Rechanneling the current cardiac risk paradigm: arrhythmia risk assessment during drug development without the thorough QT study.

What would success look like?

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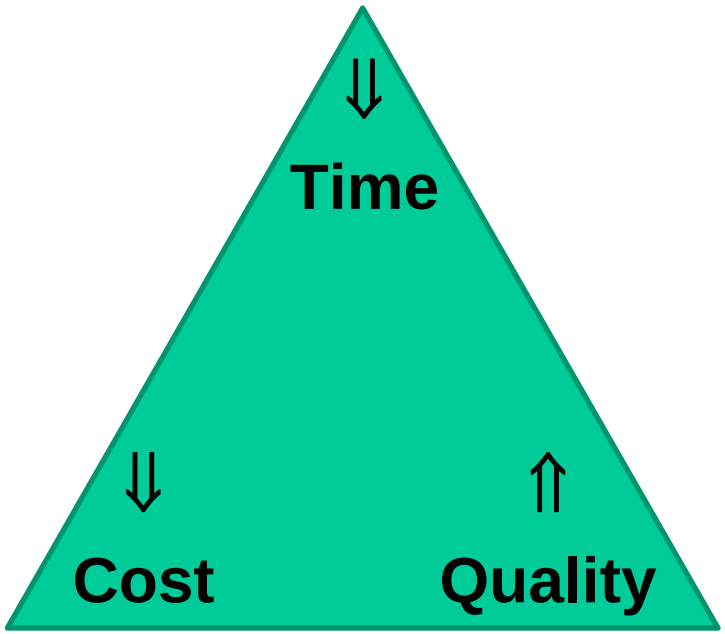
What would success look like?

- Positive implications for industry?
- How would the approach be used?
- Next steps with respect to schema refinement?

Positive implications for industry

- Increase the likelihood of success of developing efficacious & safe medicines that would benefit patients
- Reduce the likelihood of discontinuing potentially valuable medicines (devoid of TdP risk or with an acceptable risk / benefit ratio)
- Support the selection of clinical candidates
- Better predict clinical outcome at early stage



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Positive implications for industry: case studies

Test system	Species	Viozan (Sibenadet)	Ranolazine (Ranexa)
in vivo QT/QTc interval	Human	Positive	Positive
Torsades de Pointes	Human	Negative	Negative
Cardiac repolarisation models:			
in vitro Ikr / hERG	Human	Negative	Positive
in vitro APD *	Dog	Negative	Positive
in vivo QT/QTc interval	Dog	Negative	Positive
Proarrhythmia models:			
Isolated heart	Rabbit	Negative	Negative
Wedge preparation	Dog	-	Negative
Isolated myocyte	Guinea-pig	-	Negative
A-V block *in vivo*	Dog	-	Negative

- Other examples may include: Alfuzosin, Verapamil, Ebastine, Clozapine...
- Can the assessment of the proarrhythmic potential of drugs add value to the drug development paradigm?
- Negative in non-clinical assays: no statistically/biologically significant effect at exposures ≥100-fold the therapeutic free plasma concentration. * Purkinje fibre and epicardial cells for Viozan and Ranolazine.

Data extracted from: Viozan: Newbold et al., Br J Clin Pharmacol 2007; Valentin et al., JPTM, 2006
Ranolazine: Antzelevitch C., J Electocardiol, 2004; Scham et al., BJP 2004; Song et al., JCP 2004; Antzelevitch C et al., JCPT 2004; Antzelevitch C et al., Circulation 2004; Belardinelli et al., 2003; Anon., FDA Briefing Information
(http://www.fda.gov/ohrms/dockets/ac/03/briefing/4012B2.htm)

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How would the new approach be used?

Current vs. Proposed (?) screening paradigm

- Need 25 projects to generate 1 marketed drug (Paul et al., *Nat Rev Drug Discov.* 2010, 9: 203-14).

