diseases. This pilot study may lead to larger studies into whole genome-based blood biomarker approaches for monitoring abstinence and other clinical co-morbidities to be addressed in cocaine addiction recovery.

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Using Computer Vision and Wearable Devices to Improve Care of Parkinson's Disease

Jacob Simmering, Nandakumar Narayanan and Philip Polgreen
University of Iowa

OBJECTIVES/GOALS: Inexpensive, accurate home monitoring is the standard-of-care in many diseases like hypertension or diabetes; however, it has yet to be widely used in neurodegenerative diseases. We used wearable activity monitors and computer-vision evaluated assessments to estimate Parkinson's disease (PD)-related disease burden. METHODS/STUDY POPULATION: We recruited 22 people from the University of Iowa Movement Disorders Clinic. Each person completed a standardized set of 3 fine motor tasks using their hands. We recorded a video of this activity, which was evaluated using MediaPipe - an open-source pose classification program from Alphabet - as well as had an nurse-practitioner evaluate the performance on a validated scale (UPDRS). Participants wore a Fitbit Inspire 3 activity tracker at home for the next two weeks. We quantified disease burden using the Parkinson's Disease Questionnaire 39 - a validated 39-item survey about the intensity of PD-related impairment. Using data from the videos and activity trackers, we estimated 1) the standardized UPDRS assessment of motor impairment and 2) the total PDQ-39 score. RESULTS/ANTICIPATED RESULTS: We found observationally recorded fastest sustained (at least 5 minutes) walking speed was a strong predictor of PDQ-39, explaining over one third of the variability in the measure. Range of motion in the videos was a significant predictor of UPDRS scores; however, was only weakly related to the overall PDQ-39 score. Further processing of the signals from the video, including wavelets and frequency domain analysis, may provide better predictive capabilities. PDQ-39 subscores (e.g., cognition, social support, mobility) will be the subject of further analysis. DISCUSSION/SIGNIFICANCE: Home monitoring has become the standard in other fields because of the better generalizability of home measurements. Improving the detection and evaluation of PD using home monitoring will lead to more timely and accurately changes in medication and less need for clinic visits - especially off levodopa.

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Utility of [89Zr]Trastuzumab-PET/MRI Imaging for Quantitative Assessment of Tumor Heterogeneity In HER2+ Breast Cancer

Ameer Mansur[1], Moozhan Nikpanah[2], Johnathan McConathy[2,3], Erica Stringer-Reasor[2], Gabrielle Rocque[4], Ahmed Elkhanany[3], Katia Khoury[3], Nusrat Jahan[3], Suzanne E. Lapi[5] and Anna G. Sorace[6,2,3]
[1]University of Alabama at Birmingham; [2]Department of Radiology, UAB; [3]O'Neal Comprehensive Cancer Center, UAB; [4]Division of Hematology and Oncology, UAB; [5]Department of Chemistry, UAB and [6]Department of Biomedical Engineering, UAB

OBJECTIVES/GOALS: This study was performed to explore the capabilities of simultaneous [89 Zr]trastuzumab-PET/MRI acquisition in a cohort of metastatic HER2+ breast cancer. The insights derived provide additional noninvasive characterization and precise intratumoral analysis tools for healthcare providers. METHODS/STUDY POPULATION: A total of 13 patients, aged between 40 and 70, diagnosed with HER2-positive breast cancer, were selected to participate in this study. Whole-body [89 Zr]trastuzumab-PET/MR imaging was performed 5 ± 1 days post-injection of the radiopharmaceutical during ongoing HER2-directed therapy. Concurrently acquired T1-weighted MRI facilitated the identification of normal organ and tumor regions of interest, which were further analyzed for mean ADC and mean standardized uptake value. Multiparametric intratumoral habitat analysis was performed. Utilizing the median metric values, tumors were evaluated for heterogeneity, specifically assessing high and low HER2 expression through an image processing framework in conjunction with ADC metrics. Long-term treatment response evaluation is ongoing. RESULTS/ANTICIPATED RESULTS: Initial analysis indicate all tumors exhibited higher overall uptake of [89 Zr]trastuzumab across various sites including the bone (p=0.019), brain (p=0.014), and breast (p=0.069), when compared to corresponding normal organs. Additionally, increased ADCmean values were observed in all regions besides brain tumors (bone: p=0.002, brain: p=0.5, breast: p=0.03, juxtapulmonary: p=0.037), indicating distinct patterns of cellularity. Notably, one of five patients with a breast lesion, who exhibited a complete response to HER2-targeted therapy, exhibited the highest breast lesion SUVmean. Brain and lymph node lesions demonstrated intratumoral heterogeneity of HER2 expression. Qualification of multi parametric maps is anticipated to inform on intratumoral heterogeneity DISCUSSION/SIGNIFICANCE: Despite limitation in clinical applications of quantitative approaches due to lack of standardization of processing, initial investigations, in combining molecular imaging of HER2 and quantitative MRI demonstrate potential in characterizing metastatic HER2+ breast cancer for intratumoral classification and therapeutic stratification.

