Pathways to Cures: Translational Science Research Day

Breakthroughs in Translational Sciences
Oral Presentation

These presentations represent the exemplary, innovative research being conducted at UCI toady!

Moderator: *Dan Cooper, MD*

Dr. Cooper is a Professor of Pediatrics and the Founding Director of the Institute for Clinical Translational Science and the Program Director of the UC Irvine Clinical Research Center. His research seeks to identify how exercise can best be used to prevent asthma and obesity in children; in particular how brief bouts of exercise alter gene expression and functional responses of neutrophils.

Oral Presentations:

90 Year Olds are Less Likely to Fall if they were Physically Active Two Decades Earlier: The 90+ Study
Presenter: **Dana Greenia R.N., M.S**
Claudia M.D.; Corrada, Maria Sc.D.
Affiliations: UCI Institute for Memory Impairments and Neurological Disorders Department of Neurology

Abstract: OBJECTIVE: To determine if physical activity reported 24 years earlier is associated with the risk of falling and to examine factors related to falls in the oldest-old. BACKGROUND: The risk of falls and injuries sustained from falls increase with age. Although risk factors for falls in the elderly have been well characterized, only limited information is available about the oldest-old, people 90 years and older. METHODS: The study included 1536 participants from The 90+ Study, a longitudinal investigation of aging and dementia in the oldest-old. Participants were originally members of the Leisure World Cohort Study (LWCS), an epidemiological study of life style practices. Falls (yes/no) were reported by a participant or informant at the baseline examination of The 90+ Study. Other factors also reported at the baseline examination and known to be related to falls in younger elderly were also examined. Physical activity information was collected in the LWCS 24 years earlier (range: 16-34) and was reported as 15 minutes, 30-45 minutes, or 1+ hour/day. Using logistic regression we examined the relationship between physical activity reported approximately 24 years earlier and falls. RESULTS: At The 90+ baseline visit, participants were on average 94 years (range=90-107), most were women (78%), and had at least a college degree (52%). Falls were reported by 52% (N= 799) of participants and were associated with a higher number of prescription medications, history of TIA or stroke, depression, arthritis, vision disease, heart disease, presence of dementia, and use of assistive devices. After adjusting for potential confounders, and compared to people who reported no physical activity, activity of 30+ minutes/day was associated with approximately a 30.

Pathways to Cures: Translational Science Research Day

Breakthroughs in Translational Sciences
Oral Presentation

Engineering Pompe disease models using CRISPR-Cas9 genome editing
   Presenter: **Jeffrey Huang, PhD**
   Authors: Huang, Jeffrey Y, PhD; Wang, Raymond Y, MD
   Affiliations: CHOC Children's Research Institute

Abstract: Pompe disease (PD) is a serious and progressive disorder caused by a genetic deficiency in acid alpha glucosidase (GAA) – an enzyme that recycles stored muscle cell glycogen for energy. PD patients with near-complete GAA deficiency – infantile-onset PD - present within the first few months of life with severe heart enlargement, heart failure, weakness of the muscles, respiratory failure, and demonstrate rapidly progressive, fatal disease. Without treatment, the average age that infantile-onset PD patients require permanent breathing support is about 6 months; the average age of death is about 9 months. Enzyme replacement therapy for Pompe disease using recombinant GAA enzyme (rhGAA) was developed and approved by the FDA in 2006. The treatment is very effective at getting rid of glycogen in heart muscle and reversing the heart symptoms. However, surviving children still have buildup of glycogen in other muscles and struggle with basic activities like talking, walking, eating, or even breathing. Furthermore, the outcomes of infantile-onset PD vary according to cross-reactive immunologic material (CRIM) status – one's immunogenic response to rhGAA. CRIM- patients develop significant antibody responses to rhGAA and typically have poorer prognoses, while CRIM+ patients tend to have better responses to rhGAA treatment. Currently, there are no models of PD featuring single nucleotide GAA mutations – which may be amenable to personalized genome editing. The goal of this project is to engineer PD-specific GAA mutations in C2C12 cells - a mouse myoblast line. We will seek to introduce single nucleotide GAA mutations homologous to common mutations found in CRIM- or CRIM+ infantile-onset PD using CRISPR-Cas9 genome editing. This set of experiments will allow us to determine the efficacy and specificity of our CRISPR-Cas9 system in a cultured cell line prior to in vivo testing.

