The Application of Systems Biology to Safety Assessment

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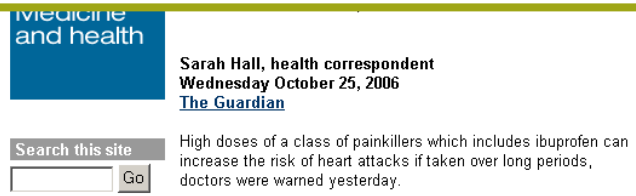
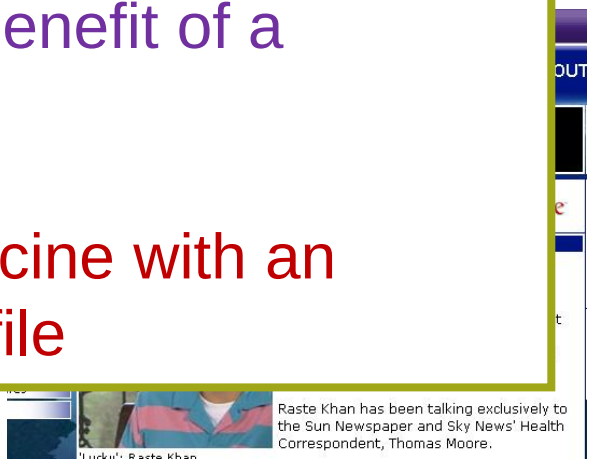
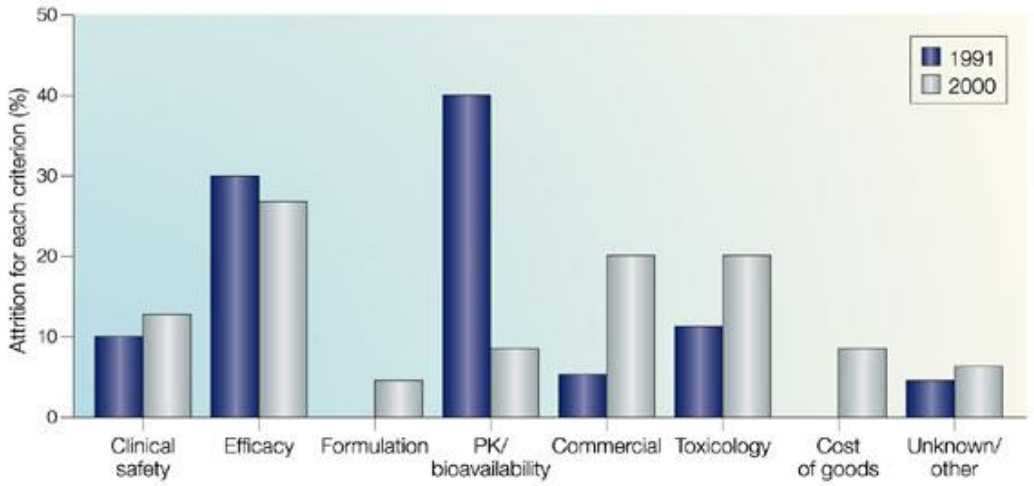
- The assessment of the safety of medicines is taken very seriously by the industry and regulatory authorities
- Getting the toxicological risk assessment wrong can have significant impacts on patient health
- The perception of a risk can reduce the benefit of a potential medicine

It benefits no-one to produce a medicine with an unacceptable safety profile





Beyond the risk to the patient
Cost of toxicological failure



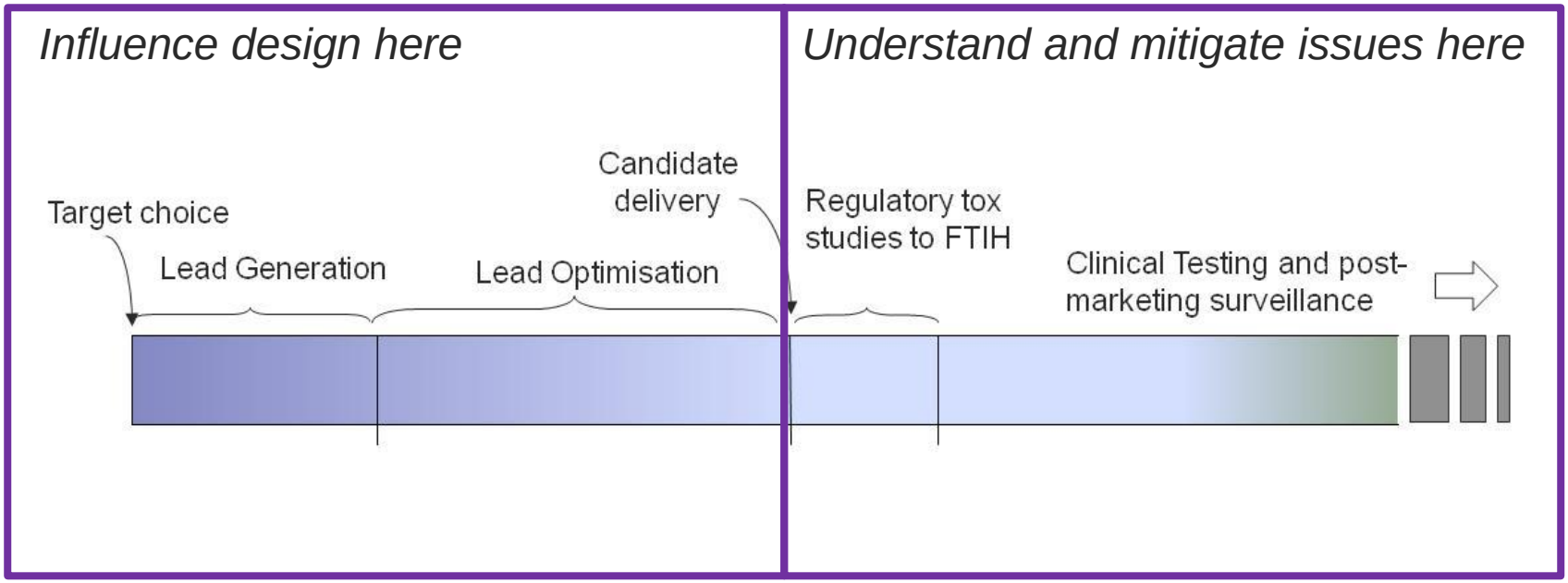
Kola and Landis Nature Reviews Drug Discovery 3, 711-716 (August 2004)

- >20% of candidate drugs fail due to unpredicted toxicology
- Additionally, some drugs fail to reach efficacy due to **dose-limiting toxicology**
- Each compound failure in the clinic costs between $10M and >$100M depending on when it fails
- Better prediction of potential risk early
  - Avoid the problem
- Better understanding of potential risks in patients (or subsets of patients)
  - Manage the risk
- **Only small changes = huge benefits**

