neuroservices ALLIANCE

AnaBios
Early Human Insights

CASE STUDY

Cloned Cardiac Ion Channel Data Not Predictive of Human Tissue Responses

In a recent study, the cardiac safety margin was established based on hERG, as well as voltage-gated sodium and calcium channel data. The safety margin was estimated to be more than 30-fold the expected unbound therapeutic plasma concentration.

AnaBios performed a pro-arrhythmia risk assessment in a human ex vivo cardiac action potential assay and identified the potential for serious cardiac problems at a concentration as low as the expected therapeutic level. In fact, the drug candidate was predicted to have no margin of safety. Analysis indicated the problem was most likely related to the inhibition of the inward sodium current.

By focusing on lowering sodium channel inhibitory activity, a new compound series was created and tested in the human ex vivo cardiac action potential assay. These molecules were found to have no toxic effects at 50-fold above the expected therapeutic concentration.

This case study illustrates the difficulty and complexity in measuring drug action against cardiac ion channels. Due to the frequency and voltage dependence of drug-induced inhibition, it is incredibly problematic to measure accurate IC50 values—a problem which often leads to erroneous safety margin estimates.

The use of fully-integrated physiological systems, such as adult human cardiac tissues or cardiomyocytes, provides the most effective strategy to assess ion channel-related risks.