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The Impact of CIPA on Drug Development: Pharmaceutical Industry Perspective

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Impact of CIPA on Pharma: The Upside

- **Positive impact on drug development → no TQT**
  - Prevent ‘inappropriate’ attrition of beneficial candidates
  - Improve probability of success of new drug candidates
  - Benefits Many:
    - Large-sized & Smaller-sized sponsors (emerging)
    - Patients

- **Leverage nonclinical pro-arrhythmia assays**
  - Opportunity for cost-effective drug development
  - Potential to advance drugs with “safe” QTc prolongation

Impact of CIPA on Pharma: The Anxiety

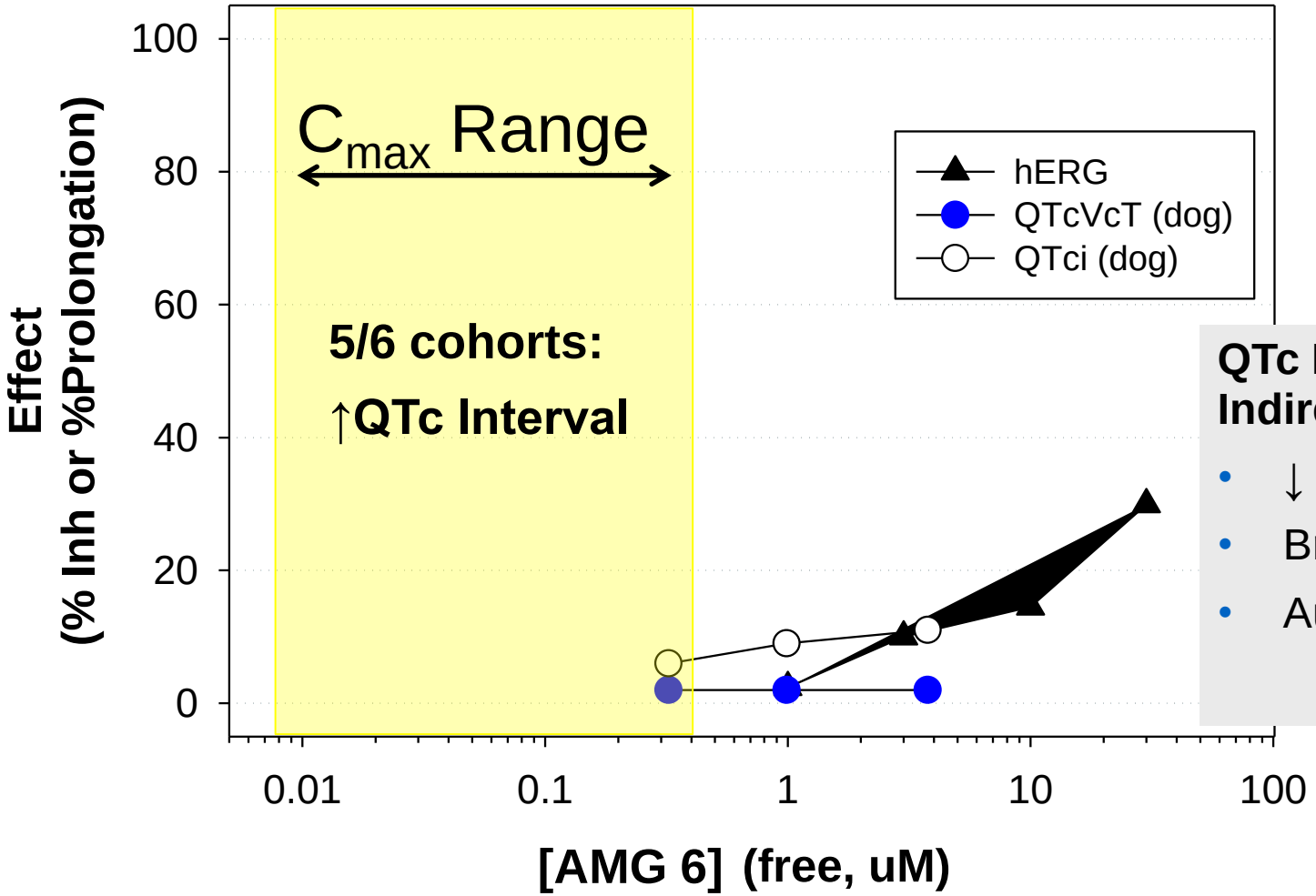
- **CIPA: unproven for predicting proarrhythmic risk**
  - Multi-channel assays: what protocol & parameters (e.g., kinetics)
  - In silico Action Potential evaluation (isAP)
  - Human stem cell-derived cardiomyocytes (hSC-CM)
- **Confidence in Assays: Integrating new risk signals**
  - S7B paradigm: hERG risk → QTc prolong. → TdP risk
  - CIPA paradigm: [7 channels + isAP + hSC-CM] risk → TdP risk
- **Resource impact**
  - New assays: apply to all chemical leads or "the one that matters"?
    - *Front-loaded or staged (tiered) approach?*
- **Challenges**
  - Interpretation of signals → what is low pro-arrhythmic risk?
  - Conflicting data signals → how to progress drug candidates?