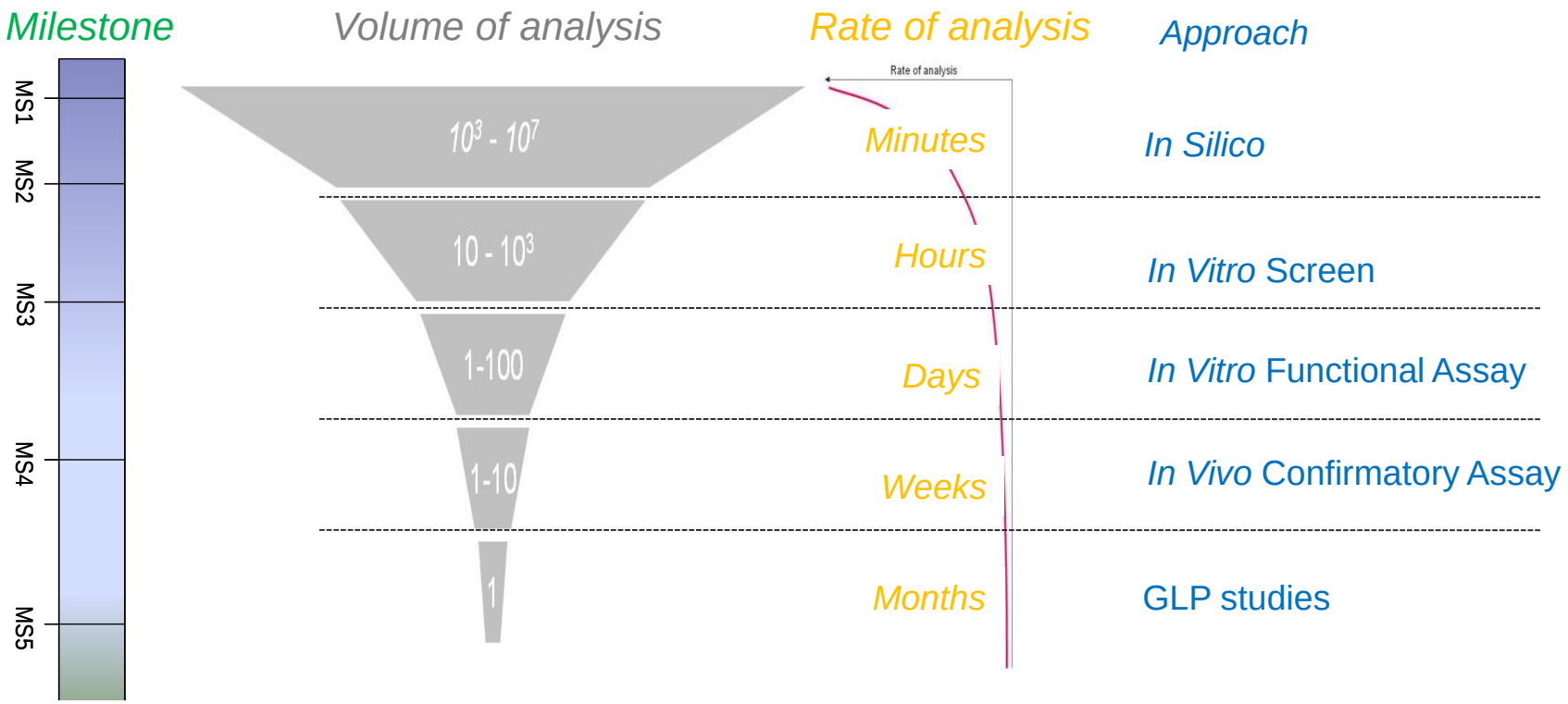
Influencing choice in drug discovery

- Successful drug discovery and development is about making the *right decision* at *the right time*
  - The “big” decision points (milestones, tollgates etc.) are not the important ones
- The *right decision* requires access to the right information
- The *right time* is dictated by the phase of the drug-discovery process

- Scale approaches to deliver to the decision-making cycle
  - *data delivered late, might as well have not been generated at all!*



Influencing choice in drug discovery
Needs: Scaling approaches to the volume and rate of analysis



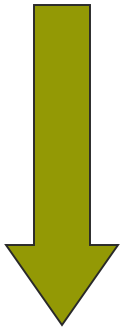
- Cannot simply move the “traditional” testing paradigm to earlier phases in drug discovery
  - Unethical and incompatible with 3Rs and animal usage
  - Cannot handle the volume of analysis
  - Cannot handle the rate of data delivery
- Need to adopt more in vitro and *in silico* approaches
  - **Computational Biology**

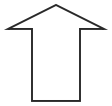
Toxicologists are Systems Biologists

Efficacy consideration

- One disease
- One mechanism in one disease
- One target in one mechanism in one disease
- One therapy against one target in one mechanism in one disease

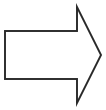
"Reductionist Drive"





Has the drive produced here limited our understanding here?

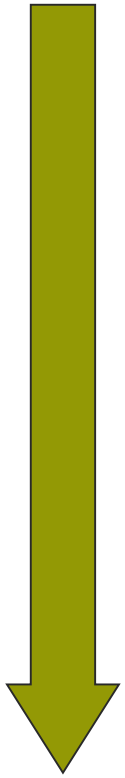
•The "single protein" model of cause and effect



