CiPA Ion Channel Panel

Background

As it is anticipated that nonclinical ion channel data will play an important role for regulatory decision-making in drug development programs, standardized protocols, methods for data quality assessment, and data analysis plans to quantify drug effects are recommended. The following contains detailed voltage protocol recommendations for hERG, Cav1.2, and Nav1.5 ion channel studies using patch clamp method to support an evaluation of torsade de pointes risk using the Comprehensive in vitro Proarrhythmia Assay (CiPA).

Assay specifics

- Compound profiling against the voltage-gated potassium channel hERG, calcium channel Cav1.2, sodium channel Nav1.5 and slow Nav1.5 to evaluate potential cardiac liability
- Manual Patch Clamp with a chamber temperature of 35C°
- Standardized test protocols from CiPA IC cardiac safety guidelines
- Positive control and vehicle control in every assay
- Three concentration profiling and full concentration response curves (15 pt. curves; n=3 cells)
- This assay is performed by PharmaCore Labs who specialize on cardiac safety assessment of preclinical drug candidates

hERG current traces and IC50 of blocking effects by dofetilide with standardized experiment protocol

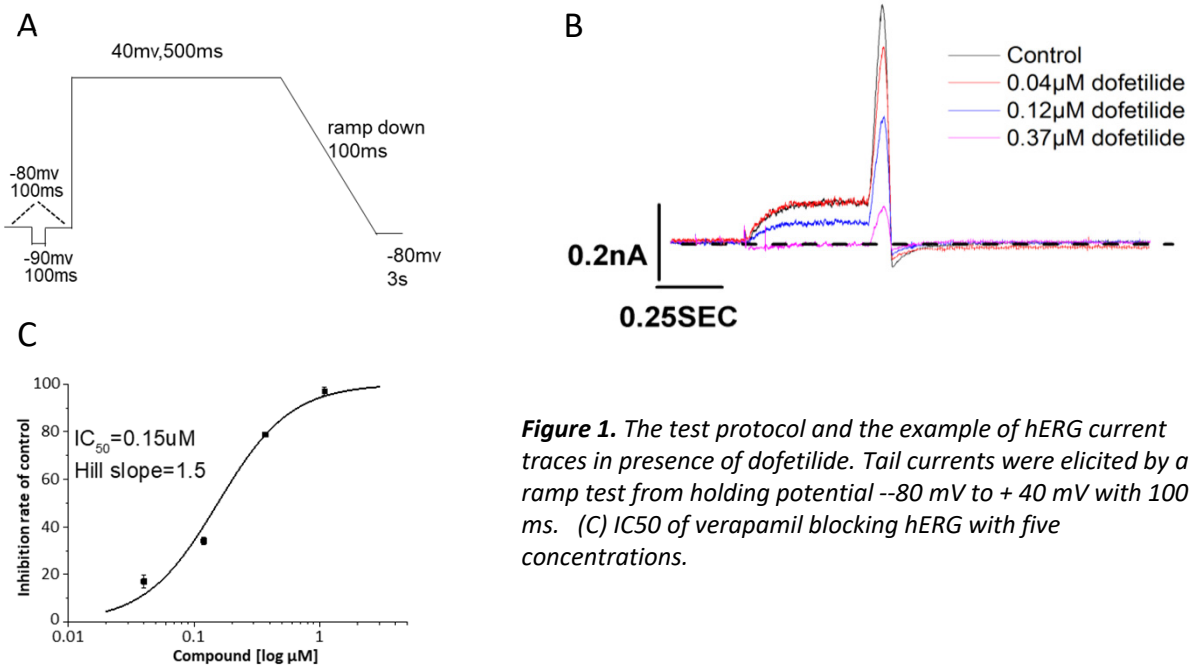
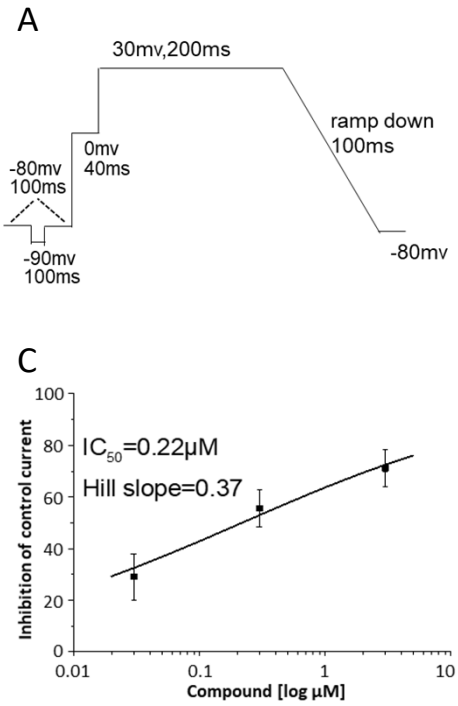


