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Integrating adult human primary cardiomyocytes into early cardiac safety assessment

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Drug-induced pro-arrhythmia and/or changes in contractility can limit the utility of potential novel therapeutics. Since abnormal ventricular repolarization can cause not only electrical disorders, but also affect the heart's contractile function, we developed a new model based on adult human primary cardiomyocytes to provide a preclinical tool for the simultaneous prediction of drug-induced inotropic and pro-arrhythmia risks. We recorded fractional sarcomere shortening (SS) using a digital, cell geometry measurement system (IonOptix™) and then record changes in the contractility transients to infer both inotropic (SS) as well as pro-arrhythmia risk (aftercontraction). Validation data were generated with 38 clinically well characterized controls: 23 torsadogenic and 10 non-torsadogenic drugs, and 5 positive inotropes. When the assessment of pro-arrhythmia risk was based on effects observed at 10x of the free effective therapeutic plasma concentration, human cardiomyocyte-based model had excellent assay 96% sensitivity and 100% specificity. Human cardiomyocytes also identified drugs associated with negative and positive inotropic effects. Moreover, positive inotrope-induced changes in contractility parameters illustrated the potential for finger-printing different mechanisms of action. Thus, human cardiomyocytes can simultaneously predict risks associated with pro-arrhythmia and inotropic activity. This approach enables the generation of predictive preclinical human-based cardiotoxicity data and appears to be more predictive than the stem cell-derived cardiomyocyte models.

Recent Publications

1. Nguyen N et al. (2017) Adult human primary cardiomyocyte-based model for the simultaneous prediction of drug-induced inotropic and pro-arrhythmia risk. Frontiers in Physiology. 8:1073. Doi: 10.3389/fphys.2017.01073.

Biography

Najah Abi Gerges, PhD, is the Vice President of Research and Development at AnaBios Corporation, USA. He holds a PhD in Cardiac Physiology from Paris XI University, France. Prior to joining AnaBios, he was involved in drug discovery programs at AstraZeneca. With over 17 years in the pharmaceutical industry, he is an innovative Leader, having made substantial contributions to drug approvals (Tagrisso®), research across several areas of cardiac physiology and pharmacology resulting in over 40 published articles, and novel paradigms to advance cardiovascular translational science. He is the Editor for the Journal of Pharmacological and Toxicological Methods, Vice President Elect for Southern California Chapter of the Society of Toxicology. His interest lies in drug discovery and development.

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