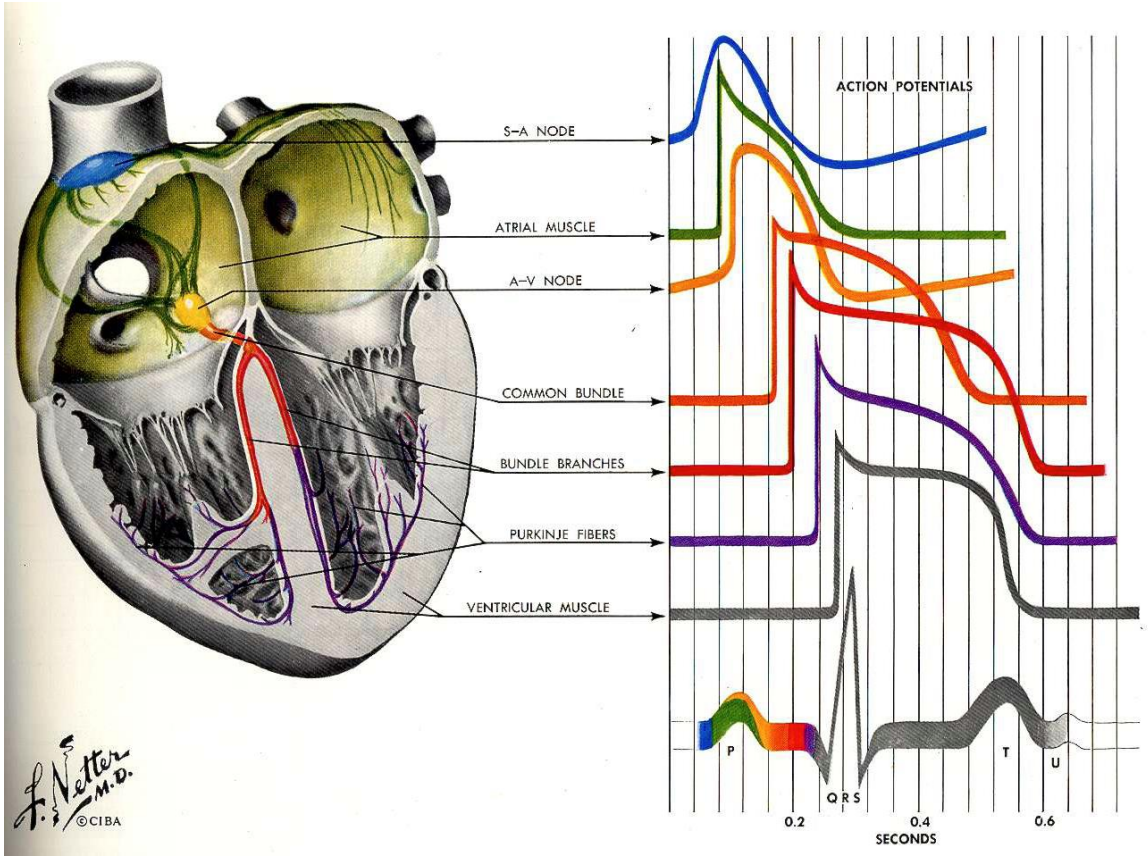
Toxicological consideration

- One therapy (perturbation)
- Multiple mechanisms
  - Primary effects
  - Predicted secondary effects
- Effect(s) in healthy volunteers
  - Effects on normal biochemistry
- Effect(s) in the patient
  - Effects on potentially abnormal biochemistry
  - Interaction with other therapies
- Effect(s) in a population of patients
  - Idiosyncrasy

"Systems Drive"



Cardiac Ion channel liabilities
Background biology: Origin of the ECG

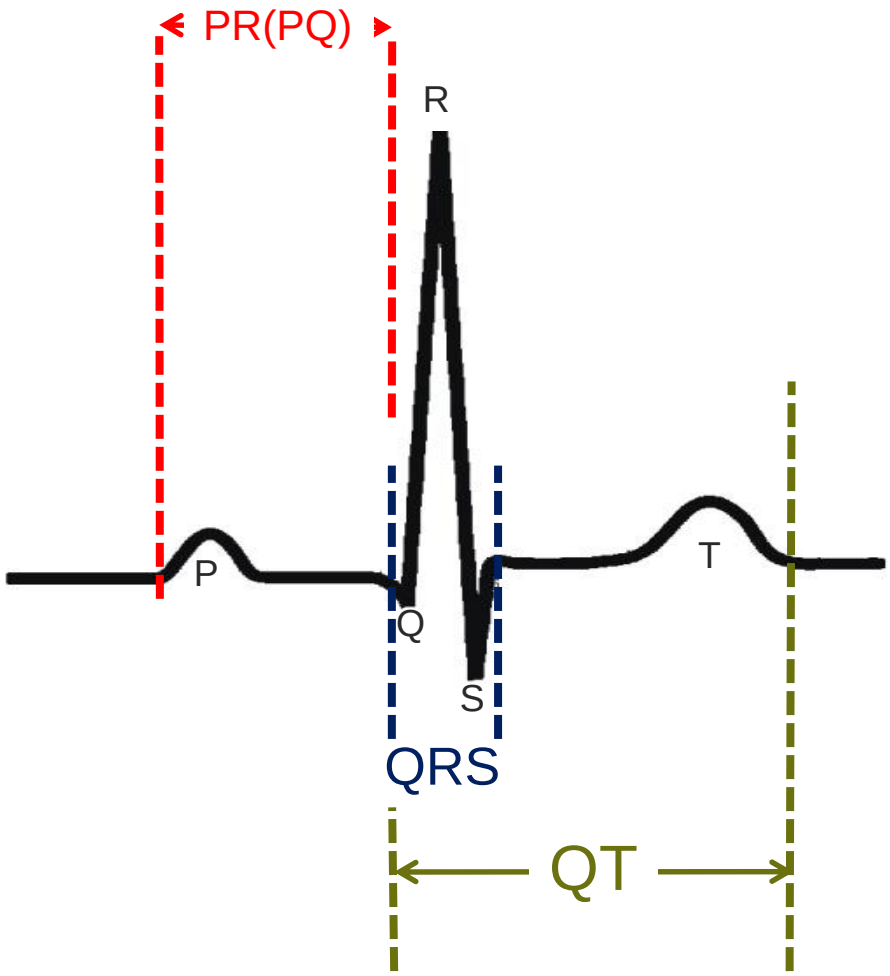


Excitation initiated in the sino-atrial node spreads through the heart

Action potential morphology varies according to cardiac region

The wave of excitation can be detected on the body surface: the electrocardiogram (ECG)

Background biology
Information derived from the ECG: PR, QRS & QT intervals



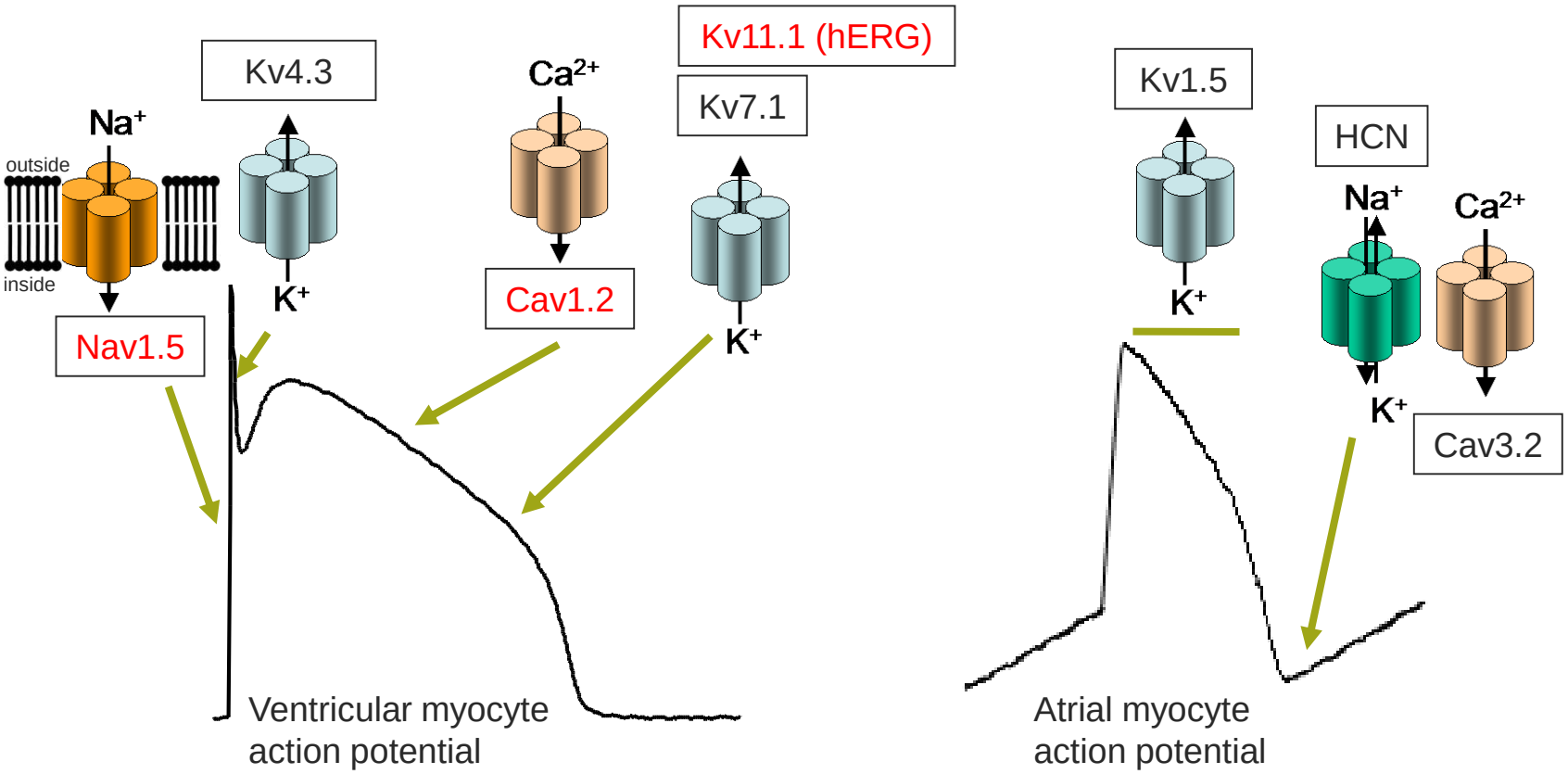
PR(PQ): an index of conduction through the atrio-ventricular node

