New cell-based system can screen drug candidates for cardiac toxicity long before they leave lab

December 17 2012

A new stem cell-derived system for screening experimental drugs for cardiotoxicity could identify dangerous side effects early in the development process, thereby potentially saving time, lives and money, according to Evan F. Cromwell, PhD, of Molecular Devices, LLC, Sunnyvale, CA, in a presentation at the American Society for Cell Biology's Annual Meeting, Dec 17 in San Francisco.

Vioxx is probably the most notorious example of a blockbuster drug removed from the market after FDA approval because of adverse cardiac side effects, Dr. Cromwell explained, but it was not the only drug to fail because of unexpected negative effects on the heart.

Cardiotoxicity remains one of the primary reasons new drugs wash out in preclinical or even full clinical trials, he said. There is often a huge cost for these failures, both to the pharmaceutical companies whose long-term investments can be wiped out in a single study and to consumers who face the risk of unintended harm.

Currently cardiotoxicity is detected using electrophysiology-based assays for interactions of compounds with potassium ion channels. However, available assays are not effective at assessing potential adverse interactions with other biochemical or contractile processes.

The need for better cardiotoxicity assays more predictive of myocardial

performance led Dr. Cromwell, Oksana Sirenko, PhD, and colleagues at the California biotech, Molecular Devices, to develop an in vitro system that employs stem cell-derived cardiomyocytes to screen for potential adverse cardiac effects.

Stem cell-derived cardiomyocytes are especially suitable for an in vitro system, Dr. Cromwell explains, because they express ion channels vital for the cardiomyocytes' function and demonstrate spontaneous mechanical and electrical activity similar to that of native cardiac cells. When these cultured cardiomyocytes form a confluent layer and reach sufficient maturity, they begin to contract spontaneously. The team then employs a fast kinetic fluorescence imaging method to monitor fluctuations in intracellular calcium ion (Ca2+) levels during contractions. This provides a direct assessment of Ca2+ handling with surrogate assessments of electrophysiological activity in the muscle cell membrane and beat rate.

Phenotypic deviations from normal contractions that can be measured in the improved assay include beat rate, peak width and pattern irregularities. This multiparametric characterization of a compound's perturbation of cardiomyocyte contractions can also yield insights into mechanisms of action (MOA).

Dr. Cromwell reports, "We have characterized numerous pharmacological compounds and detected concentration-dependent modulation of beating rate and atypical patterns consistent with their MOA." This assay shows great promise to exclude preclinical candidates that have cardiotoxicity or other cardio safety issues, according to Dr. Cromwell.

More information: "Predictive assays for high throughput assessment of cardiac toxicity and drug safety," Sunday, Dec.16, 2012, 2- 3:30 pm, Session: New Technologies for Cell Biology I, presentation: 938, poster:

B1496

Provided by American Society for Cell Biology