	Target to Hit	Hit to Lead	Lead Opti.	Pre-clinical	Phase 1	Phase 2	Phase 3	Post-approval
Projects	25	20	15	12	9	5	2	1
Nb cpds	>10^6	10 000	7500	12	9	5	2	1
Current paradigm "basic" S7B-E14				GLP-hERG GLP-NR-Telemetry			TQT	
Current paradigm "enhanced"		hERG screening	hERG screening	GLP-hERG GLP-NR-Telemetry	ECG		TQT	
Proposed paradigm "basic"				•GLP-hERG •GLP-NR-Telemetry •Cardiac Ion Channels •Stem Cell-CM-AP •Poly-pharmacology •In silico AP-ECG				
Proposed paradigm "enhanced"		•Cardiac Ion Channels •Stem Cell-CM-AP •Poly-pharmacology •In silico AP-ECG	•Cardiac Ion Channels •Stem Cell-CM-AP •Poly-pharmacology •In silico AP-ECG	•GLP-hERG •GLP-NR-Telemetry •Cardiac Ion Channels •Stem Cell-CM-AP •Poly-pharmacology •In silico AP-ECG	ECG			

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How would the approach be used?

Pre-clinical screening & Clinical (TQT) costs - Estimates (detailed breakdown)

- Assume 2 TQTS at $2M each

		ICH S7B & E14	New Paradigm
Testing Candidate Drugs only	Pre-clinical	**$1.44M**	**$1.80M**
	TQTS	**$4.00M**	**$0.00M**
	GRAND TOTAL	**$5.44M**	**$1.80M**
Testing multiple compounds	Pre-clinical	**$3.44M**	**$38.69M**
	TQTS	**$4.00M**	**$0.00M**
	GRAND TOTAL	**$7.44M**	**$38.69M**

- Companies may decide to implement different pre-clinical approaches from minimalistic to comprehensive.
- Discovery and/or Development time, cost and level of de-risking may vary.

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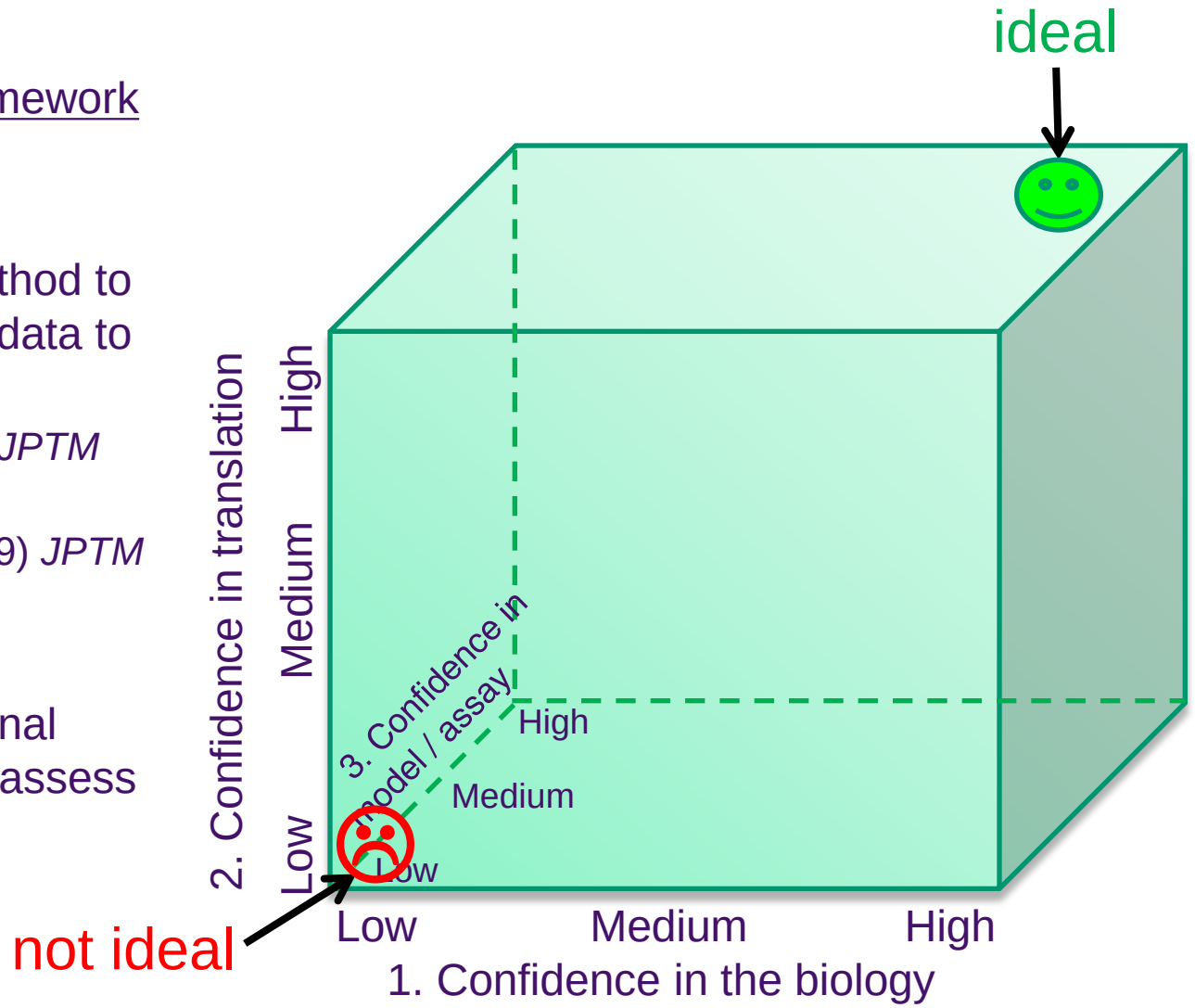
Next steps with respect to schema refinement? Confidence in non-clinical testing cascade