QRS: an index of conduction through the ventricles

QT: an index of action potential duration in the ventricles

Background biology
Key ion channels underlying action potentials*

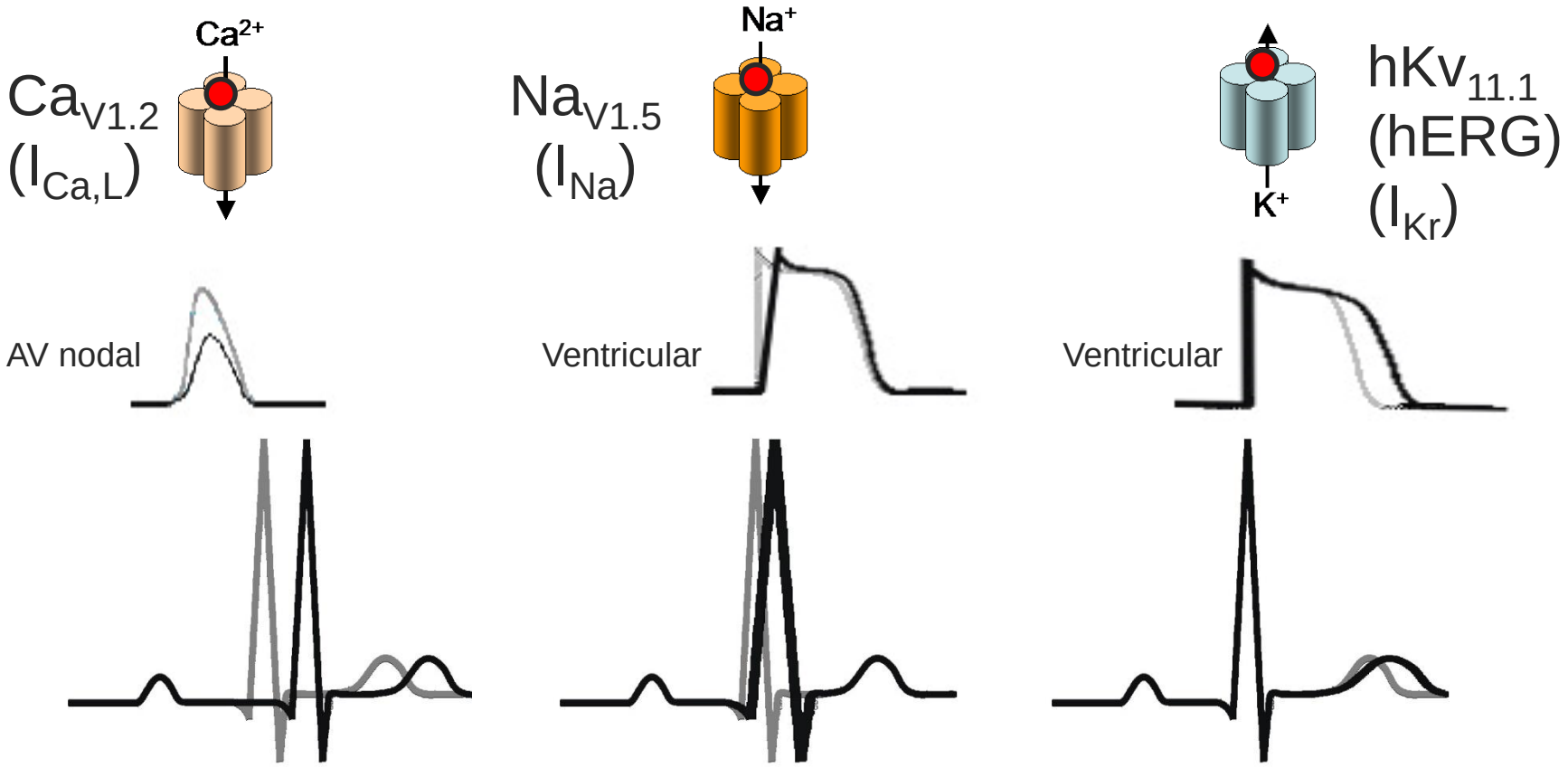
* Only α sub-units shown



From a pre-clinical perspective, this molecular understanding is fundamental to being able to prevent or minimise ECG risk

Bers (2001). Excitation-Contraction Coupling and Contractile Force. Kluwer Academic Publishers, Netherlands. ISBN 0-7923-7157-7.

What's the problem?
Effect of channel block on action potentials & ECG



What's the problem?

Strong evidence that inhibition of cardiac ion channels can lead to life-threatening arrhythmias

Channel	Congenital "loss of function" mutations can lead to:	Pharmacological inhibition can lead to:	Example drugs
Nav1.5	Atrial fibrillation; Ventricular fibrillation; Sick Sinus Syndrome	Ventricular Tachycardia	Encainide; Flecainide[1]
Cav1.2	ST segment elevation	AV block	Verapamil[2]; Diltiazem
Kv11.1 (hERG)	Torsades de Pointes	Torsades de Pointes	Astemizole; Cisapride; Droperidol; Terfenadine; Thioridazine; Terodiline[3]

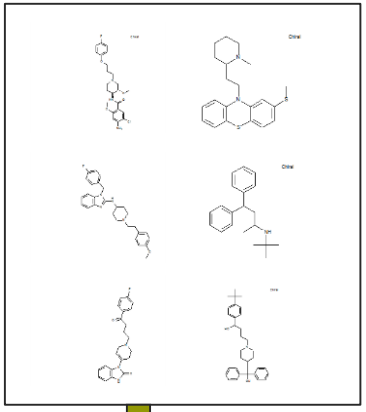
1 Echt et al., N Engl J Med. (1991); 324, 781-8. 2 Cohen et al. Neurology (2007); 69, 668-75. 3 see Redfern et al. Cardiovasc Res (2003) 58, 32-45.

In Silico Cardiac Ion Channel strategy

In silico

Target Selection → Lead Gen → Lead Optimization → Pre clinical → Phase I → Phase IIa → Phase IIb → Phase III/ Launch → Product Maint.