Pathways to Cures: Translational Science Research Day

Breakthroughs in Translational Sciences
Oral Presentation

Development of novel biologic and nanotechnology-based therapeutic agents to enhance insulin secretion and counter beta cell dysfunction and loss in diabetes

Presenter: **Steven Chessler MD, PhD**

Authors: Chessler, Steven, MD, Ph.D.; Gruzman, Arie-Lev, Ph.D.; Lee, Abraham, Ph.D.; Lee, Donald; Munder, Anna; Shih-Hui Lee, Michelle; Lellouche; Jean-Paul; Vallejo, Derek

Affiliations: UCI, Department of Medicine, Dept of Biomedical Engineering; Bar Ilan University, Department of Chemistry and Institute for Nanotechnology

Abstract: Dysfunction and loss of the insulin-secreting pancreatic beta cells are central to the development of diabetes. In type 2 diabetes, ever more aggressive therapy and then insulin treatment become necessary in the face of worsening beta-cell failure and depletion. In type 1 diabetes, insulin therapy is necessary at the outset. Only two classes of drugs target the beta cell: sulfonylureas (and meglitinides) and GLP-1-related agents. These increase insulin secretion but do not act on the key pathogenic mechanisms: beta cell dedifferentiation and loss. Neuroligin-2 (NL2) and neurexin (Nrxn) are transmembrane proteins originally identified in the brain. There they engage in trans-cellular interactions essential for GABAergic synapse formation and function. We have found that NL2 and Nrxn are present on the beta cell surface and, through similar extracellular interactions, promote beta-cell proliferation, function, and resistance to injury. NL2 activates the protein gephyrin and triggers the formation of GABAergic signaling mechanisms, both recently found to be potent drivers of beta-cell regeneration and promising therapeutic targets. To test the utility of targeting the NL2-Nxn interaction, we designed an NL2 peptide based on the Nxn binding site and also produced a recombinant protein incorporating the NL2 extracellular domain. These were separately clustered by attachment to nanoparticles and artificial lipid vesicles. Dose-response and time course studies with beta cells showed that these reagents increase insulin secretion, insulin content and resistance to oxidative stress. The candidate agents also increase beta cell proliferation, expression of maturational markers and, in a pilot study with diabetic mice, reduced blood glucose levels. In summary, we have developed and tested promising therapeutic agents based on a novel mechanism—the neuroligin-neurexin interaction—and provided proof of principle for the value of this mechanism as a therapeutic target.

Pathways to Cures: Translational Science Research Day

Breakthroughs in Translational Sciences
Oral Presentation

Validation of a Microfluidic Device to Study Patient-Derived Colon Cancer Cells and Determine Clinical Predictive Value

Presenter: **Stephanie J Hachey, MS**

Authors: Hachey, Stephanie J MS; Zell, Jason A MPH DO; Hughes, Christopher CW PhD; Sobrino, Agua PhD; Celaya, Elizabeth I; Phan, Duc TT; Klempner, Samuel J MD; Lee, John G MD; Edwards, Robert A MD, PhD

Affiliations: UCI Department of Molecular Biology & Biochemistry, Department of Medicine, Department of Biomedical Engineering; Cedars-Sinai Medical Center Department of Medicine, The Edwards Lifesciences Center for Advanced Cardiovascular Technology

Abstract: Cancer accounts for 25% of US deaths, and the majority of patients die from metastatic disease that is refractory to current therapies. The low rates of effective preclinical compounds reaching the clinic can be largely attributed to drawbacks in current model systems that are poor predictors of drug response in patients. To address the need for improved preclinical models, the Hughes lab and collaborators designed and fabricated a microfluidics device that supports the formation of a perfused, vascularized micro-tumor (VMT) via co-culture of multiple cell types in an extracellular matrix. This novel platform, truly one of a kind in the field, more accurately mimics the in vivo tumor cell biology and microenvironment than standard drug screening modalities. The VMT represents a major breakthrough in tissue engineering by providing an environment amenable to establishment of perfused vasculature supported by stromal cells in the tissue construct, allowing long-term culture for drug sensitivity and molecular studies. What we propose is to test how an individual patient's tumor cells respond to a set of drugs – a truly personal drug screening methodology. Important questions we aim to address with our pilot study are whether the VMT model is representative of patient tumors and whether findings from the VMT can translate to clinical practice. To determine the clinical relevance of the VMT model, primary VMTs will be established from patient-derived colon cancer samples collected in excess of clinical need as part of a prospective clinical studyand then analyzed for responsiveness to multiple drug combinations. Findings will then be correlated to patient outcomes based on the drug combinations they actually received. The translational infrastructure providing real-time information from patient-derived tumor cells in our VMT will support efforts to improve patient outcomes.

