

# Validation of the IonWorks Barracuda System for hERG Ion Channel Assay

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## Introduction

Drug-induced inhibition of the human ether-à-go-go-related gene (hERG) ion channel has been implicated in the susceptibility of patients to potentially fatal ventricular tachyarrhythmia, torsade de pointes. In recent years, a number of FDA approved drugs were withdrawn from the market due to this reason. As a result, identification of hERG blockade represents a central task in the safety assessment of drug candidates. Over the years there has been a clear trend of implementing hERG screening in early stages of drug discovery and development. Among all existing automated electrophysiology systems for hERG screening, the IonWorks® Quattro Automated Patch Clamp System had the highest throughput and lowest data point cost. However, the throughput (~400 data points per hour) is too low for primary screening of large compound libraries.

To address the unmet need for a higher-throughput, low data point cost electrophysiology system for ion channel screening, we built on the success of the IonWorks Quattro System and developed the IonWorks Barracuda™ Automated Patch Clamp System which features a 384-well consumable and the ability to record from all 384-wells in parallel. A typical assay with one compound addition per well can be completed in as little as 20 minutes. This provides the IonWorks Barracuda System with an unsurpassed throughput of > 1,100 data point per hour, for measuring both ligand- and voltage-gated ion channels. By using the same perforated patch-clamp technology and consumable substrate as the IonWorks Quattro System, assays can easily be transferred to the IonWorks Barracuda System from the IonWorks Quattro System. To validate this point, we report a pharmacological assay of hERG channel blockers on the IonWorks Barracuda System using the same experimental conditions as previously applied on the IonWorks Quattro System.

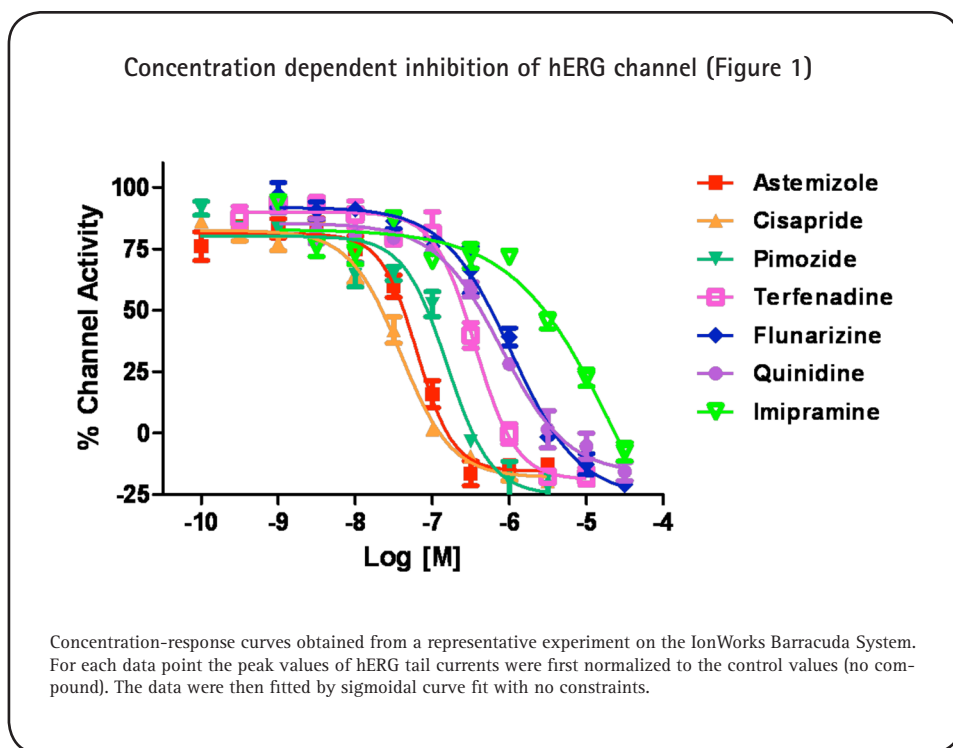
## Methods and Results

Chinese hamster ovary (CHO) cells stably transfected with human  $K_v$ 11.1 channel were provided by ChanTest® Corporation (Cleveland, OH). All compounds used in this study were obtained from Sigma-Aldrich.

