Comparative Analysis of Human iPSC-derived Cardiomyocytes in Diversity and Disease Modeling

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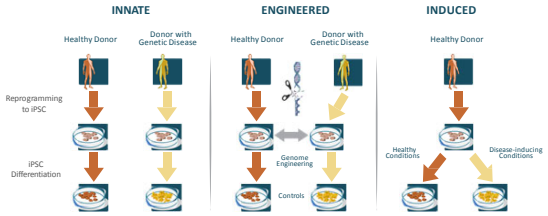
Abstract

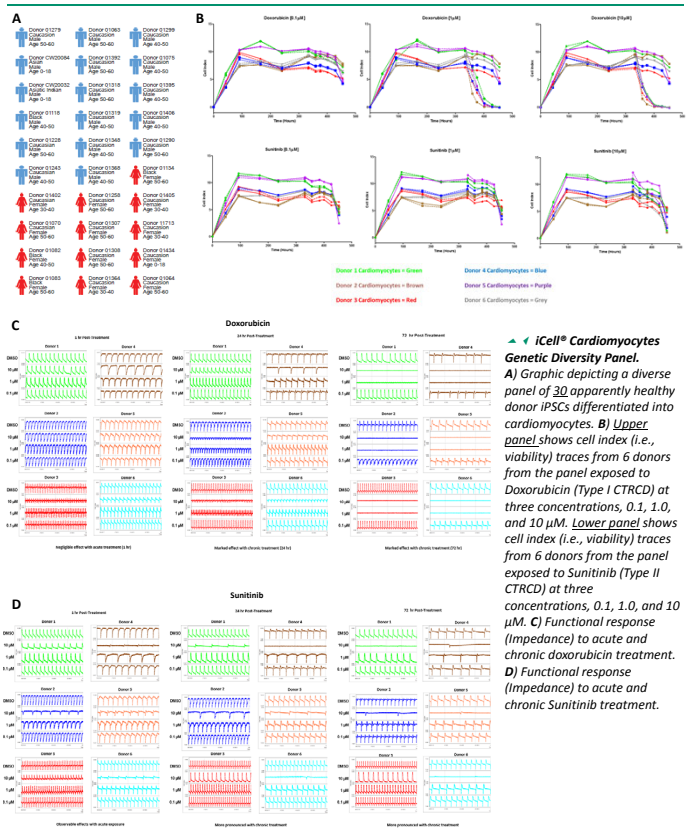
Human cell types differentiated from induced pluripotent stem cells (hiPSC) offer a unique access to human cellular material for safety and toxicity screening. Here, we present data demonstrating the utility of hiPSC-derived cardiomyocytes (hiPSC-CMs) in safety assessment and disease modeling. We include a comparative assessment of cancer therapeutics-related cardiac dysfunction (CTRCD) compounds doxorubicin (type I) and sunitinib (type II) across hiPSC-CMs derived from 6 healthy donors (DIV 14) at three concentrations [0.1, 1.0, and 10 µM]. Clinically Type I CTRCD may be associated with cellular death, structural changes, and permanent damage while Type II CTRCD may be associated with cellular dysfunction, no structural changes, and reversible damage. Here we were able to identify both type I and type II CTRCD using a selected in-vitro cohort of hiPSC-CMs. These data provide additional insight into sensitivities to cancer therapeutics across different donors. We then examined basic characterization data from several hiPSC-CM disease models including hypertrophic cardiomyopathy MYH7 (R403Q), LMNA-related dilated cardiomyopathy LMNA (L35P), and Brugada syndrome (BrS) type 3 CACNA1C (G490R) each with its respective isogenic control at DIV 14. We further identify the functional consequences of each mutation and demonstrate that each model recapitulates classical hallmarks of the disease phenotype. These data illustrate how hiPSC-CMs provide an excellent model system for assessing compound effects across multiple donors and disease models. Taken together, these examples should help to create new avenues for safety liability assessment and toxicology studies, as well as serve as a template for future opportunities in disease modeling with hiPSC-CMs.

Healthy and Diseased Cardiomyocytes for Basic Research and Toxicity Testing



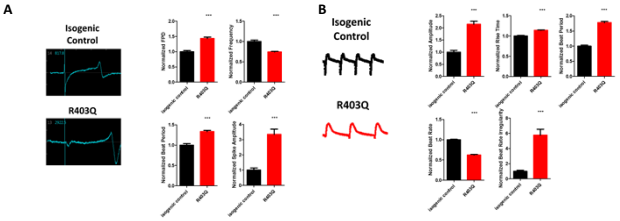
▲ ***Diversity and Disease Modeling Approaches.*** *Graphic depicting three primary disease modeling approaches: i) Innate modeling where a sample is taken from a healthy or diseased donor; ii) Engineered modeling using genome engineering strategies to introduce or correct a mutation; and iii) Induced modeling where cells are exposed to disease causing conditions (e.g., ET-1).*