Figure 1. *The test protocol and the example of hERG current traces in presence of dofetilide. Tail currents were elicited by a ramp test from holding potential --80 mV to + 40 mV with 100 ms. (C) IC50 of verapamil blocking hERG with five concentrations.*

➢ Cav1.2 current traces and IC50 of blocking effects by verapamil with standardized experiment protocol



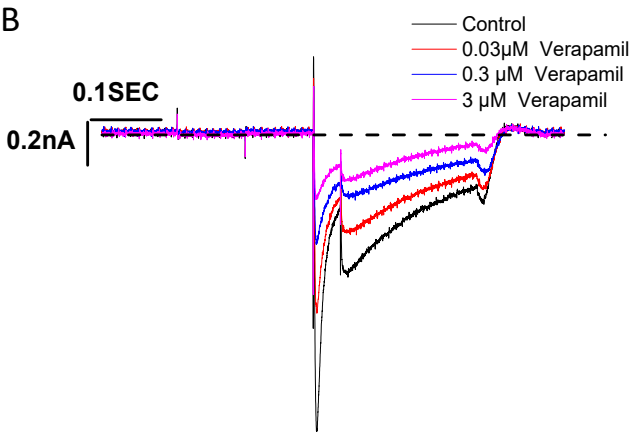
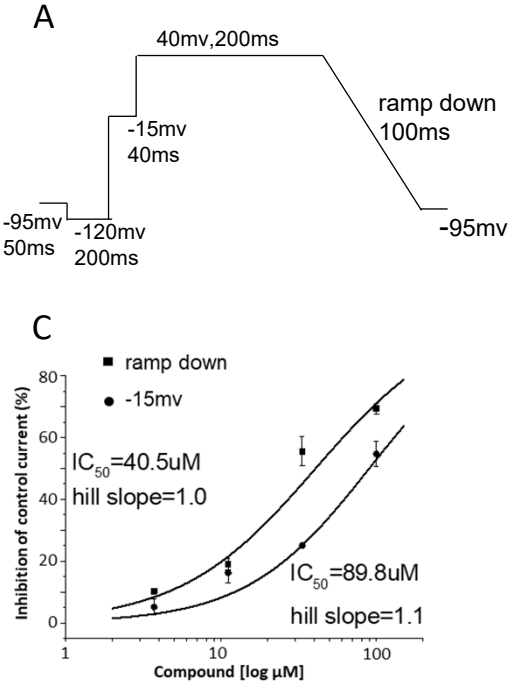


Figure 2. *The test protocol and the example of Cav1.2 current traces in presence of verapamil. Depolarization and tail currents were elicited by the protocol shown in A. (C) IC50 of verapamil blocking Cav1.2 with three concentrations.*

➢ Slow Nav1.5 current traces and IC50 of block effect by ranolazine with standardized experiment protocol



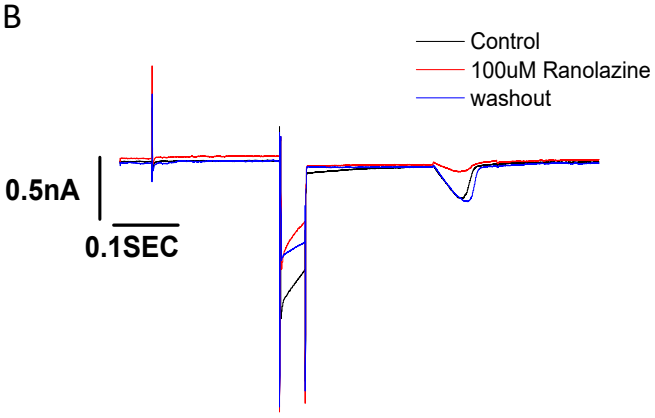


Figure 3*. The test protocol and the example of Nav1.5 current traces in presence of ranolazine. Slow Nav1.5 current was induced by ATX II. Both fast and slow Nav1.5 were elicited by a standardized protocol shown in A. (C) IC50 of ranolazine blocking slow Nav1.5 with five concentrations.*