- A multi-dimensional framework approach:

- What? Quantitative method to relate preclinical safety data to clinical outcome in man
  - Valentin et al., (2009) *JPTM* 60:152-8.
  - Trepakova et al., (2009) *JPTM* 60:45-50

- How? A multi-dimensional framework approach to assess confidence in the:
  - Biology
  - Translation
  - Model / Assay



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1. Confidence in the biology

e.g., Animal model to predict QTc

Conscious dog telemetry model

	Model		
Score	**1**	**2**	**3**
Matching the clinical end point x2			Measure same end point in humans and dogs
Matching the pathway/ mechanism (conservation of pathways) x1		Close similarity between receptors, ion channels, intracellular pathways etc	
Matching the physiology x1			Similar anatomy and physiology

Overall confidence:
High

Conscious rat telemetry model

	Model		
Score	**1**	**2**	**3**
Matching the clinical end point x2			Measure same end point in humans and rats
Matching the pathway/ mechanism (conservation of pathways) x1	Some similarity between receptors, ion channels, intracellular pathways etc		
Matching the physiology x1	Repolarisation driven by I_{to} current; physiology dissimilar		

Overall confidence:
Medium

Larval zebrafish 'QT' model

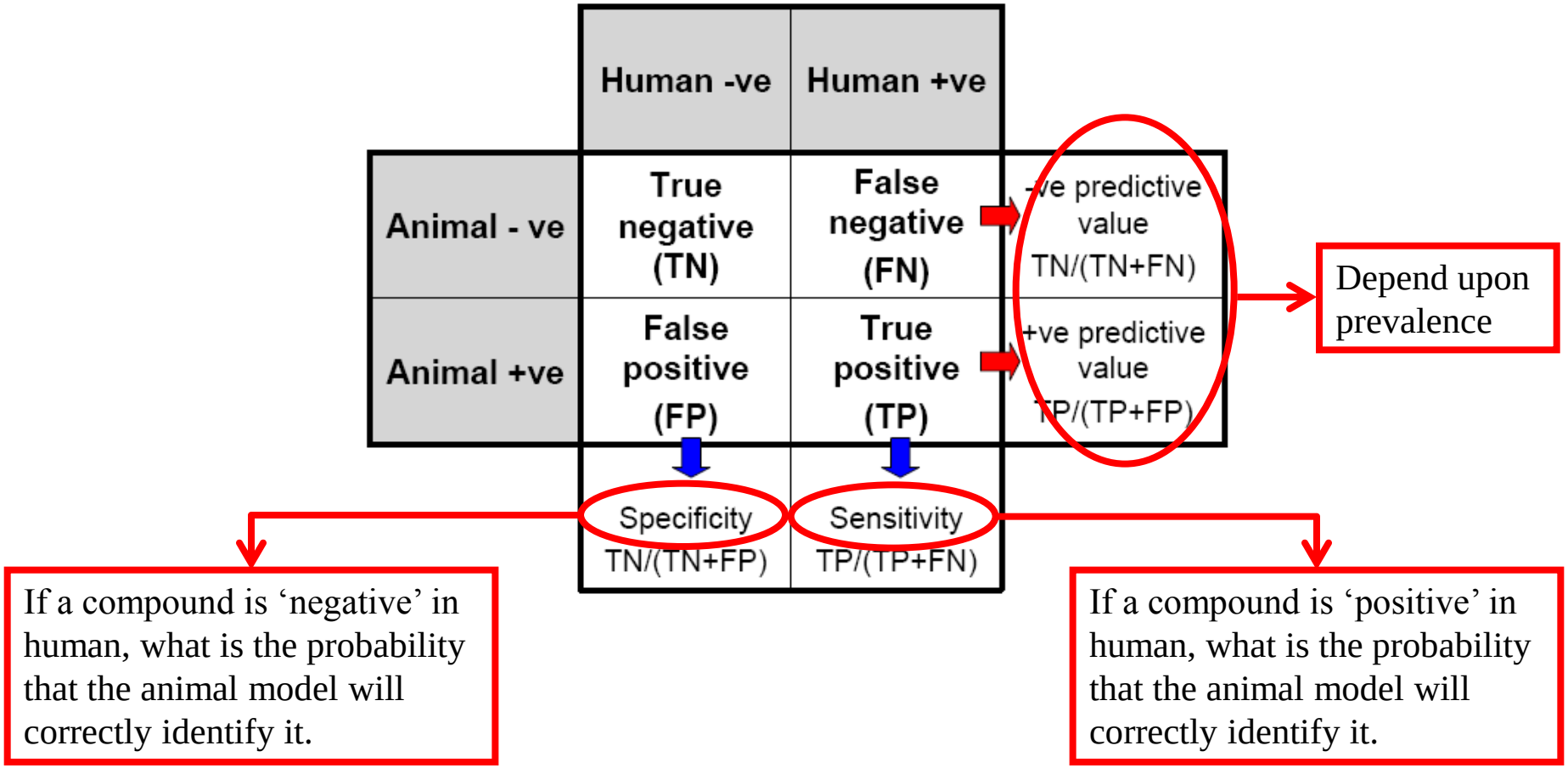
	Model		
Score	**1**	**2**	**3**
Matching the clinical end point x2	Image synchronicity of contraction between atria and ventricle		
Matching the pathway/ mechanism (conservation of pathways) x1		Some similarity between receptors & ion channels (based on limited validation data)	
Matching the physiology x1	Anatomy and physiology of the heart dissimilar		

Overall confidence:
Low

Adapted from: Valentin et al., (2009) *JPTM* 60:152-8.

2. Confidence in the translation: non-clinical to humans

- Compare the response to drugs in the model and in humans
- Quantification using a statistical approach:



- Overall predictive capacity = (True Negatives + True Positives) / Total
  - A value of 50% is no better than chance!

