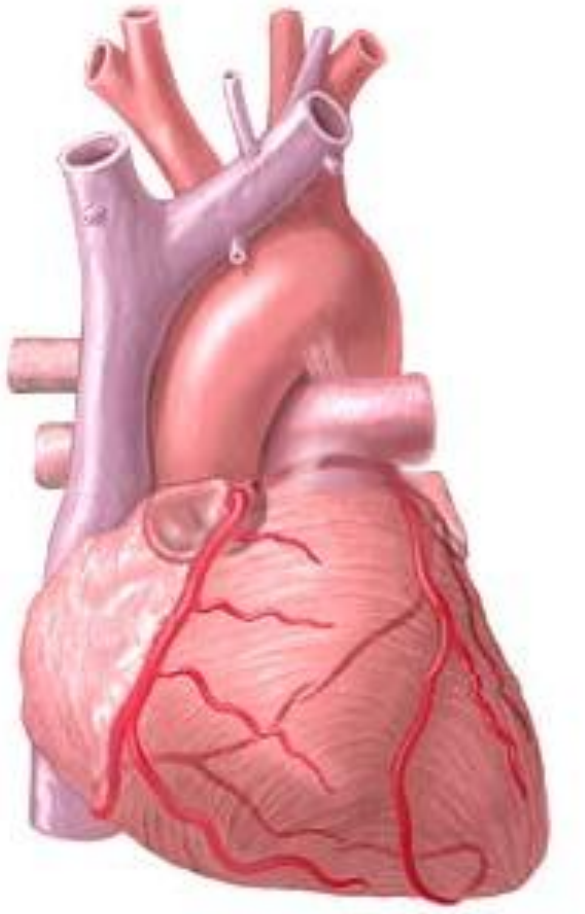
Benefits and limitations of the current paradigm on Preclinical evaluation of pro-arrhythmic

Professor Tim Hammond PhD. FRCPath

Independent Consultant

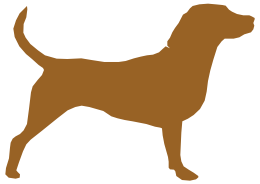


Disclosure

- Dr Hammond has worked in the pharmaceutical industry for over 35 years and until March 2012 was Vice President of Preclinical Safety Assessment in AstraZeneca. Since 2012 Dr Hammond has provided consultancy on Preclinical safety including safety pharmacology to many companies involved in new drug discovery/development and to CROs engaged in preclinical QT studies
- Dr Hammond is a recipient of the Distinguished Service Award from the Safety Pharmacology Society
- Dr Hammond's financial arrangements are fee for service.

QT risk assessment – before S7B and now

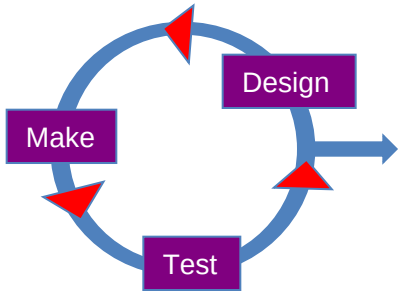
1993



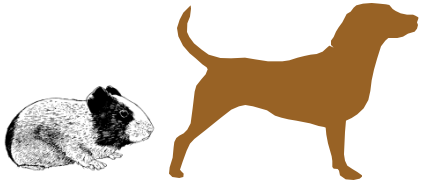
Low resolution QT data in repeat-dose conscious dog studies

