

optogenetics in treating such severe arrhythmias. RESULTS/ANTICIPATED RESULTS: Immunostaining shows 87.339% of iPSC-CMs, treated with All-trans retinoic acid (RA) (1 μ M) 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 β II-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 β II-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

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OBJECTIVES/GOALS: RNA-seq of urine and kidney allograft biopsies (bx) found that urinary cell immune landscape reflects intra-graft 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.

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OBJECTIVES/GOALS: The objective of this research was to determine the associations of candidate genetic variants with drug-induced long QT syndrome (diLQTS) risk, an adverse effect of over 150 FDA-approved drugs that 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 for KCNE2-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

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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