Prediction of activity at individual channels

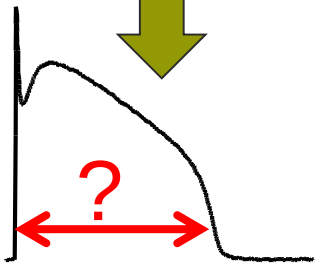


Predicted Activity at:
hERG
Nav1.5

Test compound

Channel	Data
Nav1.5	inactive
Kv4.3	inactive
Cav1.2	IC_{50} 10 μM
Kv7.1	inactive
Kv11.1	IC_{50} 5 μM

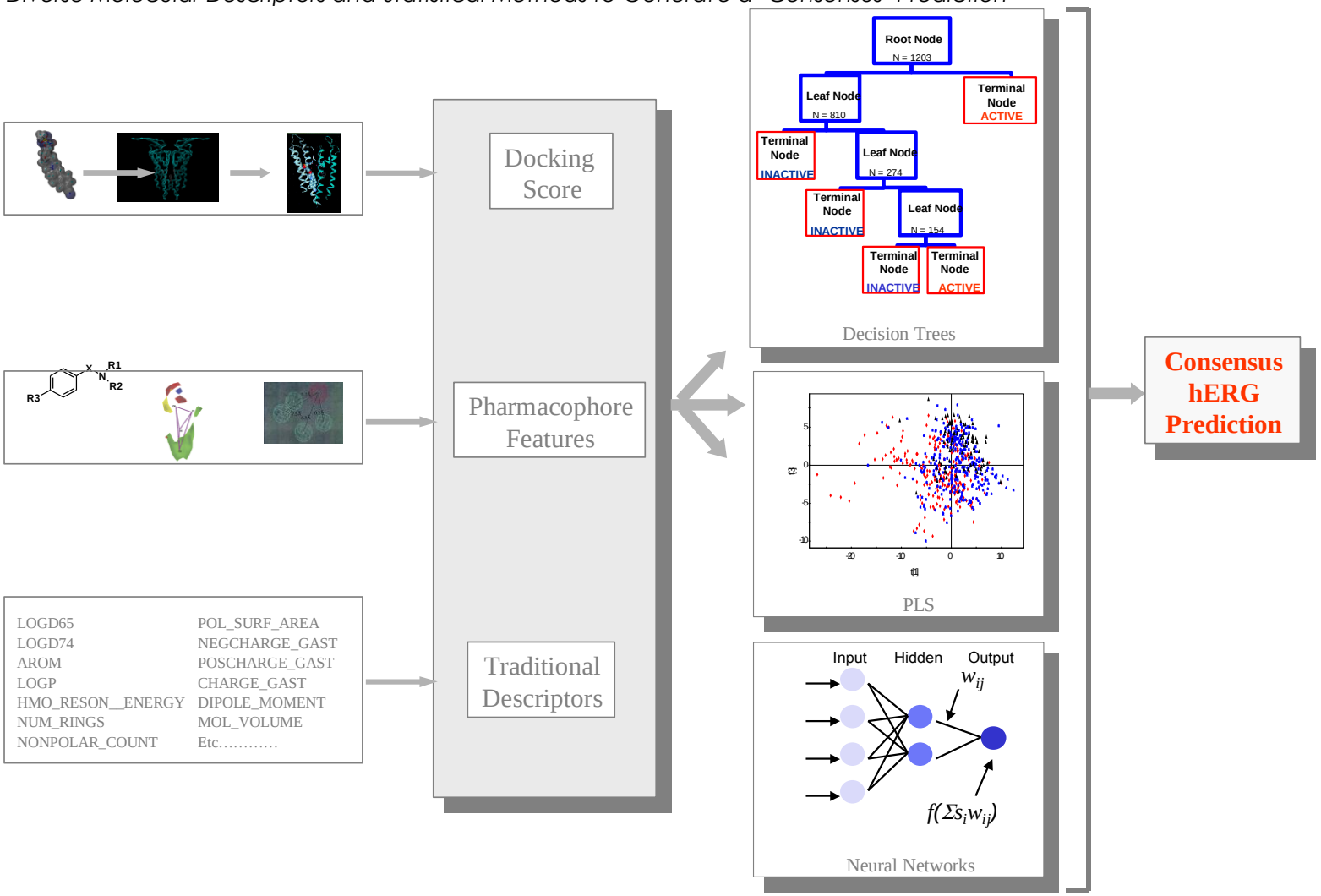
Prediction of effect on ventricular action potential duration based on measured activity at individual channels