Progressing New Drug Candidates:
Considering the Impact of CIPA

AMG #	hERG (IC50, μM)	[Cmax] $_{free}$ (MTD, μM)	hERG / [Cmax] $_{free}$	QTc Signal (FIH) (≥20 msec)
1	126	0.496	253	-
2	>89	0.538	>160	-
3	17.3	0.394	346	-
4	128	0.306	418	-
5	>3.9	0.005	>780	-
6	>30	0.44	>68	+

- **S7B paradigm was used to advance all agents into FIH**
  - #1-6: low risk for hERG-mediated QTc prolongation
  - #1-6: FIH-QTc signal agreed with dog telemetry
- **CIPA implementation challenge:**
  - Would pro-arrhythmia risk assessment change for #1-5?
  - What additional CIPA assay information would help #6?

AMG 6: QTc/hERG vs FIH-SAD Exposure



QTc Prolongation-Indirect:

- ↓ Body temp
- Bradycardia
- Autonomic effects

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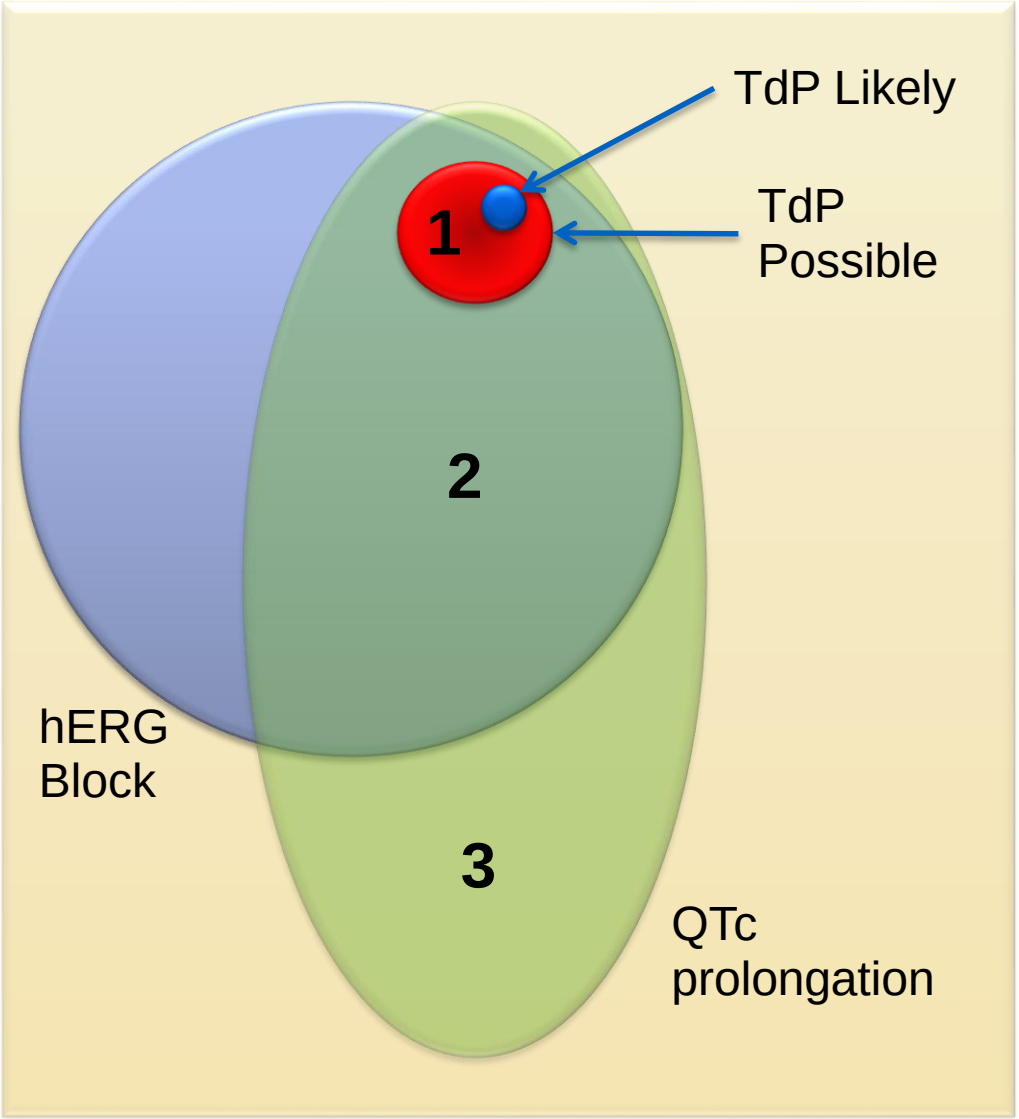
Identifying Different Phenotypes