2013

hERG screening in silico



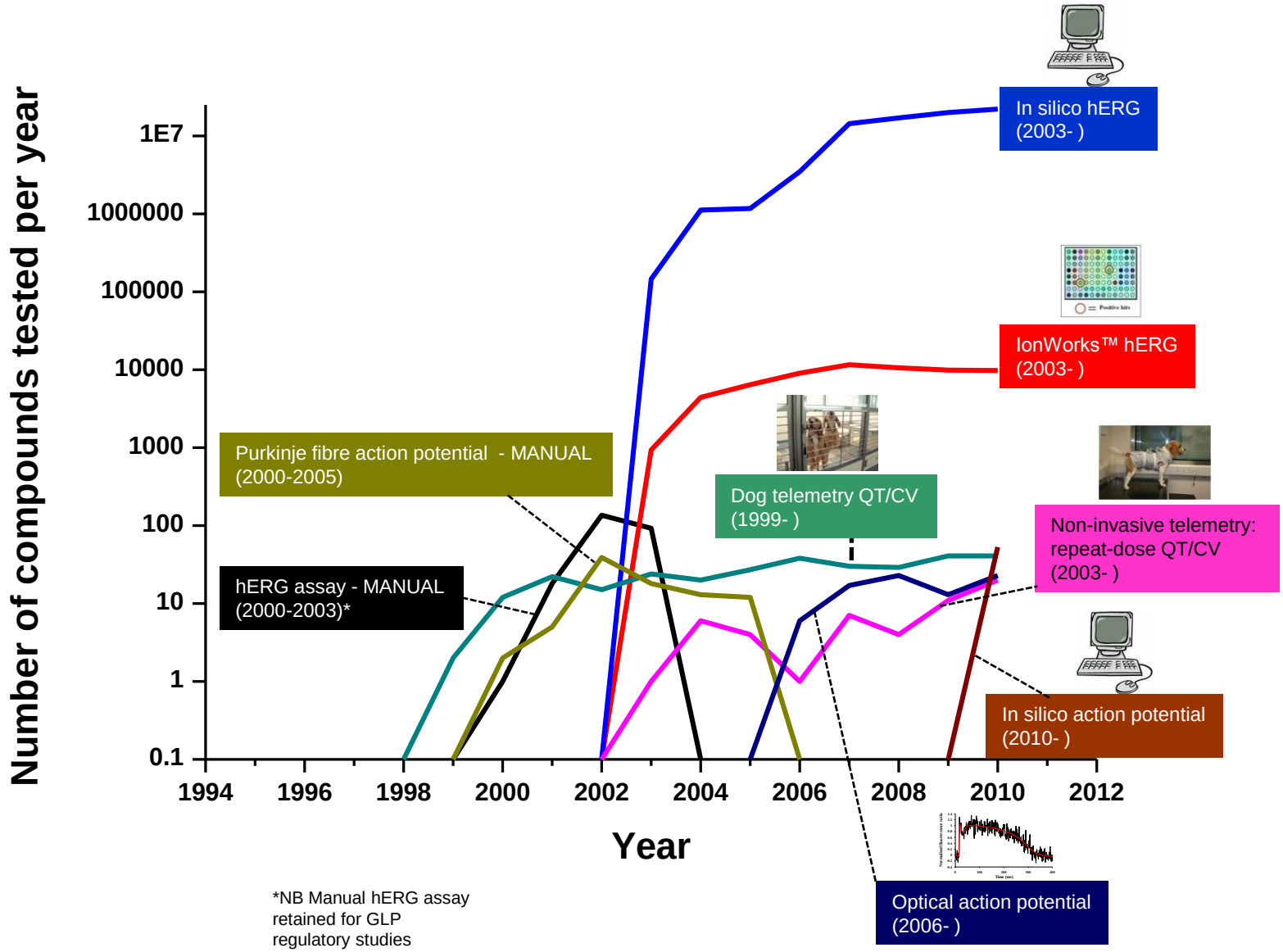
hERG screen



High resolution QT data in guinea-pig, and single & repeat-dose conscious dog studies

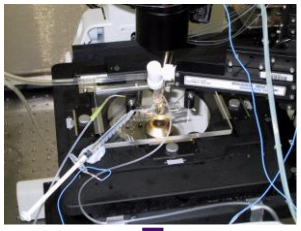
Evolution of methodologies to detect QT risk preclinically

'QT' liability has been under intense regulatory scrutiny since the mid-1990s

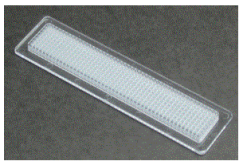


Technology for a high throughput <u>functional</u> screen of hERG was developed that provided medicinal chemists with:

