A Human Cardiomyocyte-Based Platform for the Profiling of Positive Inotropes with Potential to Treat Heart Failure

Najah Abi-Gerges, Tim Indersmitten, Ky Truong, William Nguyen, Nathalie Nguyen, Guy Page, Paul E Miller and Andre Ghetti

AnaBios Corp., San Diego, CA 92109, USA

Contact email: Najah.abi-gerges@anabios.com

Introduction and Methods

Heart failure remains a major unmet medical need. From a therapy development standpoint, a key challenge originates from the lack of a relevant model to aid the selection of the best candidates for clinical development. Over the last few years, we have focused on the development of strategies and tools to bridge the translational gap by enabling large scale utilization of human primary cells and tissues. Access to cardiac tissue and cardiomyocytes from healthy as well as heart failure hearts, obtained from organ donors, allows for functional, biochemical, and omics-based investigation of the pathophysiology to a level unattainable in the past. To facilitate the identification of molecules with the most desirable efficacy profile, we developed a human cardiomyocyte contractility assay for the identification of positive inotropes with potential to correct contractility deficit in heart failure. Adult human primary ventricular cardiomyocytes isolated from ethically consented donor’s hearts were used to measure fractional sarcomere shortening induced by field-simulation and recorded using the IonOptix system. The stability of sarcomere shortening was assessed by continuous recording for 2 min. in Tyrode’s solution with control vehicle (0.1% DMSO). The test articles were applied for a maximum of 250 s period or when a stead-state effect was achieved. Four ascending concentrations were tested. We modulated excitation-contraction coupling with a panel of well-characterized inotropes (17 positives and 8 negatives) with diverse mechanisms of action.

Identification of drug-induced positive inotropic effects

Concentration-Effect curves

Differentiation of drugs operating via distinct mechanisms

Heatmap generated from 2nd concentration data

Heatmap generated from 4th concentration data

Panel of inotropes with diverse mechanisms of action

Contractility transient parameters

Summary

The adult human primary cardiomyocyte-based platform:

1. Can identify inotropic potential of molecules and enable the classification of inotropes in a mechanism-related mode
2. Will facilitate the identification of molecules with the most desirable pharmacological profile for the correction of forms of contractility deficit
3. Scalable, efficient and predictive