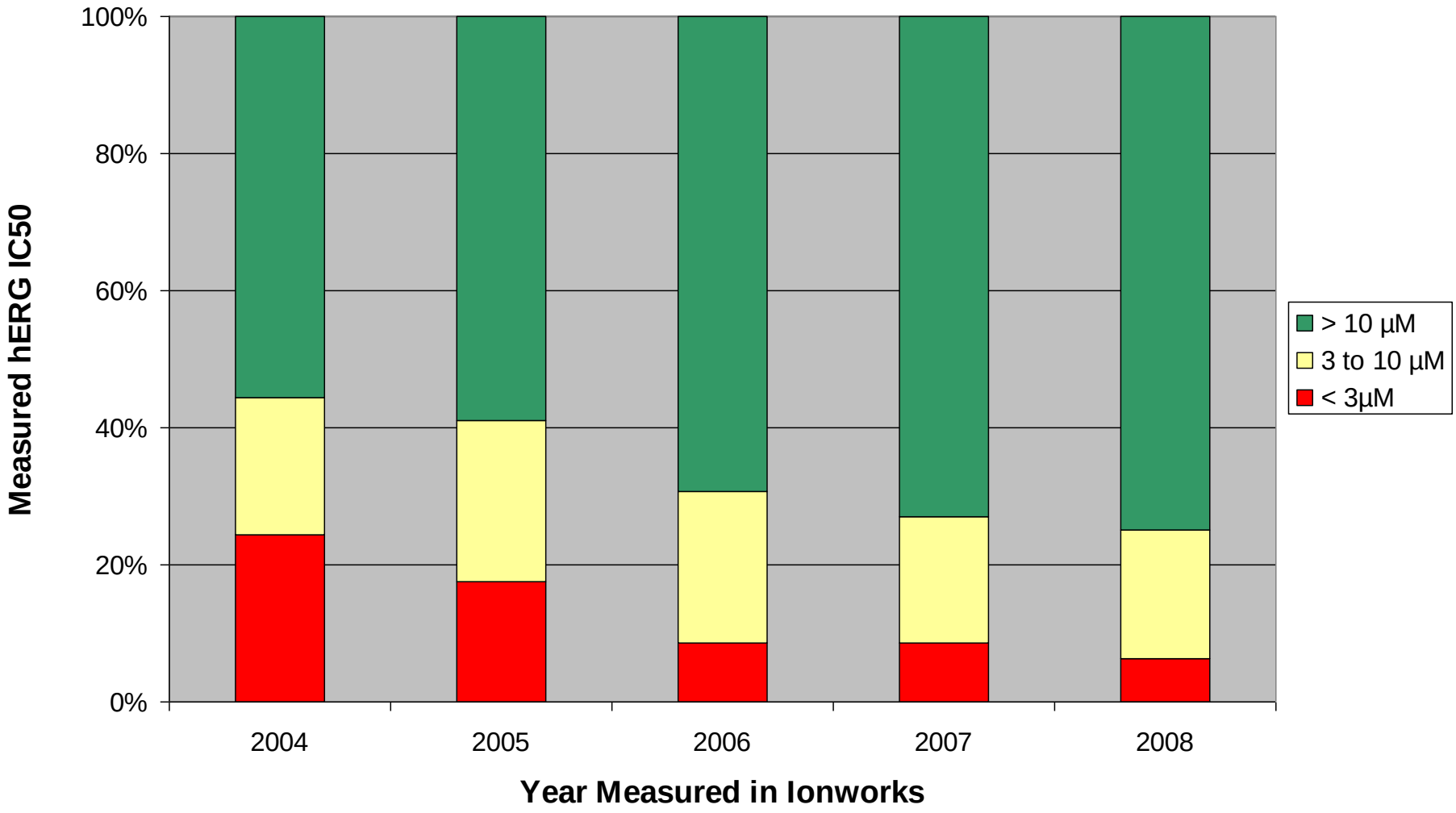
hERG QSAR in AstraZeneca

AstraZeneca hERG QSAR:

Diverse Molecular Descriptors and Statistical Methods to Generate a 'Consensus' Prediction



Impact : Less hERG related cardiac arrhythmia liability over time



In Silico Cardiac Ion Channel strategy

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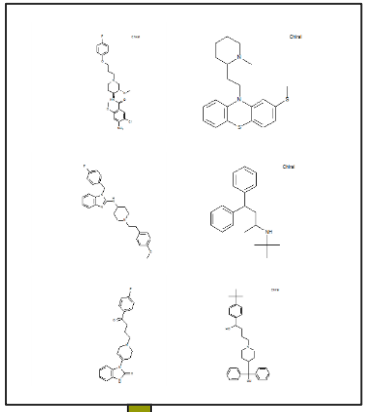

Predicted Activity at:
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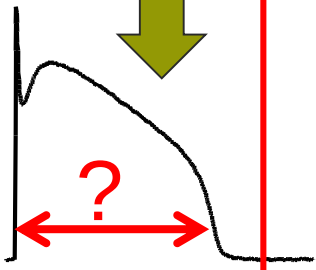
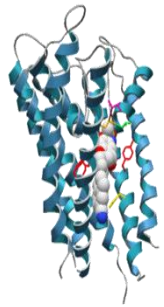
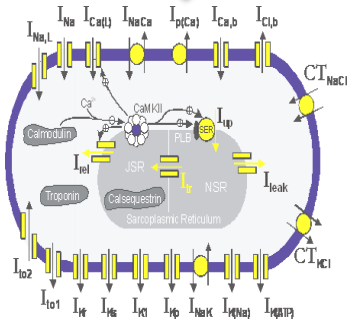


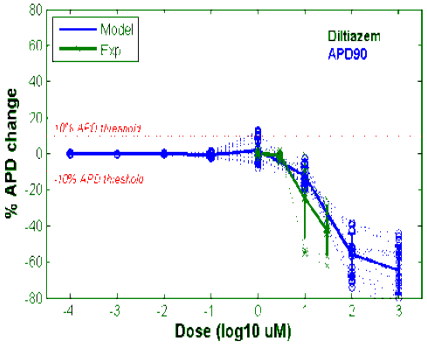
Multi-Scale Modelling: Assessing Cardiac Safety

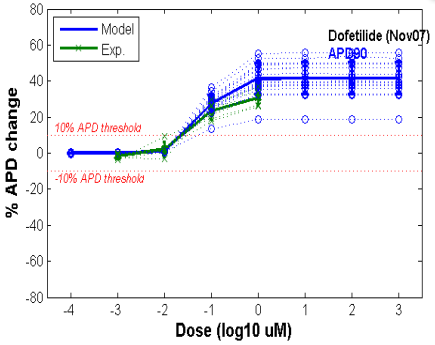


Modelling of Interactions on the Protein Level

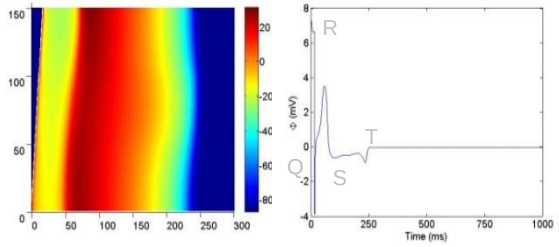


Modelling of Action Potential 'System'





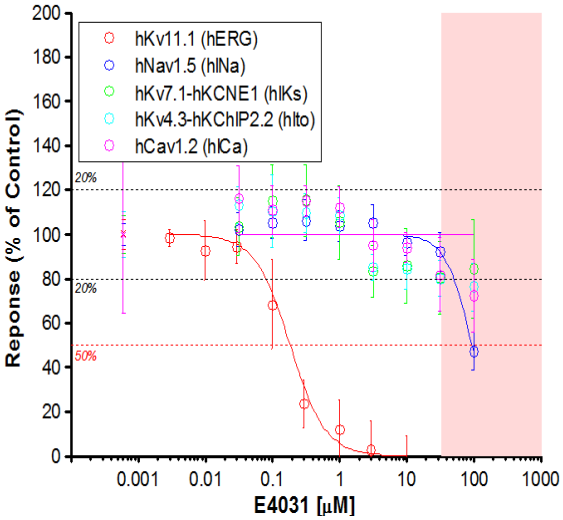
Prediction of Effects on Action Potential Duration