Pathways to Cures: Translational Science Research Day

Breakthroughs in Translational Sciences
Oral Presentation

Parent versus teacher ratings of sluggish cognitive tempo; Implications for identifying risk among children with ADHD for poor academic achievement

Presenter: Sabrina Schuck, PhD
Authors: Lago, Haley; Abdullah, Maryam, PhD; Schuck, Sabrina, PhD; Cordia, Theresa
Affiliations: UCI Department of Pediatrics

Abstract: Sluggish Cognitive Tempo (SCT) is characterized by pathological inattention, physical under arousal and slowed thinking often seen in children with Attention Deficit/Hyperactivity Disorder (ADHD). Increasing evidence suggests SCT in children with ADHD contributes to poor academic achievement (Tamm, L. et al. 2016). Sixty-five children, their parents and teachers participated. All child participants attend a school-based behavioral health program for children with ADHD. All participants completed the Strengths and Weaknesses of Attention scale (SWAN) (parent, teacher or self-report versions).Three items from the SWAN, thought to be representative of symptoms associated with SCT were selected to derive an SCT index; "challenges in remaining focused", "having a below average energy level when completing tasks", and "difficulties in engaging in goal-directed activities". Academic achievement for the child participants was measured using the Wide Range Achievement Test, (WRAT4). Teacher ratings of the SCT index were strongly negatively correlated with all academic measures, indicating that children with lower academic achievement are perceived by their teachers to also demonstrate greater impairment from SCT symptoms. Interestingly, parent ratings on the SCT index were not significantly correlated with any area of academic achievement. Similarly, child self-reports of SCT symptoms did not correlate with academic achievement. Results suggest that teacher ratings of children's SCT symptoms are better predictors of risk for low academic achievement than parent ratings and child self-report. Teachers rating of SCT symptoms are likely to be more valuable than parent ratings in assisting practitioners to identify risk for low academic achievement and tailor interventions designed specifically for SCT.

Pathways to Cures: Translational Science Research Day

Breakthroughs in Translational Sciences
Oral Presentation

Therapeutic potential of human preterm umbilical cord mesenchymal stem cells
Presenter: Raissa Fobi, MD
Authors: Fobi, Raissa, MD; Nalbandian, Angele, PhD; Bany-Mohammed, Fayez, MD; Alshammari, Sana, MD: Almadan, Fatimah, MD; Uy, Cherry, MD; Aslam, Muhammad, MD
Affiliations: UCI Department of Pediatrics, Division of Neonatology

Abstract: BACKGROUND: Bronchopulmonary dysplasia (BPD) is a chronic debilitating disease of preterm infants leading to arrested alveolar development. Current therapies lack effectiveness and cause undesirable side effects. Our previous work with mesenchymal stem cell secretome (MSC-s) demonstrated protective paracrine effects in mouse BPD models. OBJECTIVES: Objectives of the study were 1) to isolate, culture, immunodeplete and differentiate human preterm and term umbilical cord mesenchymal stem cells (hUC-MSCs), and 2) to analyze the secretome from preterm and term hUC-MSCs relevant to neonatal BPD, utilizing advanced proteomic analysis. METHODS: The human hUC-MSCs from preterm (<28 weeks') and term (37-40 weeks') cord Wharton's jelly were isolated per published protocols. Immunodepletion was performed per published guidelines followed by differentiation potential assessment into osteocytes and adipocytes. The preterm and term hUC-MSC conditioned media generated for identification of active factors via advanced proteomics. RESULTS: We determined that preterm hUC-MSCs have rapid growth compared to term hUC-MSCs (duplication time 10 ± 2 days vs. 21 ± 3 days). Similarly, the differentiation potential into adipocytes and osteocytes was faster with preterm versus term hUC-MSCs (14 ± 3 days vs. 24 ± 3 days). Advanced proteomics analysis identified several peptides related to BPD in both preterm and term group. Preterm hUC-MSC secretome showed higher concentrations of VEGF, HGF, Spp1, M-Csf1, and procollagen, whereas term hUC-MSC secretome depicted higher concentrations of PDGF, FGF, CTGF, KGF, Thromospondin 2, and complement components. CONCLUSIONS: The hUC-MSCs secrete biologically active factors into their conditioned media and can serve as a potential targeted therapy against BPD. Further studies are underway to examine the preterm hUC-MSC secretome for therapeutic efficacy in vitro and in vivo.