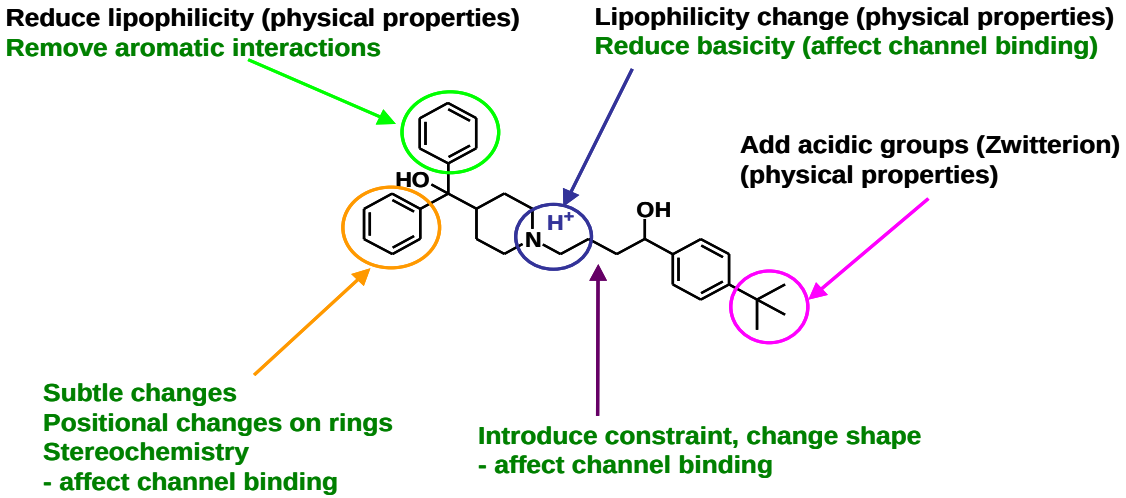
- An IC_{50} value for channel inhibition in a timeframe that influenced chemical design
- An in silico model – prediction robust enough to stop chemists making compounds we don't want!
- An understanding of structure-activity relationships - extended to other ion channels

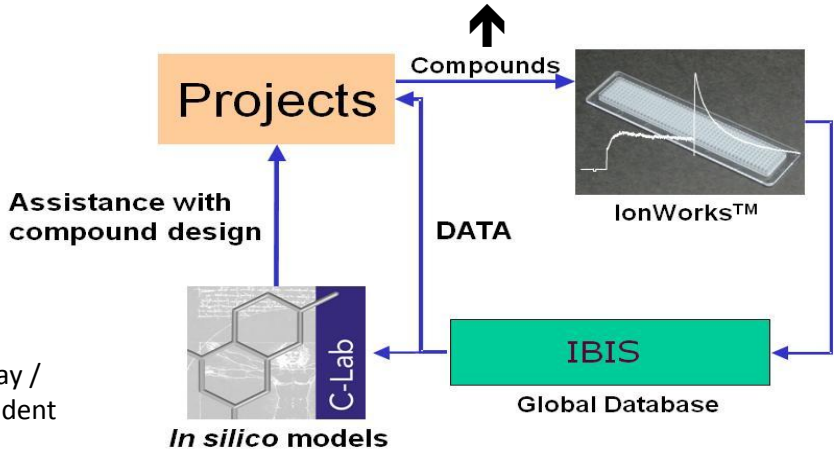


1 compound / day / post-doc



50 compounds / day / undergraduate student



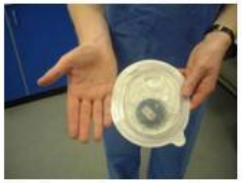


Bridgland-Taylor et al., *J Pharm Tox Methods* (2006), **54**,:189-99

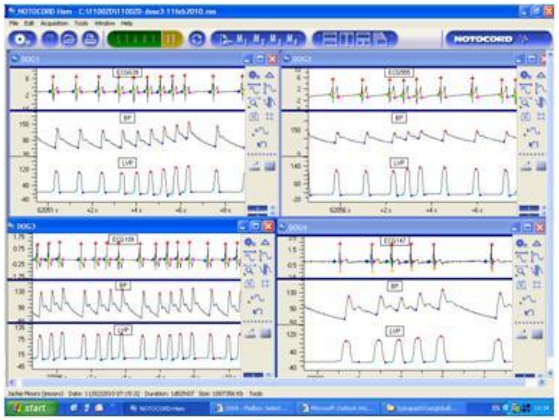
Gavaghan et al., J Comput Aided Mol Des (2007) , **21**, 189-206