CIPA Assays Must Differentiate:

- hERG blockers with substantial QTc Prolongation & associated with TdP (1)
- hERG blockers with substantial QTc Prolongation & NOT associated with TdP (2)
- Drugs with no-direct ion channel effects with modest QTc Prolongation (3)

Slide courtesy of D. Leishman (Lilly; modified with permission)

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Take Home Messages

- **Potential Positive Impact on Drug Development**
  - Prevent ‘inappropriate’ attrition of novel therapeutics
  - TQT waiver = incentive ($2-4M/study)

- **CIPA Assays: Confidence in Models Uncertain**
  - Translational performance needs to be understood → drive use

- **Clarity Needed**
  - Definition of low TdP risk (“safe QTc prolongation”)
  - Managing conflicting data signals → what is minimal data set?
  - Resourcing new assays; timing (front-loaded vs tiered)
  - Regulatory Consensus on TQT waiver

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END

In Vitro Safety Pharmacology: Summary

- **Secondary Pharmacology Profile:**
  - hERG: IC_{50} > 30 µM
    - Inhibition: 3 µM (10%); 10 µM (15%); 30 µM (30%)
  - IKs: IC_{50} > 300 µM
    - Inhibition: 100 µM (0%); 300 µM (13%)
  - NaV1.5: IC_{50} = 146 µM
  - CaV1.2: IC_{50} =98 µM

- **APD, human Purkinje fiber (1 Hz):**
  - NOEL: 1 µM
  - APD90 prolonged: 3 µM (13%); 10 µM (28%); 30µM (48%)

- **AMG 6: high selectivity for target; low risk for off-target pharmacology**
  - Target IC_{90}: 19 ± 5 nM