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Application of human induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) for modeling of Ankyrin-2 p.R990Q variant-induced ventricular arrhythmia and personalized medicine

Jyotsna Joshi, Neill Schwieterman, Nate Smole, Shuliang Guo, Xiaoping Wan, Angelina Ramirez-Navarro, Cemantha Lane, Isabelle Deschenes, Thomas Hund, Loren Wold and Sakima Smith
The Ohio State University

OBJECTIVES/GOALS: The cytoskeletal protein α^2II spectrin interacts with actin and ankyrin-2 in cardiomyocytes which is essential to orchestrate ion channels and membrane proteins in the cardiac dyad. Our goal is to understand molecular mechanism causing severe ventricular arrhythmias due to spectrin dysfunction and explore novel therapies to treat such conditions. METHODS/STUDY POPULATION: We previously published a case of a 36-year-old woman with an ankyrin-2 p.R990Q (ANK2) variant, presented with severe ventricular arrhythmias and sudden cardiac arrest, caused by a novel mutation in the ankyrin-B gene (c.2969G>A) that disrupts the interaction of ankyrin-B/βII spectrin. To model the condition, we will use human induced pluripotent stem cell (DF 19-9-7T, WiCell)-derived ventricular cardiomyocytes (iPSC-CMs) having ANK2 variant, engineered using CRISPR/Cas9 method (Synthego Corp.). We will validate the differentiation of iPSCs into ventricular lineage and characterize the ANK2 ventricular phenotype. Next, we will express light-gated cation channel Channelrhodopsin (ChR2) in the ANK2 iPSC-CMs and investigate the potential role of

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optogenetics in treating such severe arrhythmias. RESULTS/ANTICIPATED RESULTS: Immunostaining shows 87.339% of iPSC-CMs, treated with All-trans retinoic acid (RA) (1 uM) on days 7 and 12 [RA 7,12], and 23.84% of those, treated on days 3 and 5 [RA 3,5], expressed MLC-2V ($p<0.001$). Calcium reuptake (τ) is 0.5914 s in RA 7, 12 while 0.2247s in RA 3, 5 ($p<0.001$). APD90 and APD50 of RA 7, 12 are 2- and 5-fold higher than RA 3, 5, showing distinct ventricular and atrial phenotypes. Protein expression of βII-spectrin and ankyrin-2 and their co-localizations were reduced in the ANK2 phenotype compared to the healthy phenotype. We found prolongation of Ca2+ waves and τ with blue light on iPSC-CMs, expressing ChR2. We anticipate that such prolongation of calcium transients would prevent aberrant calcium spikes, rescue Ca2+/calpain-induced βII-spectrin loss and provide electrical stability. DISCUSSION/SIGNIFICANCE: Animal models cannot accurately recapitulate human cardiac electrophysiology. The proposed human iPSC-CM-based ANK2 model would provide better mechanistic insights of severe ventricular arrhythmias. Also, the proposed optogenetic cardioversion has the potential to provide safe, targeted and painless cardioversion to manage arrhythmias.

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An Investigation of Novel Urinary Cell mRNA Profiles for Noninvasive Diagnosis of Acute Rejection in Kidney Transplant Recipients

Thalia Salinas, Carol Li, Catherine Snopkowski, Gabriel Stryjniak, Shady Albakry, Ruchuang Ding, Steven P. Salvatore, Surya V. Seshan, Darshana M. Dadhania, Thangamani Muthukumar and Manikkam Suthanthiran
NewYork Presbyterian- Weill Cornell Medical College, New York, NY