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2. Confidence in the translation

Test system end-point	Species	Exp. conditions	Clinical endpoint	Exposure multiple	Number of drugs	Sensitivity %	Specificity %	Predictability %	Reference
hERG	Human	*In vitro*	⇑ QT interval	3	44	17	91	70	Koerner et al., 2012
APD	Rabbit, Dog, Guinea-P	*In vitro*	⇑ QT interval	3	43	0	93	58	
QTc interval	Dog	*In vivo*	⇑ QT interval	3	47	20	100	83	
Integrated	All of the above	*In vitro & In vivo*	⇑ QT interval	3	88	17	92	73	
QTc interval	Dog	*In vivo*	⇑ QT interval	3	114	80	70	?	Ewart et al., 2012
hERG	Human	*In vitro*	⇑ QT interval	2-3	19	82	75	79	Wallis R., 2010
APD	Dog	*In vitro*	⇑ QT interval	2-3	19	20	100	53	
QTc interval	Dog	*In vivo*	⇑ QT interval	2-3	19	83	86	85	
hERG + QTc	Human & Dog	*In vitro & In vivo*	⇑ QT interval	2-3	19	90	88	90	
hERG	Human	*In vitro*	⇑ QT interval	45	39	64	88	79	Gintant G., 2011
QTc interval	Dog	*In vivo*	⇑ QT interval	ND	17	100	90	95	Toyoshima et al., 2005
QTc interval	Monkey	*In vivo*	⇑ QT interval	ND	16	100	73	86	Ando et al.,
hERG	Human	*In vitro*	Torsades de P	30	28	89	100	93	Webster et al., 2002
hERG	Human	*In vitro*	Torsades de P	30	52	96	69	81	Redfern et al., 2003
Screenit	Rabbit	*In vitro*	Torsades de P	30	64	65	89	75	Lawrence *et al.*, 2006
hERG	Human	*In vitro*	Torsades de P	ND	12	100	83	92	Hanson *et al.*, 2006
APD	Dog	*In vitro*	Torsades de P	ND	12	33	83	58	
QTc interval	Dog	*In vivo*	Torsades de P	ND	12	100	100	100	
Arrhythmia ?	H Stem Cell Cardiomyocyte	*In vitro*	Torsades de P	?	?	?	?	?	?

ECVAM criteria (Genschow et al., 2002): <65% not sufficient; 65 – 74%: sufficient; 75 – 84%: good; > 85%: excellent

