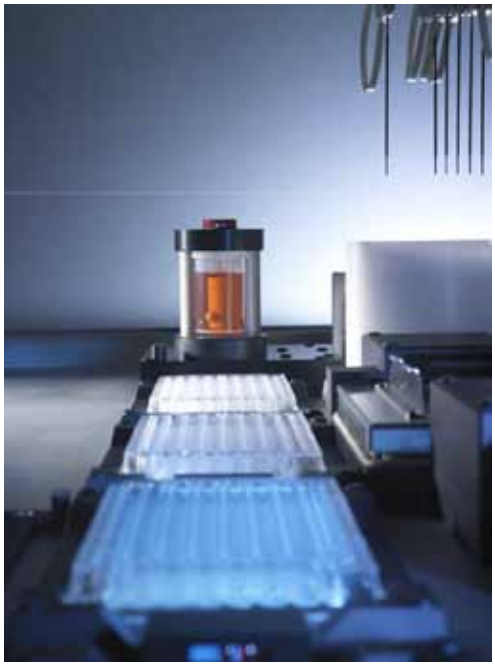
hERG Profile on QPatch

WuXi AppTec

Service Introduction

- The hERG (human Ether-a-go-go Related Gene, or KCNH2) encodes the Kv11.1 potassium ion channel responsible for the repolarizing IKr current in the cardiac action potential.
- Inhibition of hERG channel translates 70% of the time into QT interval prolongation, causing arrhythmia called torsade de pointes (TdP, malignant polymorphic tachyarrhythmia).
- Due to its unique structure, hERG is prone to be blocked by many small molecules, causing numerous marketed drugs withdrawn.
- It is important that drug candidates binding to hERG channels be screened out in the early phases of drug discovery, reducing the risks of failure at later stages of development.
- WuXi AppTec uses QPatch-HT, an automated, high-quality hERG assay platform. This system provides accurate electrophysiology data quickly at a competitive cost.



The hERG channel is unusually susceptible to blockage by drugs in comparison with other Kv channels… It is now routine practice in the pharmaceutical industry to test compounds for hERG-channel activity early in the drug-development process.

- Sanguinetti & Tristani-Firouzi (2006) Nature 440: 463-469

Assay Details

Instrument
QPatch-HT System (Sophion Inc.), 48-channel parallel recording

Assay Readout
Electric currents from voltage clamp

Cell Line
Stable CHO-K1 cells expressing the hERG channel

Test Compound Concentration
IC_{50} derived from 0.34, 1.1, 3.3, 10, 30μM (different concentrations available)
If IC_{50} <0.34μM or >30μM, the range instead of a number will be reported

Final DMSO Concentration
0.15 %

Number of Replicates
At least 3 replicates per concentration

Quality Controls
0.15 % DMSO (negative control)
Amitriptyline (positive control)
Minimum seal resistance 500 MOhms
Minimum specific hERG current (pre-compound): 0.2 nA

Compound Requirements
>30μL of 20 mM solution, or >2mg powder
>5μM aqueous solubility preferred

Results delivered
IC_{50} and % of inhibition at 30 μM
Dose-response plot
Visual inspection result if precipitation observed
Raw traces available upon request

Turnaround
<5 business days from receiving compounds

WuXi AppTec is a global leader in providing discovery, testing and manufacturing services for the pharmaceutical, biotechnology and medical device industries. Research-driven and customer-focused, with operations in China and the U.S., WuXi AppTec offers a broad and integrated portfolio of services designed to assist our customers with cost-effective and efficient outsourcing solutions.

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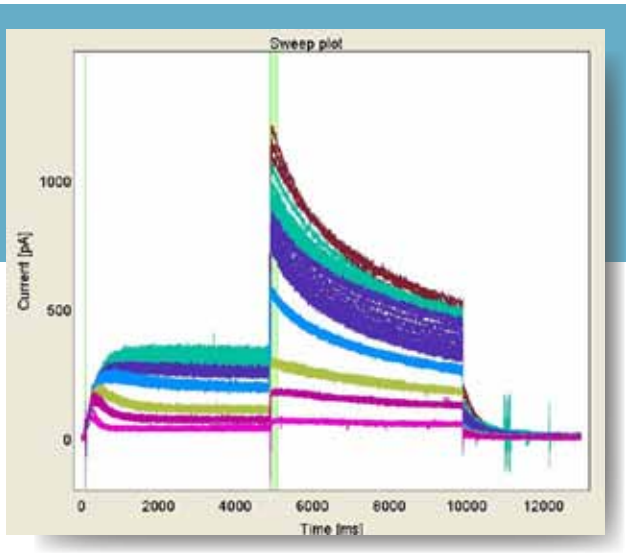


