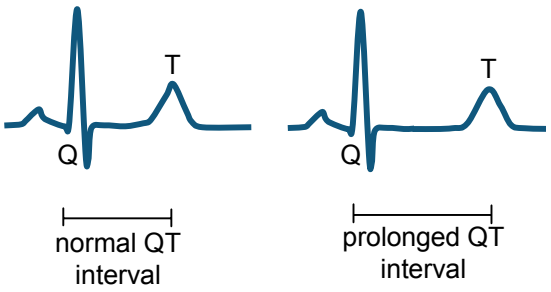
# Drug-induced arrhythmia and the potassium channel hERG

**QT interval prolongation and drug-induced arrhythmias.**

During the last decade, drug-induced arrhythmias have been a major cause of serious adverse events and have resulted in the withdrawal of many drugs from the market[1,2]. These incidents result from drug-induced delay of the cardiac repolarization. A delay in cardiac repolarization creates an electrophysiological environment that favors the development of cardiac arrhythmias. A delay in ventricular repolarization can be measured as prolongation of the interval between Q and T waves on the electrocardiogram (ECG) (normal interval is typically < 440 ms).




**Cardiac potassium channel hERG**

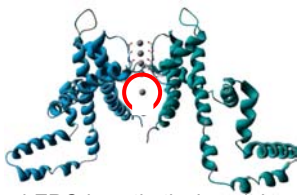
While the modulation of many cardiac ion channels could result in delayed cardiac repolarization, drug-induced arrhythmias have been highly correlated with the blockade of the $K^+$ channel hERG. The current carried by this channel is activated during cardiac repolarization and its magnitude is a key determinant of the cardiac action potential duration. Structural features of the hERG channel make it particularly prone to blockade by small molecules [3, 4, 5].

Withdrawn from the market:
- Terfenadine
- Astemizole
- Cisapride
- Grepafloxacin
- Sertindole

Denied approval:
- Lidoflazine

Labeling warning:
- Moxifloxacin
- Pimozide

Relegated to second line status:
- Thioridizine
- Bepridil



*hERG hypothetical model and drug binding pocket (in red).*

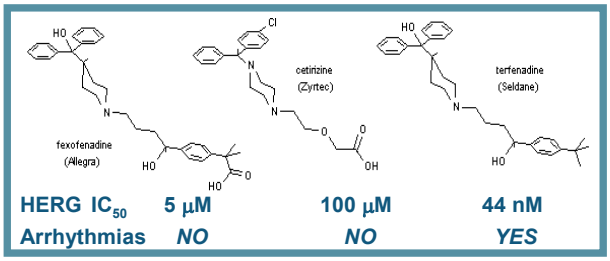
The hERG inhibition by small molecules does not seem to closely track any specific scaffold. Within the same scaffold small differences in substituents can have a profound impact on the molecule's ability to block the hERG channel.

**Thorough QT study in clinical trials.**

"*While the degree of QT prolongation is recognized as an imperfect biomarker for proarrhythmic risk, there is a qualitative relationship between QT prolongation and the risk of arrhythmias"* (ICH E14 document June 2004).

While regulatory agencies worldwide, including the FDA, have not yet reached a consensus on how to best establish drug safety as it relates to pro-arrhythmic risks, the current guidelines from the ICH set very stringent criteria for "*thorough QT studies"* to be conducted early in Phase I.

"*…a negative 'thorough QT/QTc study' is one where the largest time-matched mean difference between the drug and placebo (baseline-subtracted) for the QTc interval is around 5 ms or less, with a one-sided 95% confidence interval that excludes an effect >8.0 ms."* (ICH E14 document, June 2004).




**Early flagging of hERG blockers in drug discovery**

The high stringency of the current guidelines imply that new molecules in development programs will need to have a large therapeutic window with regard to the blockade of the hERG channel.
Electrophysiology measurements using the cloned channel expressed in mammalian cells is considered the most reliable method for measuring the activity of molecules on hERG. In addition a recent study concluded that electrophysiological measurements are good predictors of the cardiac liabilities detected in the clinics[6].
The strict electrocardiography monitoring which will soon be required in clinical trials will significantly rise the costs of drug development. However, our increased understanding of the molecular basis of drug-induced arrhythmias has created cell-based screening options for detecting potential problems early in the discovery process. This will help focusing the resources for later development only on the molecules with the best safety profile.

**References**

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3- Proc. Natl. Acad. Sci. U.S.A. 2000; 97: 12329 – 12333
4- J. Biol. Chem. 2002; 277: 23587 – 23595
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6- Cardiovasc. Res. 2003; 58: 32-45