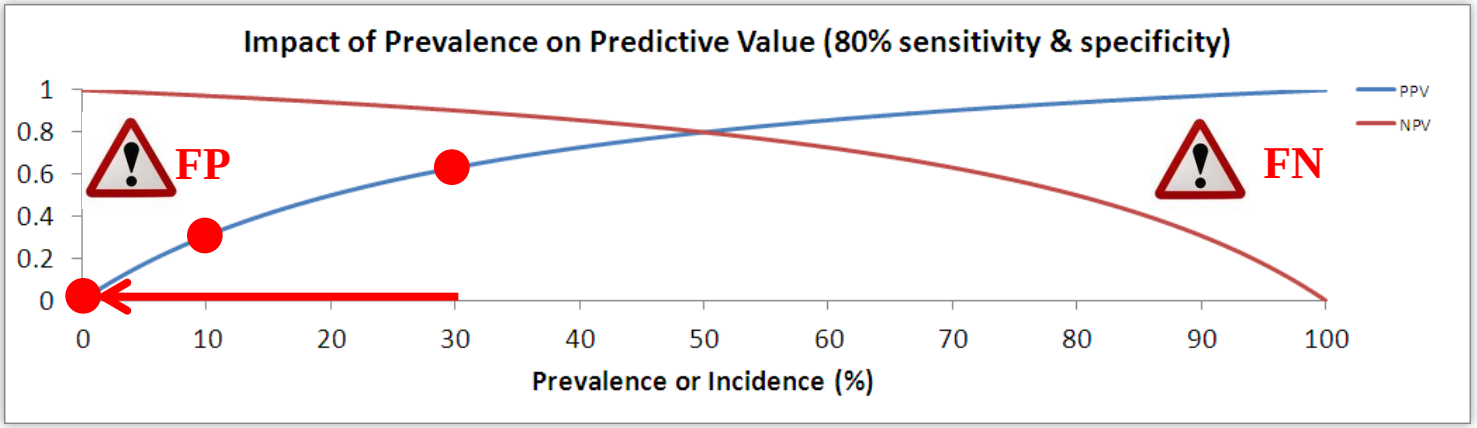
2. Confidence in the translation

Impact of Prevalence – in 1000 Compounds

1%	+ve	-ve
+ve	8	198
-ve	2	792
	Sensitivity 80%	Specificity 80%

10%	+ve	-ve
+ve	80	180
-ve	20	720
	Sensitivity 80%	Specificity 80%

30%	+ve	-ve
+ve	240	140
-ve	60	560
	Sensitivity 80%	Specificity 80%



Courtesy of Dr Derek J. Leishman, Eli Lilly and Company.

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3. Confidence in the model

- Parameters:
  - Numerous parameters to take into account.
  - May vary from model to model.
