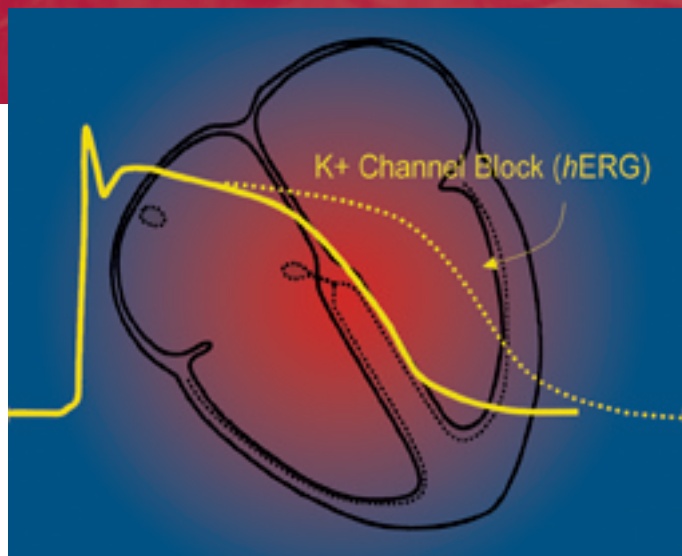


CardioTox™ Panel

For a comprehensive evaluation of cardiac toxicity with *in vivo* relevance.

This very affordable screen requires less than 5 mg of compound, provides data in 4 to 6 weeks.



Problem:

Many companies would like to improve their drug-discovery programs by incorporating toxicity information into their early evaluations of new chemical entities (NCEs). CeeTox designs panels of biochemical endpoints that provide specific information on toxicity. Adverse events in the heart are of three general types: 1) QT prolongation or ion channel effects, 2) hypertrophy, and 3) cytotoxicity.

The processes involved in the mechanical contraction and relaxation of the heart muscle are complex and controlled by ion movement. The electrophysiology of the beating heart consists of atrial depolarization (P-wave), ventricular depolarization (QRS), and ventricular repolarization (T) (depicted graphically below.) Several drugs have been shown to increase the QT interval through interference with potassium (K⁺) movement. This can lead to Torsade de Pointe, ventricular fibrillation and sudden death. Because of the serious nature of these events the FDA requires pharmaceutical companies to evaluate (NCEs) for potential QT prolongation prior to regulatory submission.

In general, cardiac hypertrophy allows the heart to maintain or increase cardiac output as a compensatory response to stress. However, a prolonged state of hypertrophy can lead to a reduction in ejection-fraction and heart failure. It is therefore important to evaluate NCEs for potential cardiac toxicity.

Cardiac specific cytotoxicity can be evaluated by monitoring compound effects on mitochondria, oxidative stress, heart cell viability, heart cell morphology, and beat rate.

Solution:

CeeTox offers a comprehensive evaluation of cardiac toxicity. The hERG channel assay is performed as a primary indicator of K⁺-channel block and QT prolongation.

To evaluate more subtle toxicity, cardiomyocytes from 7-day old rats are established in 96-well plates as primary cultures. Test compounds are added over several exposure concentrations, and the following analyses are performed:

QT-prolongation

hERG inhibition assay

Isolated Cardiomyocytes

General Cardiac Toxicity

- Membrane leakage
- Mitochondrial function
- Oxidative stress

Hypertrophy Markers (mRNA and protein)

- ANP/BNP
- Skeletal α -actin
- C-fos/C-jun

Physiology

- Percentage of beating cells
- Beat rate/30 s