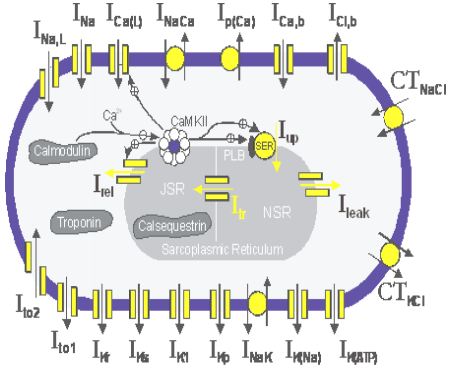


Prediction of Effects on Q-T Interval

Systems Model of Cardiac Ion Channels

Potent, selective hERG blocker





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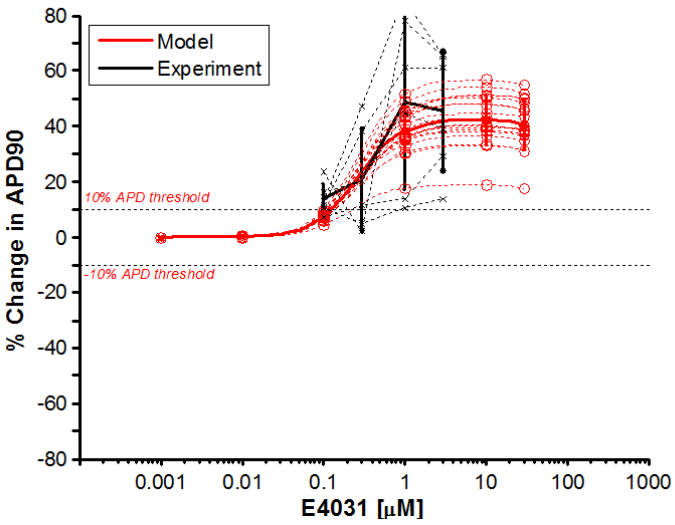
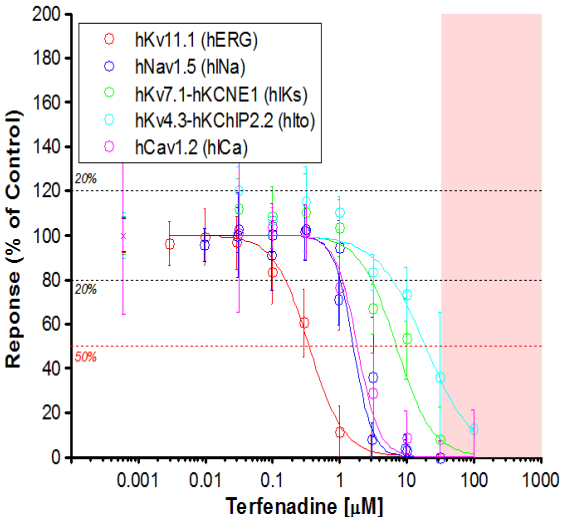
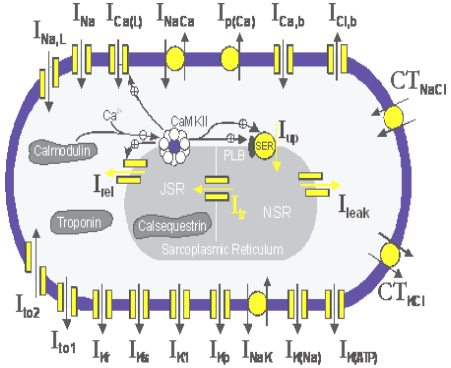


Systems Model of Cardiac Ion Channels

Potent, relatively non-selective hERG blocker





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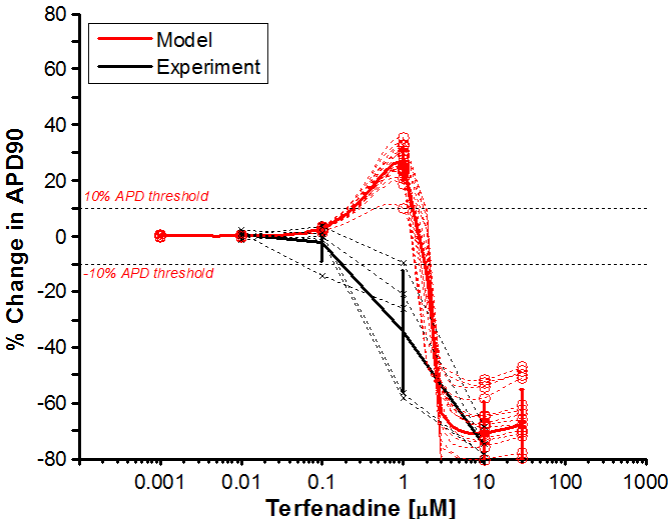
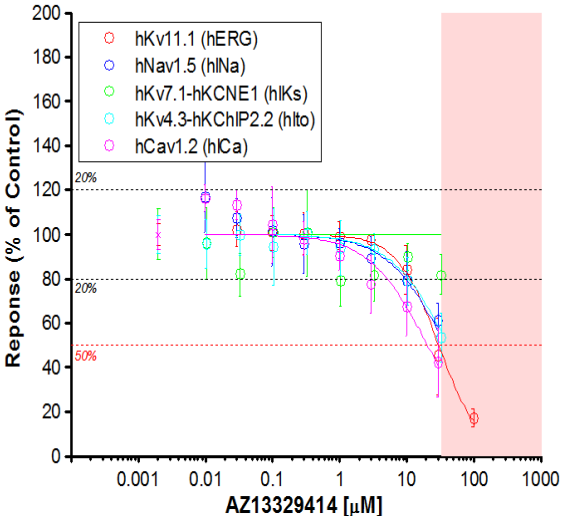
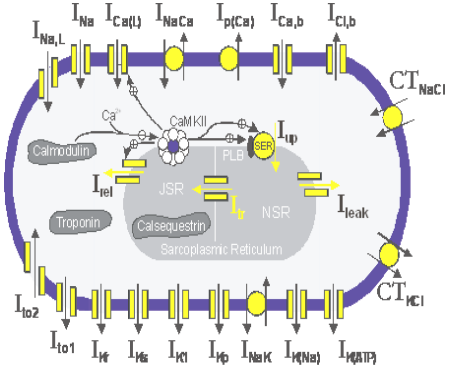


Systems Model of Cardiac Ion Channels

Low potency, non-selective blocker





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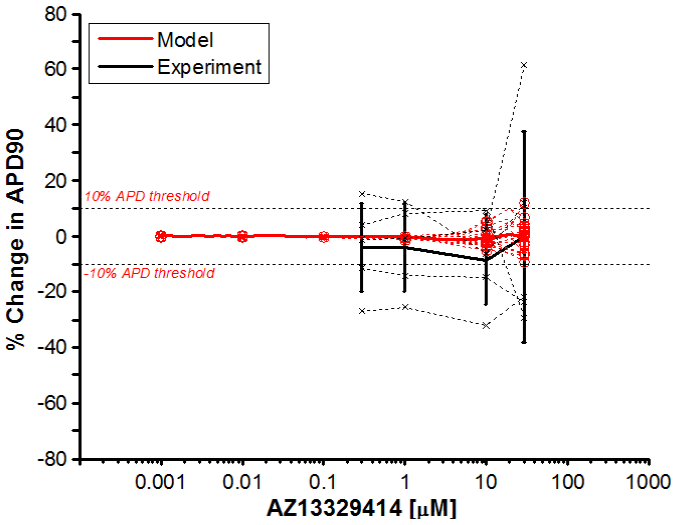
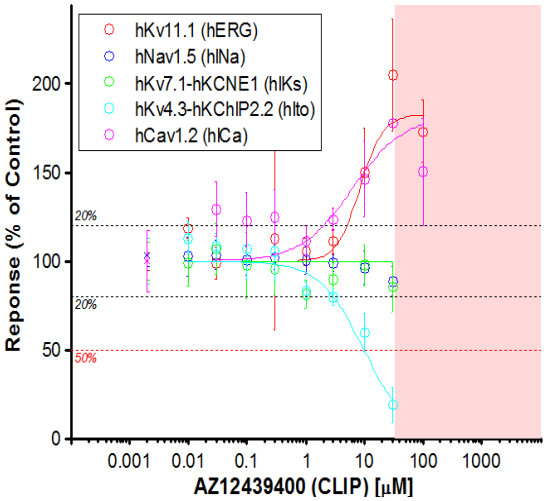
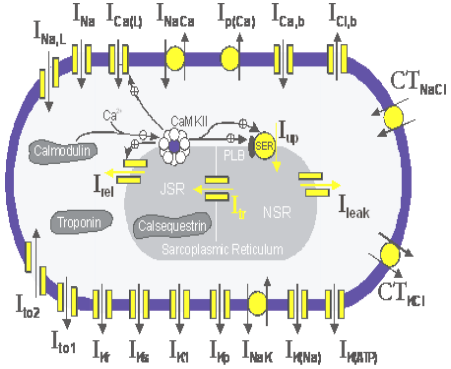