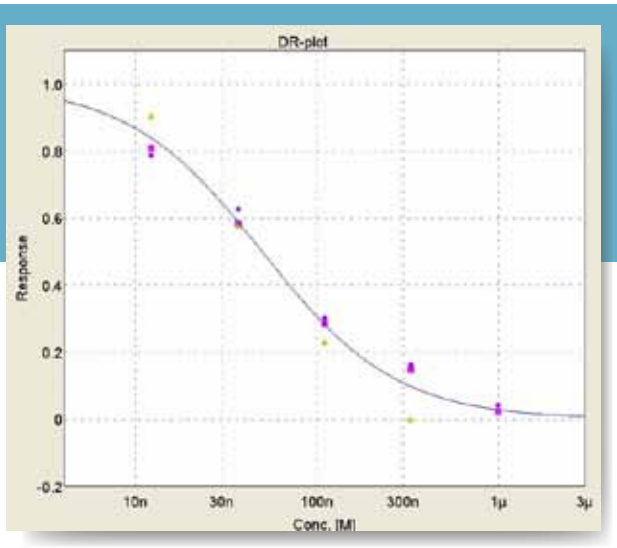
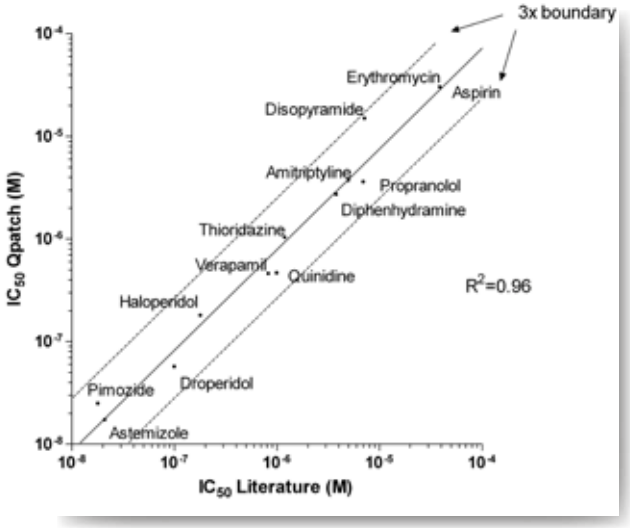


Figure 1
QPatch data with current traces and dose response

Figure 2
Comparison of QPatch and literature publications: IC_{50} plotted with 3x boundary labeled, with the correlation coefficiency of >0.9



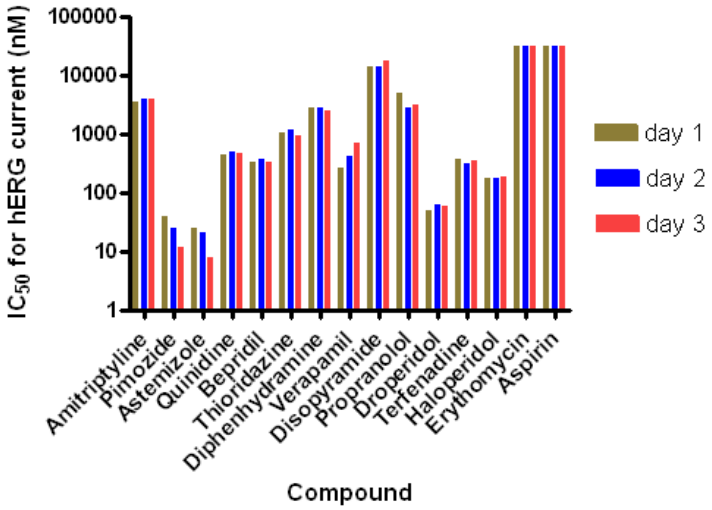


Figure 3
Robustness of QPatch Assay at WuXi AppTec: reproducibility from 3-day experiment with different cell batches

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