  - E.g., Intra & inter laboratories reproducibility; Responsiveness to positive & negative agents; Baseline values; Performance of the assay, screen or model; Understanding of strengths & limitations of the model; Availability of data in the public domain – see next slide
  - E.g., In vivo cardiovascular assessment in non-rodent : D. Leishman et al., *JPTM* 2012.
- Logistic:
  - Compatibility with the Design – Make – Test – Analyse cycle of drug discovery
  - Cost; Throughput; Turnaround Time; Availability; Capital investment & depreciation....

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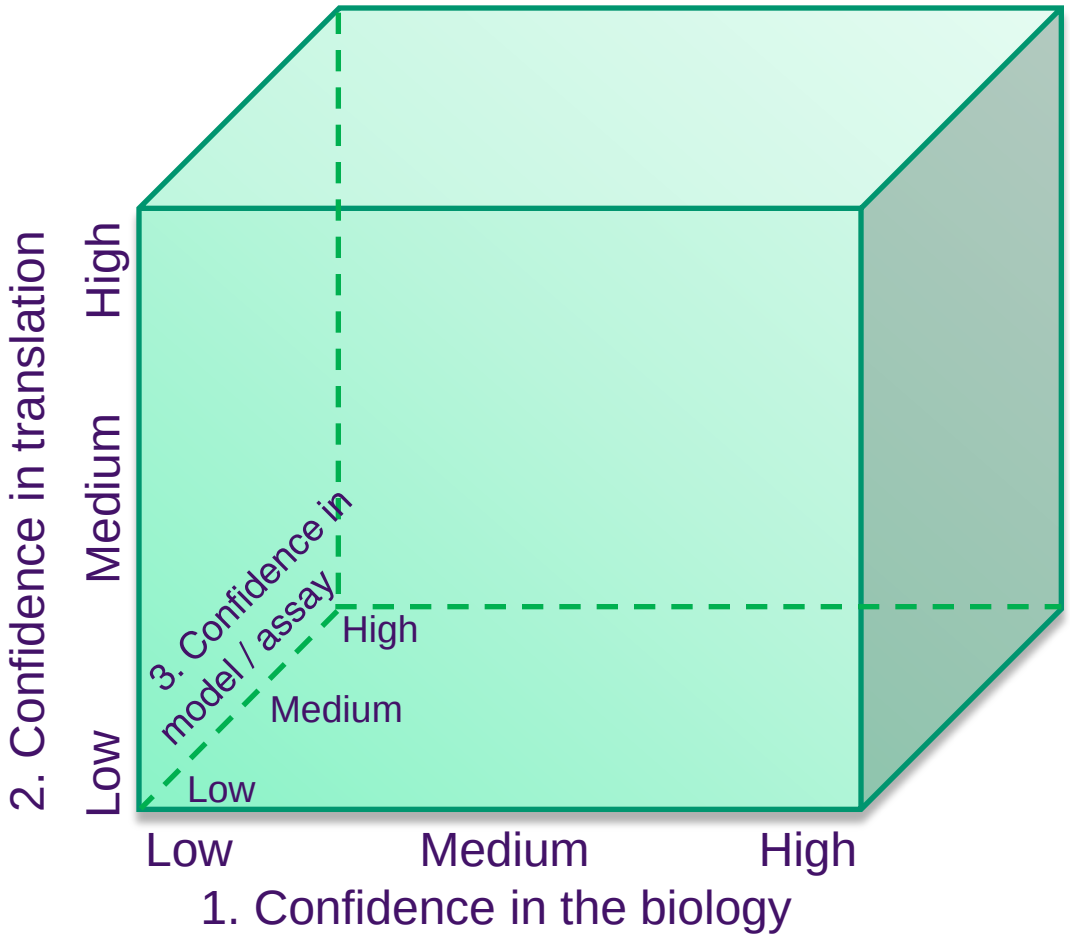
3. Confidence in the model