Technology to enable high quality ECG monitoring in conscious, freely moving dogs in single-dose safety pharmacology studies

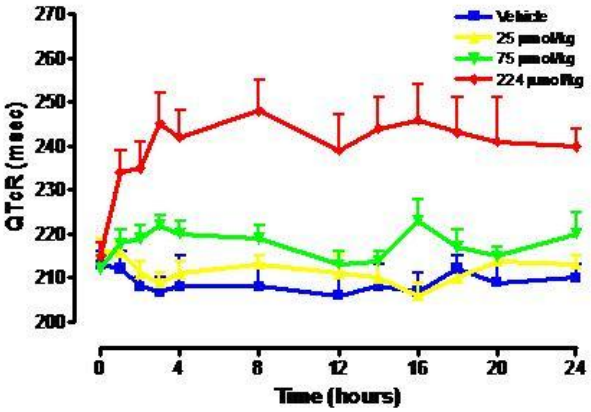
Receivers in floor



Telemetry receiver
(inside sterile packaging)



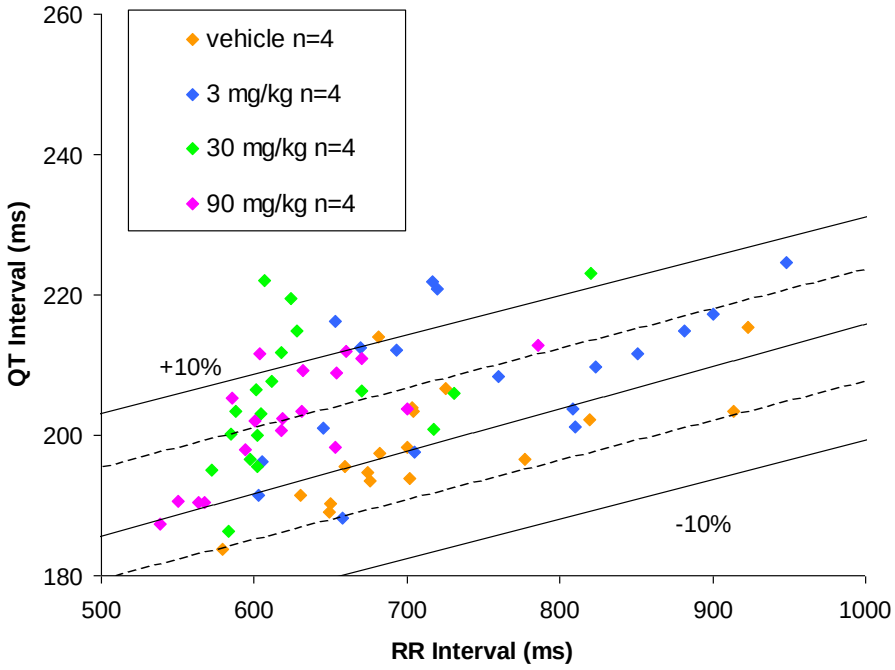
CVS data in 4 dogs



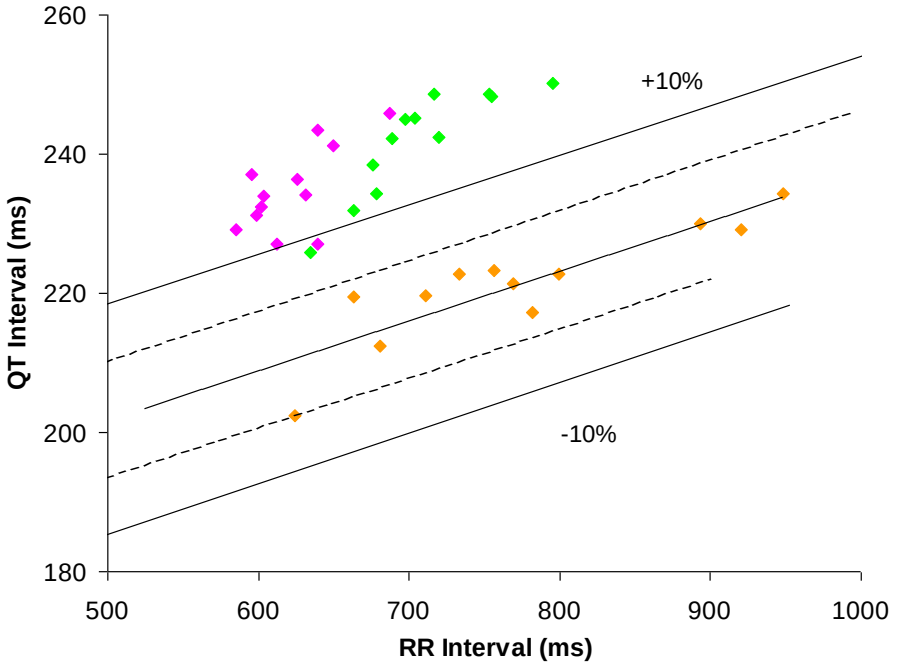
QTc response to moxifloxacin

- Increased effects with multiple dosing:
  - *In vivo* dog
    - Repeat dosing in conscious telemetered dogs
    - To investigate “borderline” effects