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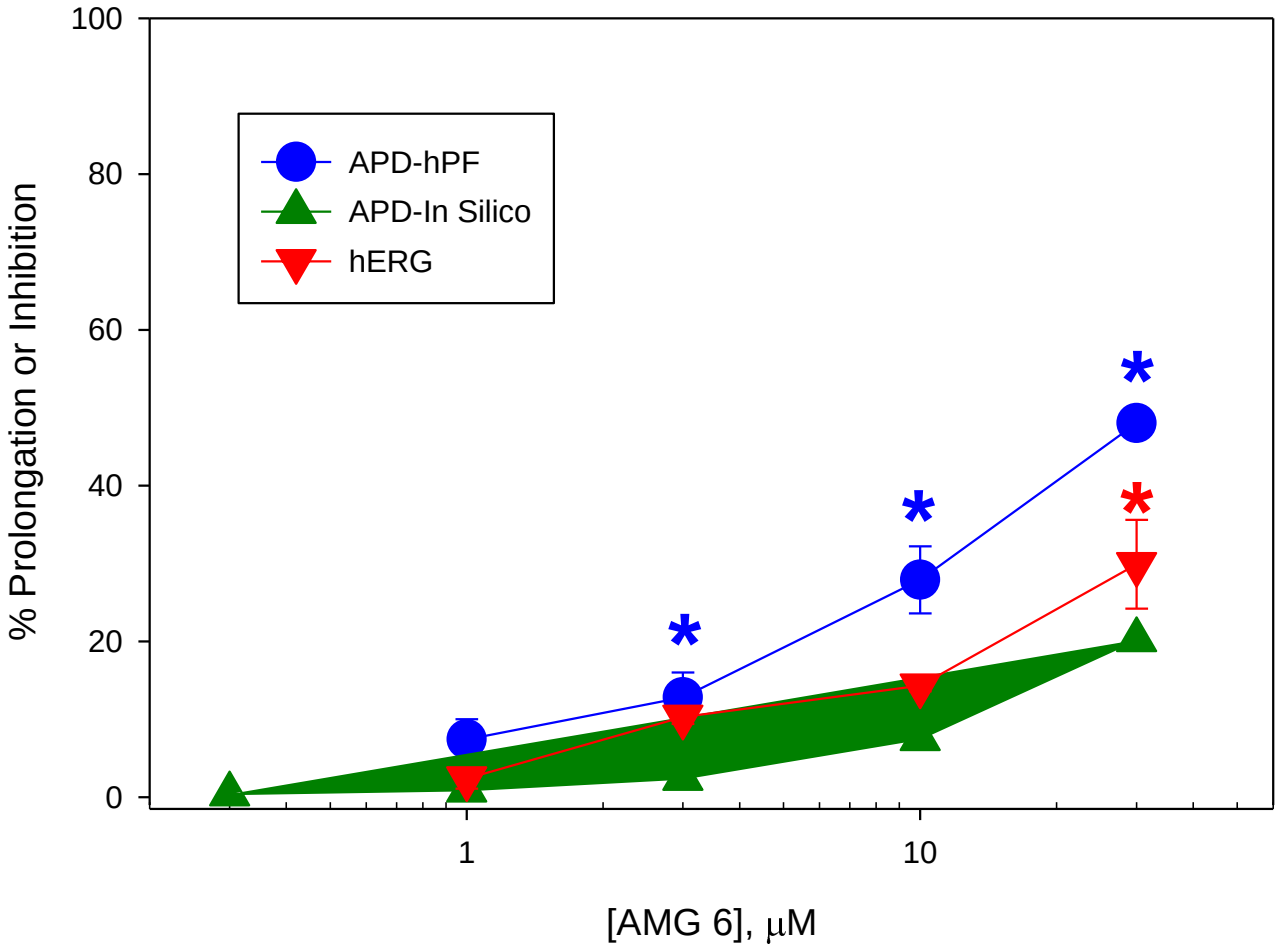
APD in human models: human Purkinje fibers vs *In Silico*



Estimated slopes of changes in body temperature and QTc in dogs and humans: Published literature

Species	Trtmt	Body Tmp Range	QTc (ms) Range	Estimated Slope (ms/degree)
Dog	Warm & Cooled	43-34	200-325	-14
	Cooled	38-32	248-329	-13.4
	Cooled	38-26	340-490	-12.8
Human	Cooled	36-29	460-570	-15.7
	Cooled	37-31	353-435	-13.7
	Cooled	36.5-33	420-520	-26*
	Re-warm	29-33	545-483	-16
	Re-warm	25.6-30.7	609-522	-17

All data taken from HJ Van der Linde Brit J. Pharmacol (2008)

*: JN Khan et al., (2010).
QTc prolongation during therapeutic hypothermia: are we giving it the attention it deserves? Europace 12:266-270.