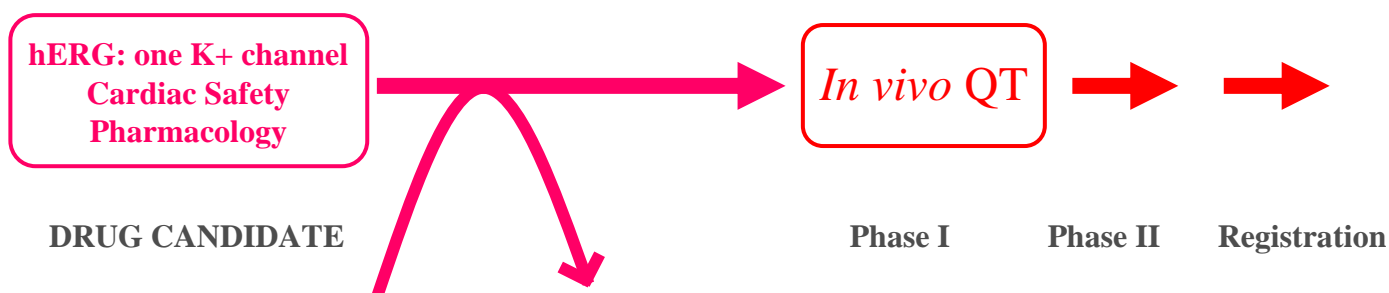




PhysioStim's letter

ACTION POTENTIAL RECORDINGS: FOLLOW UP STUDIES, WHY?



ACTION POTENTIAL RECORDINGS: NECESSARY to perform the optimum candidate selection to avoid **FALSE POSITIVE** in Phase I and is an **INTEGRATIVE MODEL** with all ionic cardiac channels represented.

↪ **hERG Channel blockade is not necessarily pro-arrhythmic**

Ranolazine $IC_{50} = 106 \mu M$

Tolterodine $IC_{50} = 17 nM$

Verapamil $IC_{50} = 143 nM$

The delay in cardiac repolarisation mediated by hERG blockade can be mitigated, and even cancelled by concurrent blockade of I_{Ca} (tolterodine, verapamil) and/or late I_{Na} (ranolazine).

IF COMPOUNDS HAVE MULTI-CHANNEL EFFECTS, *IN VITRO* PRO-ARRHYTHMIA ASSAYS ARE USEFULLY PERFORMED BEFORE THE *IN VIVO* ASSAYS.

↪ For example, well-known drugs withdrawn from the market for TdP:

DRUG	CLASS	DATE
Terfenadine	Antihistamine	02/1998
Astemizole	Antishistamine	06/1999
Grepafloxacin	Antibiotic	11/1999
Cisapride	GI Prokinetic	07/2000
Clobutinol	Cough suppressant	08/2007

ALL CLASSES OF DRUGS ARE CONCERNED BY QT PROLONGATION and not only CARDIOVASCULAR DRUGS

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