Single dose

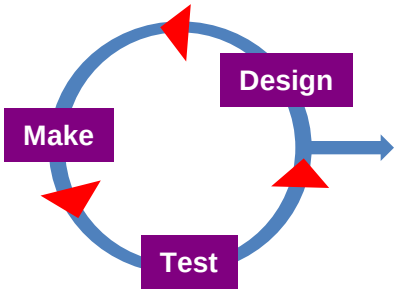


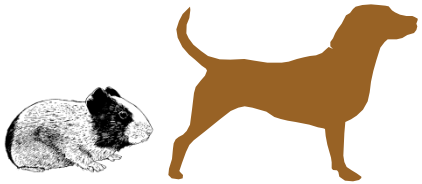
Repeat dose – 28 days



- hERG identified as main molecular mechanism

Lead ID | Lead Opt | Development





<u>In silico</u>
hERG

<u>In vitro</u>
High throughput screen:
hERG

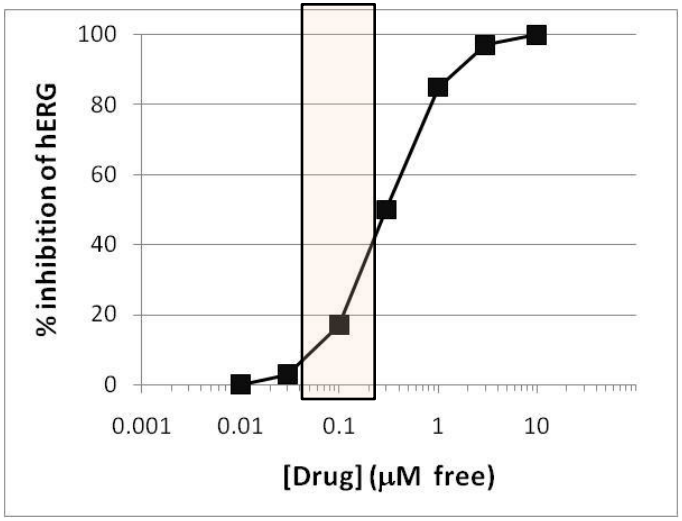
<u>In vivo</u>
Small animal model;
Monitoring in single & repeat-dose dog studies:
QT

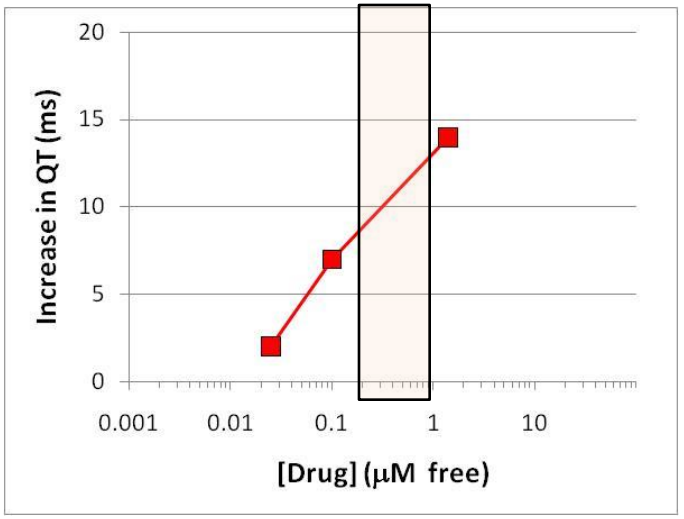
<u>Clinical</u>
High resolution monitoring in Phase 1 and TQTS:
QT