Parameter	QT in telemetered dogs	hERG electrophysiology
Assay screen or model performance	Vehicle and positive control within historical range	Z' >0.6. Reference IC_{50} within 3-fold of historical
Protocol/study design	Ability to detect compounds which affect cardiovascular parameters (haemodynamics, ECG intervals, contractility)	Ability to detect compounds which are either blockers or activators. Distinguish use/state dependence. Detect slow onset of effect.
Reproducibility of test system within laboratory	Power analysis and historical reference ranges	Z' >0.6. Reference IC_{50} within 3-fold of historical Expect replicates of test compounds to be within 3-fold
Reproducibility of test system between laboratories	Compare power analysis and historical reference ranges across sites	Absolute IC_{50} values are protocol-dependent so may vary between laboratories, but rank order of potency for reference compounds should be identical. Risk that different platforms (e.g IonWorks, Patch Clamp, Qpatch) may bias towards particlar kinds of interaction
Inclusion of both known positive and negative agents	Vehicle routinely included in each study. Reference compound can be included in each study	Reference compound and vehicle included in each assay
Method limitations	Animal variability. Lots of parameters assessed; a single positive control can not demonstrate sensitivity to all parameters	IC_{50} is dependent on assay protocol so translation requires a "standard curve"
Data supporting validity Protocols in public domain Methods and results published in peer reviewed publication Methodology and results subjected to independent scientific review	Extensive literature evaluation of several different assay platforms. Strong evidence for correlation between in vivo and clinical effects	Extensive literature evaluation of several different assay platforms. Strong evidence for correlation between in vitro activity and in vivo effect pre-clinically and clinically Risk that much attention is focussed on a single target, at the expense of other mechanisms

Next steps with respect to schema refinement?

- What confidence do we have in existing & emerging models?
- E.g., Non-Rodent telemetry to predict QT prolongation
- E.g., hERG to predict QT prolongation
- E.g., hSC-CM to predict Torsades de Pointes



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Summary & next steps

- Which pre-clinical assays should be used?
  - In silico, in vitro & in vivo? Key stakeholders agreement e.g. Industry, Regulators
- For each relevant assay, develop confidence in biology, translation and model?
- If focusing on the proposed scheme:
  - Decide which channels should be investigated, which parameters to be measured, define protocols, optimize automated platforms, etc
  - Develop in silico methods (ion channels, action potential, ECG)
  - Stem cells: in parallel, standardize stem cell preparation
  - Compare stem cell data vs. transfected cells vs. freshly isolated cardiac myocytes
- Question: Who would be doing what, where & when? Pharma & Biotech Industry, Service / Equipment providers, Consortia: CSRC, HESI, FDA, SPS.....

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  - Hugo Vargas, Amgen

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Pierre Fabre

1926 – 2013

Pierre Fabre died Saturday the 20th of July, aged 87.
The pharmaceutical and cosmetics company which he founded in 1961 employs 10,000 people and had a turnover of ~2billion € last year. *"Since its creation in 1961 and until these last few days, Mr. Fabre has dedicated all his energy to building the 3rd largest French pharmaceutical company. He led, steered and masterminded all the different stages of its development and has built, stone by stone, an international company"*.