### **hERG pharmacology are comparable between the two IonWorks Systems**

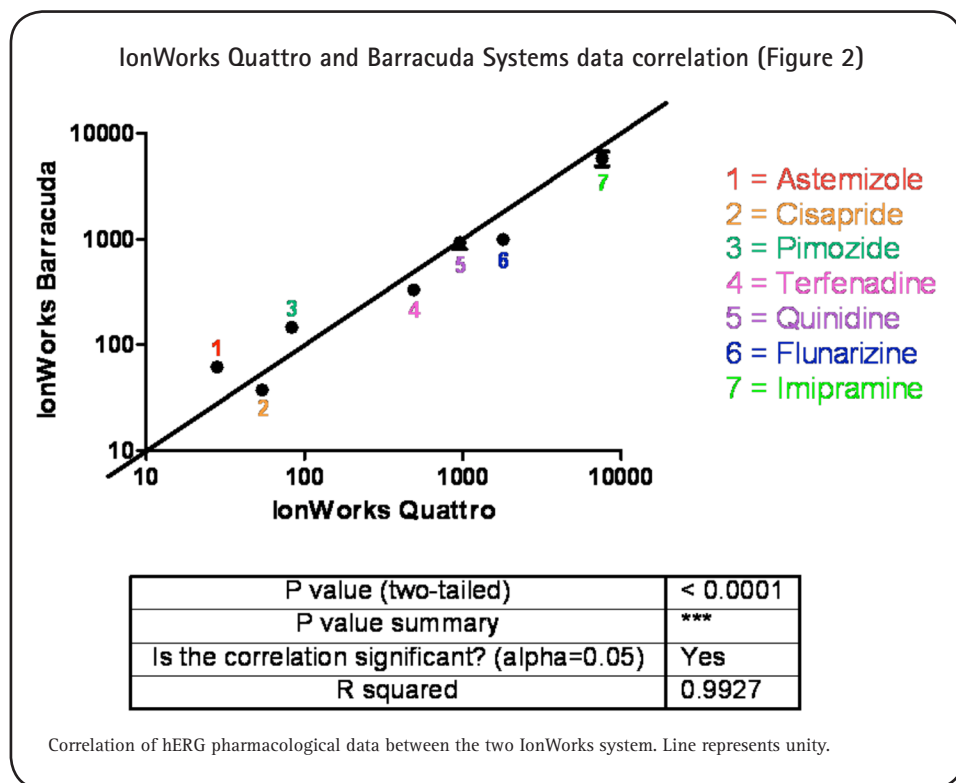
In 2005, Shawn Handran *et al.* published a hERG pharmacological assay using the IonWorks Quattro System.<sup>1</sup> Our goal was to investigate whether the assay can be easily transferred to the IonWorks Barracuda System, while producing the same pharmacological results.

To achieve this, we chose the same set of reference compounds and analyzed their pharmacological profiles under the same optimized conditions described (solution pair, voltage protocol, compound preparation and cell density). Eight replicates of the experiments were performed on the IonWorks Barracuda System; and the concentration-response relationships for all compounds were measured (Figure 1.)



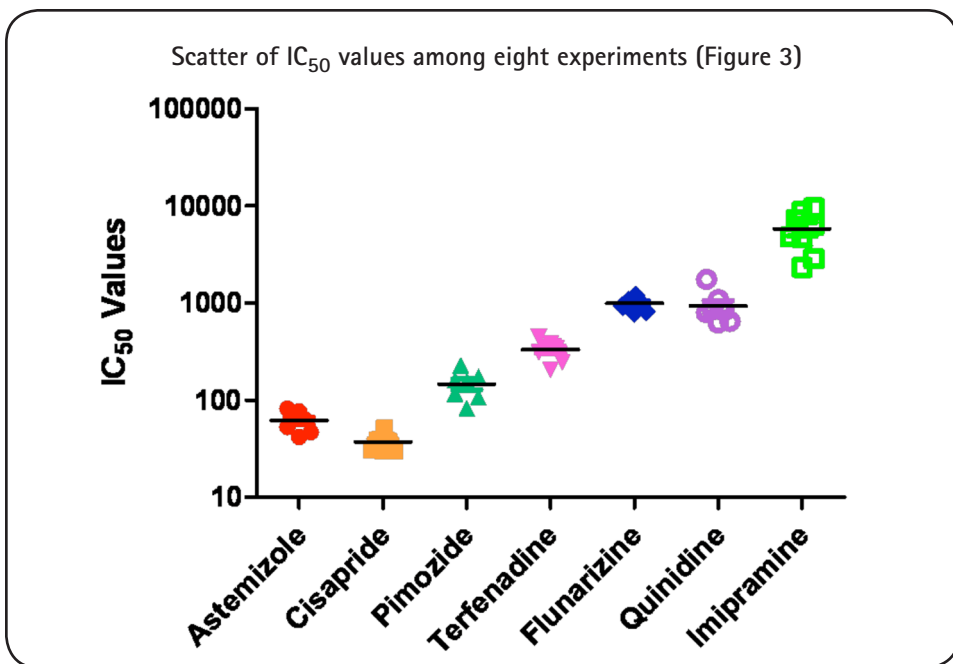
The  $IC_{50}$  values obtained from each of the eight experiments were averaged and summarized in Table 1. When compared to those obtained from the IonWorks Quattro System, the  $IC_{50}$  values for each compound are in good agreement. The correlation plot (Figure 2) also confirms a strong agreement of data collected from the two IonWorks Systems.

	IonWorks Quattro (nM)	IonWorks Barracuda (nM)	Fold difference
Astemizole	28	62	2.2
Cisapride	54	37	0.69
Pimozide	83	147	1.8
Terfenadine	490	332	0.68
Flunarizine	1800	1000	0.56
Quinidine	960	934	0.97
Imipramine	7600	5842	0.77



### Pharmacology assays on the IonWorks Barracuda System are highly reproducible

As an indication of the assay robustness, the pharmacology values obtained from 8 replicates of the experiment were compared for experiment-to-experiment variation. As shown in Figure 3, the IC<sub>50</sub> values for all compounds display excellent consistency among eight experiments, indicating this hERG assay on the IonWorks Barracuda System is highly reproducible.



## Summary

The data presented here demonstrates the applicability of using the IonWorks Barracuda System for a hERG pharmacological assay. The direct transfer of a pre-validated hERG assay from the IonWorks Quattro System to the IonWorks Barracuda System saves valuable time and yields comparable results. In addition, since the throughput of the IonWorks Barracuda System is three times higher, the same assays will take less time than the IonWorks Quattro.

In summary, the high-throughput, low running-cost and consistent pharmacology of the IonWorks Barracuda System makes it an ideal solution for primary hERG screening in early drug development.

## References

Shawn Handran, Andrew Wittel, James Costantin and Naibo Yang (2005) Optimal assay conditions for hERG pharmacology studies using the IonWorks Quattro system. *Molecular Devices IonWorks Quattro Application Note #1*



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