Confidence in predictive value of pre-clinical data = confidence in stop/go decision-making

Pollard et al. *BJP* (2010), **159**, 12-21

An assessment of the predictive value of pre-clinical data





- hERG
  - If free drug level in TQTS ≥ IC_{10} at hERG, **82%** chance of +ve TQTS
  - If free drug level in TQTS < IC_{10} at hERG, **75%** chance of -ve TQTS
- Dog QT data
  - If free drug level in TQTS ≥ concentration increasing QT by 10 ms, **83%** chance of +ve TQTS
  - If free drug level in TQTS < concentration increasing QT by 10 ms, **86%** chance of -ve TQTS

By combining hERG + dog QT data there is:
90% chance of predicting a +ve TQTS
88% chance of predicting a –ve TQTS

Wallis, *BJP* (2010), **159**, 115-121

Mitigating concerns of QT prolongation in Drug Discovery

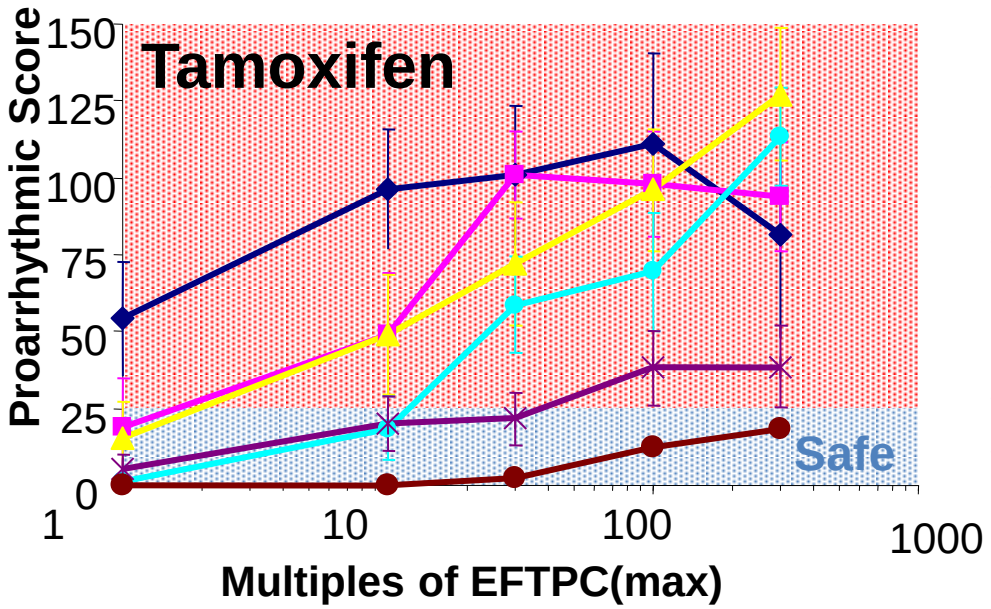
Survey Monkey – March 2013

- Selected top 15 companies based on 2012 R&D portfolio size. Response rate to the survey: 93% (14/15).
- All responders aim to reduce QT liability during discovery.
- All responders use hERG to reduce QT liability; 70% of responders use both hERG potency and safety margin.
- 50% of responders use in silico hERG models. In silico models are usually custom made/proprietary => Improvement could be gained here
- >90% of responders explore SAR to avoid hERG.
- 79% of responders use in vitro assays: Of 79%; the majority use ion channels, other molecular targets and cell and tissue assays as well.
- Finally, 100% of responders try to reduced QT liability in vivo; 100% of responders strive to increase in vivo QT safety margin.

