Patient-specific induced pluripotent stems as a platform for precision therapeutics in the treatment of an inherited cardiac arrhythmia

Thomas Comollo, Thomas Hof, Divya Kesters, Kevin Sampson and Robert S. Kass
Department of Pharmacology
Columbia University
New York, NY 10032

Understanding the genetic basis for differential responses to drug therapies is a key goal of precision medicine. Induced pluripotent stem cells (iPSCs) offer a unique system to investigate the pharmacology of disease processes in therapeutically and genetically relevant primary cell types *in vitro*. Here we report the use of patient derived iPSCs to understand limitations of clinical regimes that have been used with mixed success to treat patients carrying mutation in the SCN5A gene that cause different forms of Long QT Syndrome Variant 3 (LQT3). We studied cardiomyocytes differentiated from iPSCs derived from patients carrying the F1473C mutation the ΔKPQ mutation, and the E1784K mutation. In the case of the F147C mutation, we found that mexiletine, applied at a moderate dose, but under conditions of elevated heart rate, was an effective therapeutic regimen to control cardiac arrhythmias in a long QT Syndrome patient who was found to have a de novo *SCN5A* LQT-3 mutation and a polymorphism in *KCNH2*, the gene for LQT2. Analysis of iPSCs derived from patients with ΔKPQ and E1784K mutations revealed that the beta blocker isoproterenol preferentially inhibited late sodium channel activity in cells expressing both mutants, but not all cells, and hence patients, had the same off target inhibition of hERG channels, revealing distinct patient-specific therapeutic approaches to management of LQT3. The work confirms the utility of iPSc-derived myocytes in developing precise patient-specific clinical regimens.