OBJECTIVES/GOALS: RNA-seq of urine and kidney allograft biopsies (bx) found that urinary cell immune landscape reflects intragraft molecular events and we discovered a shared set of 127 mRNAs in urine matched to T cell mediated and antibody mediated rejection bx. We prioritized ITM2A, SLAMF6 and IKZF3 mRNAs and herein investigate if these accurately predict rejection. METHODS/STUDY POPULATION: We collected urine samples from adult kidney allograft (KA) recipients at the time of KA bx. KA bx were classified by pathologists by Banff criteria. Total RNA was isolated from KA bx-matched urine samples. Absolute copy numbers of ITM2A, SLAMF6, and IKZF3 mRNAs and 18S rRNA were measured using our customized RT-qPCR assays. Logistic regression used to derive an equation for a combined signature score of 18S-normalized urinary cell mRNA levels of ITM2A, IKZF3, and SLAMF6 that best predicts Acute Rejection (AR= both T cell mediated rejection and antibody mediated rejection). Area under the ROC curve (AUC) was calculated to discriminate between AR and No Rejection (NR) biopsies for 18S-normalized urinary cell levels of ITM2A, IKZF3 and SLAMF6 and the composite signature score. AUCs were compared by DeLong Method. RESULTS/ANTICIPATED RESULTS: Urinary cell 18S-normalized levels of ITM2A, IKZF3, and SLAMF6 mRNAs in urine discriminated KA recipients with AR biopsies (n=95) from those with NR biopsies (n=160) (All P values <0.05, Mann-Whitney test) and the AUC was 0.69 (95% CI, 0.62 to 0.76) for ITM2A, 0.61 (95%CI, 0.53 to 0.68) for IKZF3, and 0.60 (95%CI, 0.53 to 0.68) for SLAMF6. The derived combination signature score of urinary cell 18S-normalized levels of ITM2A, IKZF3, and SLAMF6 mRNA discriminated KA recipients with AR from those with NR ($P<0.0001$, Mann Whitney test) and the combined signature score AUC was 0.72 (95%CI, 0.65 to 0.79). The combination signature score discriminated AR vs NR better than IKZF3 and SLAMF6 alone, but was not significantly different than ITM2A alone (DeLong method). (Additional results/figures to be included in poster) DISCUSSION/SIGNIFICANCE: Our RNA-seq offered a unique opportunity to diagnose AR by measuring the mRNAs in urine. We now found that urinary cell mRNA levels of ITM2A, IKZF3, SLAMF6 and the combined signature are diagnostic of AR, a major and serious post-transplant complication. This allows for much-needed KA molecular surveillance and personalization of immunosuppression.

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Genetic risk factors for drug-induced long QT syndrome: Findings from a large real-world clinical cohort.

Ana Lopez Medina[1], Alessandra M. Campos-Staffico[1], Choudhary Anwar A Chahal[2], Isabella Volkers[1], Juliet P. Jacoby[1], Mohammed Saeed[1], Omer Berenfeld[1] and Jasmine A. Luzum[1]
[1]University of Michigan, Ann Arbor, Michigan and [2]Mayo Clinic, Rochester, Minnesota; Royal Papworth Hospital, Cambridge, United Kingdom.

OBJECTIVES/GOALS: The objective of this research was to determine the associations of candidate genetic variants withdrug-induced long QT syndrome (diLQTS) risk, an adverse effect of over 150 FDA-approved drugsthat can lead to cardiac arrhythmias and sudden cardiac death. METHODS/STUDY POPULATION: This was a retrospective observational study of the genomic biobank at the University of Michigan Health System. Patients treated with a high-risk QT-prolonging drug and ECG measurements were included. The primary outcome was exaggerated prolongation of the QTc interval (i.e., >60 ms change from baseline and/or >500 ms absolute value) corrected using Bazett. We analyzed 3 genetic variants: KCNE1-D85N (rs1805128), SCN5A-G615E (rs12720452) and KCNE2-I57T (rs7415448) in the dominant genetic model. A Bonferroni-corrected p-value of 0.017 was considered statistically significant using logistic regression adjusted for clinical covariates. RESULTS/ANTICIPATED RESULTS: In total 6,083 self-reported white patients were included (12% event rate). The adjusted odd ratio for KCNE1-D85N was 2.24 (95%CI: 1.35-3.57; p=0.0011). The adjusted odds ratio forKCNE2-I57T was 1.40 (95%CI: 0.26-5.78, p=0.662). Only 4 total patients carried the SCN5A-G615E variant, and none of the carriers had prolonged QTc. DISCUSSION/SIGNIFICANCE: This is the largest study of candidate genetic variants in cardiac ion channels associated with the diLQTS risk. KCNE1-D85N was associated with diLQTS risk, while KCNE2-I57T was suggestive of a potential association. KCNE1-D85N should be considered in clinical guidelines as a risk factor of diLQTS.

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Evaluating the therapeutic efficacy of combination IL-12 and trabectedin for the treatment of triple negative breast cancer

Emily Schwarz[1], Himanshu Savardekar[1], Sara Zelinskas[1], Abigail Mouse[1], Lianbo Yu[1], Gregory Behbehani[1] and Timothy Cripe[2]
[1]The Ohio State University and [2]Nationwide Children's Hospital William E. Carson III[1]

OBJECTIVES/GOALS: IL-12 has potent immune effects but the presence of myeloid-derived suppressor cells (MDSC) can inhibit IL-12-induced NK cell cytotoxicity. Thus, we hypothesized that combining IL-12 with trabectedin, an immunosuppressive myeloid cell

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