SCIENCE FOR THE BENEFIT OF HUMANITY

A cell-free, high-throughput hERG safety assay

RU 1286

Technology Summary

The human ether-a-go-go-related gene (hERG) codes for a potassium (K^+) channel present in cardiac cells which regulate the electrical activity of the heartbeat. The hERG channel is highly susceptible to blockage by small molecule drugs and unwanted off-target inhibition of the hERG channel can cause a drug-induced lethal arrhythmia called *torsade de pointes.* Our ability to predict which drugs will block hERG is poor, therefore all compounds under drug development are screened for hERG. Several assays exist, but currently the electrophysiological method represents the gold standard technology to monitor hERG activity. However, this methodology is not amenable to high-throughput platforms and because of its high cost, the electrophysiology screen is used at a much later stage in the drug development process often after considerable investment has been made in developing a compound. Therefore, there is a need for a robust, cost-effective, high-throughput hERG assay which can be used to assess cardiac safety early on in drug development to avoid drug attrition in late phases of development or withdrawals of approved drugs because of cardiotoxicity.

Dr. MacKinnon, Dr. Zhenwei Su and colleagues have developed a new cell-free assay that enables the identification of inhibitors of hERG channel at an early stage of drug development. This assay consists of an easy to purify, engineered hERG protein that is stably reconstituted in a liposome vesicle, with a fluorescent dye which fluoresces in the absence of hydrogen (H^+) protons. The assay is carried out in a salt solution which has a gradient of K^+. Addition of the drug compound of interest causes K^+ to move out of the vesicles and H^+ to move in, bind to the fluorescent dye and quench the signal. The assay operates with an excellent signal-to-noise ratio and can be scaled up to 1536-well plates, one of the highest density formats used in screening. Thus, the high-throughput assay represents a best in class, cost-effective way to evaluate the selectivity and cardiac safety of new drugs.

Area of Application:

- Novel high-throughput method to evaluate cardiac safety of drug compounds and to screen for novel inhibitors of hERG K^+ channel.

Advantages:

- Low-cost, easy to operate, high capacity

Stage of Development: Fully developed assay

The Rockefeller University Office of Technology Transfer
502 Founders Hall
1230 York Avenue
New York, NY 10021-6399
www.rockefeller.edu/techtransfer

Lead Inventors:
Dr. Rod MacKinnon and Dr. Zhenwei Su

Patent Information:
PCT patent application filed.

References:
Zhenwei, et al 2016. Novel cell-free high-throughput screening method for pharmacological tools targeting K+ channels. PNAS Vol.113 No.20, 5748-5753.
http://www.pnas.org/content/113/20/5748.abstract

For more information please contact:

Manjula Donepudi, Ph.D. Assistant Director mdonepudi@rockefeller.edu 212-327-7091	Categories: Drug Development; Tox screening Keywords: hERG assay, cardiac safety, toxicology, high-throughput screening, K+ channels