iPSC-derived Genetic Diversity Cardiomyocyte Panel



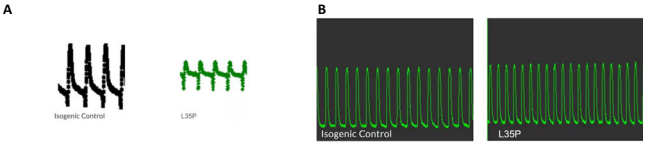
▲ ***iCell® Cardiomyocytes Genetic Diversity Panel.*** ***A)*** *Graphic depicting a diverse panel of 30 apparently healthy donor iPSCs differentiated into cardiomyocytes.* ***B)*** *Upper panel shows cell index (i.e., viability) traces from 6 donors from the panel exposed to Doxorubicin (Type I CTRCD) at three concentrations, 0.1, 1.0, and 10 µM. Lower panel shows cell index (i.e., viability) traces from 6 donors from the panel exposed to Sunitinib (Type II CTRCD) at three concentrations, 0.1, 1.0, and 10 µM.* ***C)*** *Functional response (Impedance) to acute and chronic doxorubicin treatment.* ***D)*** *Functional response (Impedance) to acute and chronic Sunitinib treatment.*

HCM *MYH7* R403Q iPSC-derived Cardiomyocytes Display Increased Contractile Properties



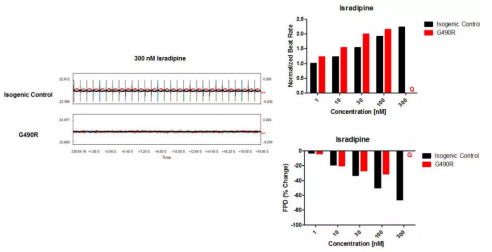
▲ ***HCM Baseline Characterization.*** ***A)*** *Electrophysiological analysis: HCM Cardiomyocytes (R403Q) display abnormal electrophysiological properties in multi-electrode array (MEA) analysis, including field potential (FDP) prolongation, slowed spontaneous beat rate, and increased spike amplitude.* ***B)*** *Contractility measurements (Impedance): HCM Cardiomyocytes (R403Q) display enhanced contraction and increased arrhythmic events compared to the isogenic control.* *P<0.05 (DIV 14)*

DCM *LMNA* L35P iPSC-derived Cardiomyocytes Exhibit Reduced Contractile Properties



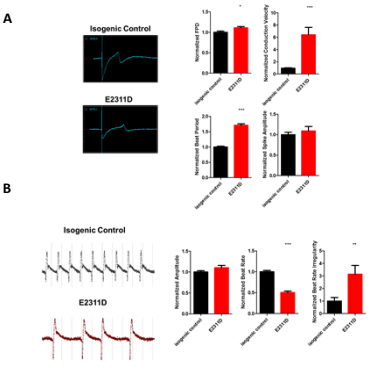
▲ ***DCM Baseline Characterization.*** ***A)*** *Contractility Measurements (Impedance): DCM Cardiomyocytes (L35P) display reduced contraction amplitude relative to isogenic control.* ***B)*** *Calcium Handling Assessment: Representative calcium transients reveal that DCM Cardiomyocytes (L35P) display increase beat rate relative to isogenic control. (DIV 14)*

BrS *CACNA1C* G490R iPSC-derived Cardiomyocytes Exhibit Increased Sensitivity to Calcium Block



▼ ***Pharmacological Response to L-type Calcium Channel Antagonist.*** *Contractility and electrophysiology measurements: BrS3 Cardiomyocytes (G490R) display increased sensitivity to a calcium channel block compared to the isogenic control. (DIV 14, 30 minutes after treatment) Q = quiescence.*

CPVT *RYR2* E2311D iPSC-derived Cardiomyocytes Display Reduced Beat Rate *in vitro*



▼ ***CPVT Baseline Characterization.*** ***A)*** *Electrophysiological analysis: CPVT Cardiomyocytes (E2311D) display abnormal electrophysiological properties in multi-electrode array (MEA) analysis, including field potential (FDP) prolongation, increased beat period, and increased conduction velocity relative to isogenic control.* ***B)*** *Contractility measurements (Impedance): Contractility was monitored by measuring impedance over time. CPVT Cardiomyocytes (E2311D) display comparable contraction amplitude, reduced beat rate, and increased beat rate irregularity relative to isogenic control.* *P<0.05 (DIV 14)*

Conclusion

Human iPSC-CMs from apparently normal and disease donor backgrounds can be used to develop models for clinical trials-in-a-dish and disease-in-a-dish enabling researchers to investigate novel mechanisms and therapies. Here we demonstrate:

- Patient-derived hiPSC-CMs recapitulate innate disease pathophysiology.
- Genome engineering strategies in hiPSCs enable the correction of the disease specific mutations, thus creating an isogenic control.
- Induced and inherited diseased models display clinically relevant structural and functional features in the dish.

These results demonstrate convenient, novel human cell models for cardiovascular research supporting hiPSC technology as a platform capable of generating cardiomyocytes from healthy and disease relevant genetic backgrounds.