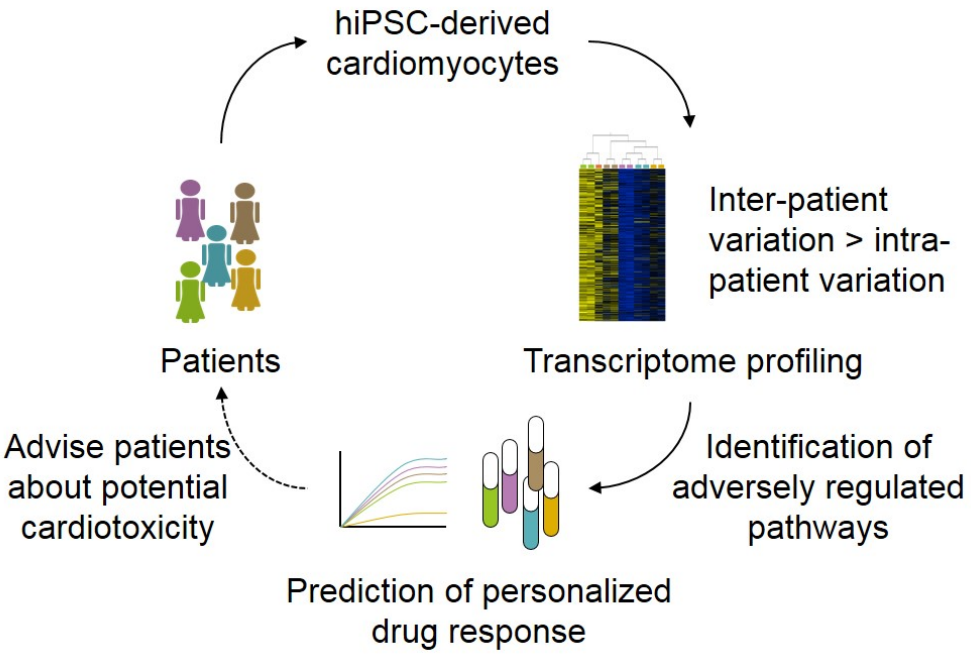
Transcriptomic Analysis of Inter- and Intra-patient Variation in Human iPSCs: Platform for Precision Medicine to Predict Drug Toxicity

Elena Matsa, Paul W Burridge, Kun-Hsing Yu, Haodi Wu, Vittavat Termglinchan, Chun Liu, Praveen Shukla, Nazish Sayed, Ioannis Karakikes, Michael P Snyder, Joseph C Wu, Stanford Univ Sch of Med, Stanford, CA

Rapid improvements in human induced pluripotent stem cell (hiPSC) differentiation methodologies have allowed previously unattainable access to high-purity, patient-specific cardiomyocytes (CMs) for use in disease modeling, cardiac regeneration, and drug testing. In the present study, we investigate the ability of hiPSC-derived cardiomyocytes (hiPSC-CMs) to reflect the donor's genetic identity and serve as preclinical functional readout platforms for precision medicine. We used footprint-free Sendai virus to create two separate hiPSC clones from the fibroblasts of five different individuals lacking known mutations associated with cardiovascular disease. Whole genome expression profiling of hiPSC-CMs showed that inter-patient variation was greater than intra-patient variation, thereby verifying that reprogramming and cardiac differentiation technologies can preserve patient-specific gene expression signatures. Gene ontologies (GOs) accounting for inter-patient variation were mostly metabolic or epigenetic. Toxicology analysis based on gene expression profiles predicted patient-specific susceptibility of hiPSC-CMs to cardiotoxicity, and functional assays using drugs targeting key regulators in pathways predicted to produce cardiotoxicity showed inter-patient differential responses in hiPSC-CMs. Our data suggest that hiPSC-CMs can be used *in vitro* to predict and help prevent patient-specific drug-induced cardiotoxicity, potentially enabling personalized patient consultation in the future.



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