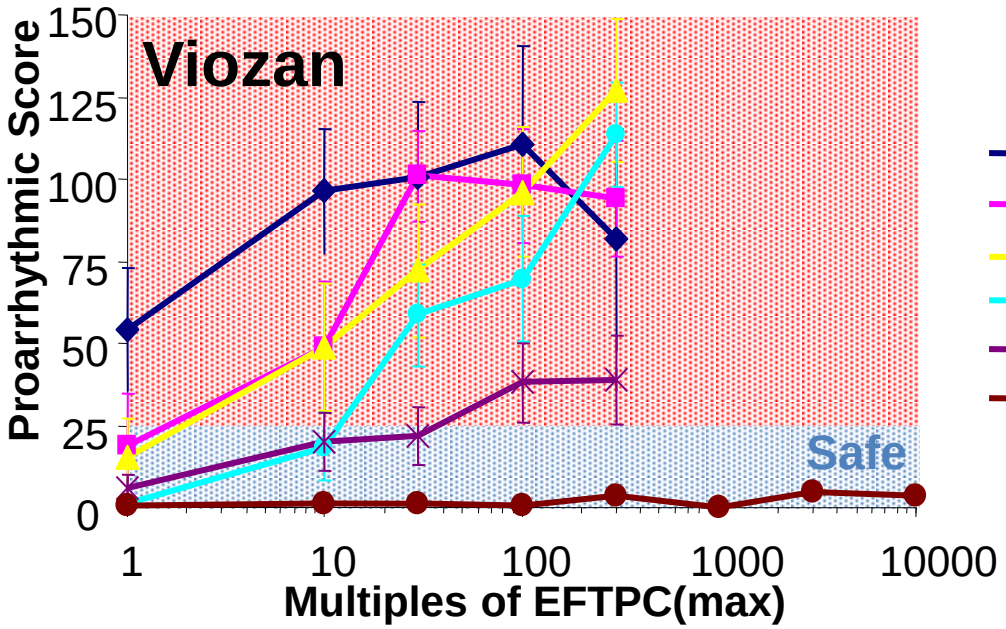
Slide Courtesy Jean-Pierre Valentin

Do Pro-arrhythmia models have value?

Is it possible to discriminate between compounds that prolong QT?



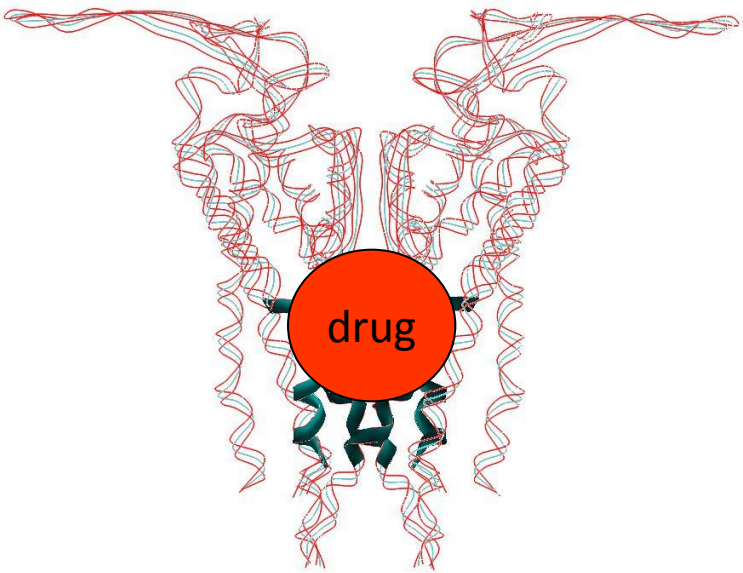
Have we under valued pro-arrhythmia models?



Lawrence et al., 2006

Conclusions – where we are today…

- Despite massive investment by the pharmaceutical companies and academia to put in place a screening cascade to reduce risk of QT prolongation :-
  - It has taken since 1996 to develop our current understanding
  - It has taken around 16,000 scientific papers to get to the bottom of this problem
    - We are very good at predicting QT prolongation due to hERG block – but is one of the more simple problems to solve…….



hERG

Prompts:
Have we neglected the real issue – pro-arrhthymia?

Would risk benefit be improved with greater focus on arrhythmia? (not all QT prolongation carries equal risk!)

With the experience gained can we place more confidence on preclinical and early clinical data?

With the experience gained can we define compounds with low risk without the TQT study?