotype (n = 2667; 13%), patients had more liver dysfunction and septic shock. Phenotype distributions were similar in the validation cohort. There were consistent differences in biomarker patterns by phenotype. In the derivation cohort, cumulative 28-day mortality was 287 deaths of 5691 unique patients (5%) for the α phenotype; 561 of 4420 (13%) for

the β phenotype; 1031 of 4318 (24%) for the γ phenotype; and 897 of 2223 (40%) for the δ phenotype. Across all cohorts and trials, 28-day and 365-day mortality were highest among the δ phenotype vs the other 3 phenotypes (P<.001). In simulation models, the proportion of RCTs reporting benefit, harm, or no effect changed considerably (eg, varying the phenotype frequencies within an RCT of early goal-directed therapy changed the results from >33% chance of benefit to >60% chance of harm).

CONCLUSIONS AND RELEVANCE: In this retrospective analysis of data sets from patients with sepsis, 4 clinical phenotypes were identified that correlated with host-response patterns and clinical outcomes, and simulations suggested these phenotypes may help in understanding heterogeneity of treatment effects. Further research is needed to determine the utility of these phenotypes in clinical care and for informing trial design and interpretation.

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;303:77-90. doi: 10.1016/j.jconrel.2019.04.022. [Epub ahead of print] PubMed PMID: 31004666.

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**.

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