Novel 3D Primary Human Cardiomyocyte Culture System for Evaluation of Candidate Drug Related Cardiac Safety Profile

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Drug discovery and development are hampered by high attrition rates that are largely attributed to the reliance on model systems that are minimally representative of the underlying human biology. Although the animal models are a good overall proof of concept, safety and efficacy evaluations in such models are hard to extrapolate to the human situation. Thus, there is an urgent need for high-throughput human *in-vitro* cell based assay systems to predict safety profile of drugs for cardiac related ailments prior to clinical evaluation. Such human *in vitro* culture systems can be utilized in mechanism-based assays for cardiotoxicity assessment. It is becoming increasingly apparent that human primary cardiomyocytes can serve as the biological and physiological relevant *in-vitro* model system for drug discovery/ cardiotoxicity screens. In this study we screened 10 potential newly synthesized small molecules:CEP2001,2002,2003,2004,2005,2006,2007,2008,2009 and 2010. These molecules were screened for their toxicity and electro-physiological activities in a 3D cardiac cell based assay. Of the 10 molecules that were screened, we found CEP2005 & CEP2010 to enhance the electro-physiological activity when compared to the untreated controls. The IC_{50} values for CEP2005 are 5ng /ml and CEP2010 25 ng /ml determined from 3D cardiac model system. The newly synthesized compound CEP2005, when tested *in-vivo* system, demonstrated an increased heart rate in mice 20% from baseline measurements. When compared to the control group both compounds showed 15-20% increase of heart rates. From the above experiments we can conclude that we were able to screen two new compounds with the 3D culture system and determine their IC_{50} values prior to screening those further *in-vivo* systems. The results obtained from 3D culture system of new compounds were simultaneously tested with proper controls to validate the system. The following known drugs: Verapamil, Sotalol, Nicorandil, and Nilvadlpine were tested in our 3D cardiac and the electro-physiology measurement systems as positive control. Additional studies are ongoing to determine the mechanism of action for these newly synthesized compounds.