Systems Model of Cardiac Ion Channels

Compound that activates some channel types and blocks others





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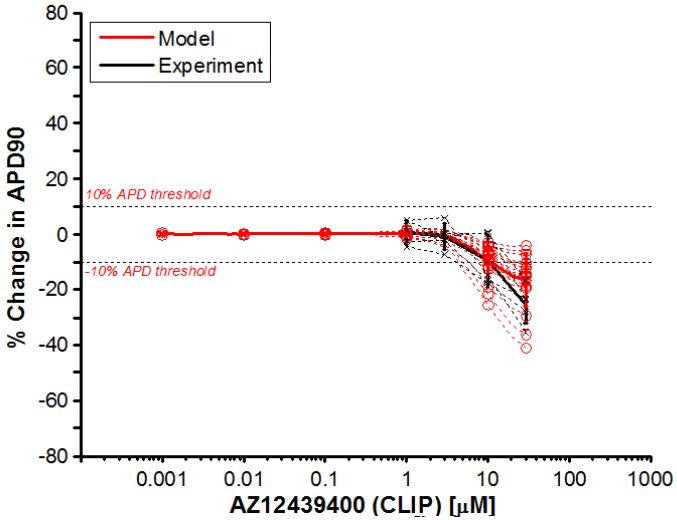
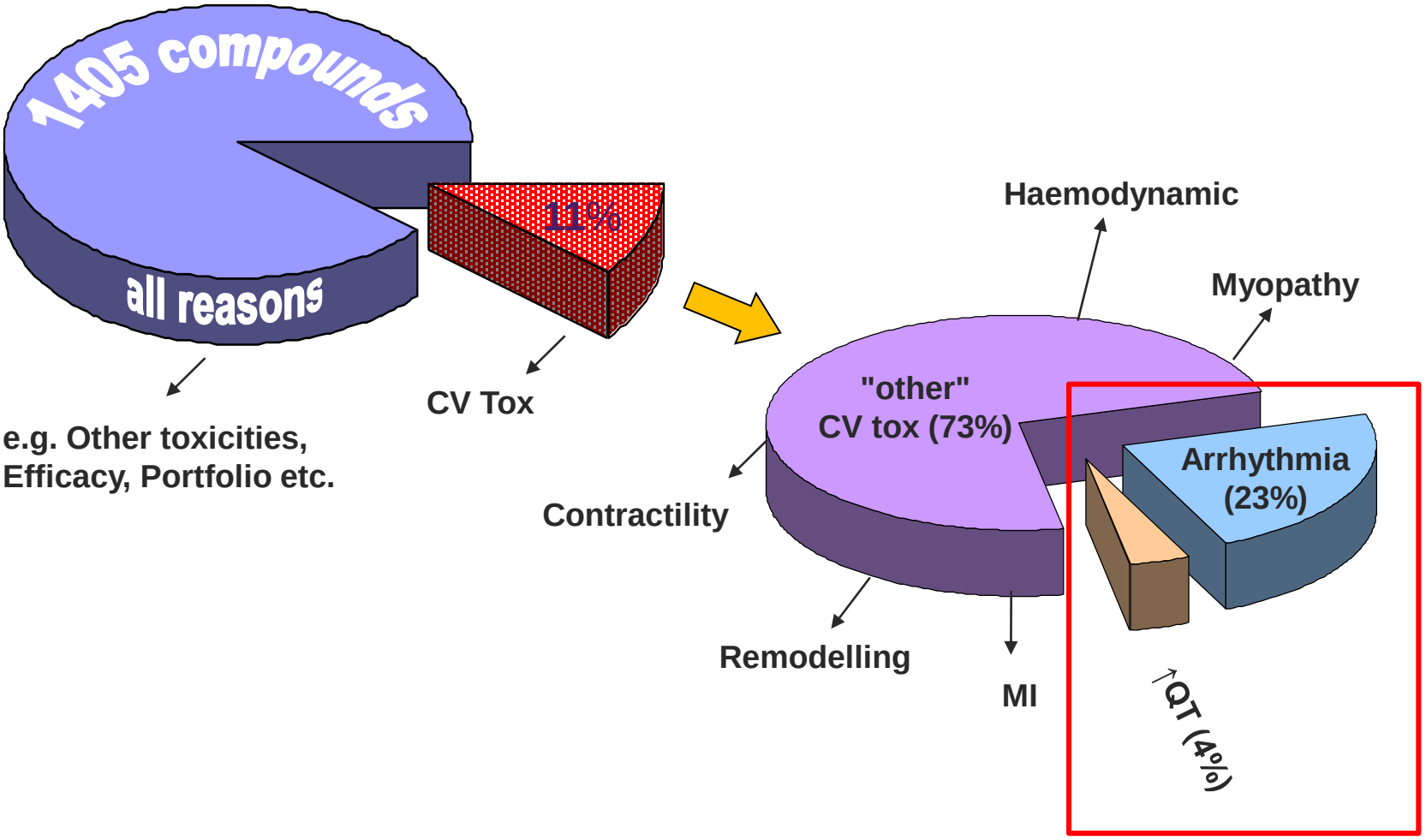
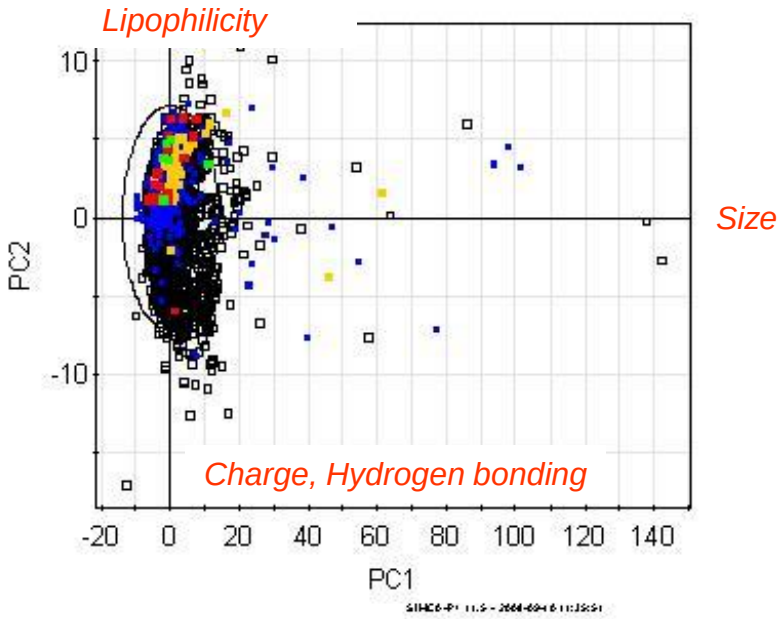


Moving beyond arrhythmias
Cardio-Vascular toxicity and Drug Withdrawals post Phase I



Moving beyond arrhythmias

- Drugbank
- Withdrawn CV (Arrhythmia)
- Withdrawn CV (Long QT syndrome)
- Withdrawn (other CV tox)
- Withdrawn (other)



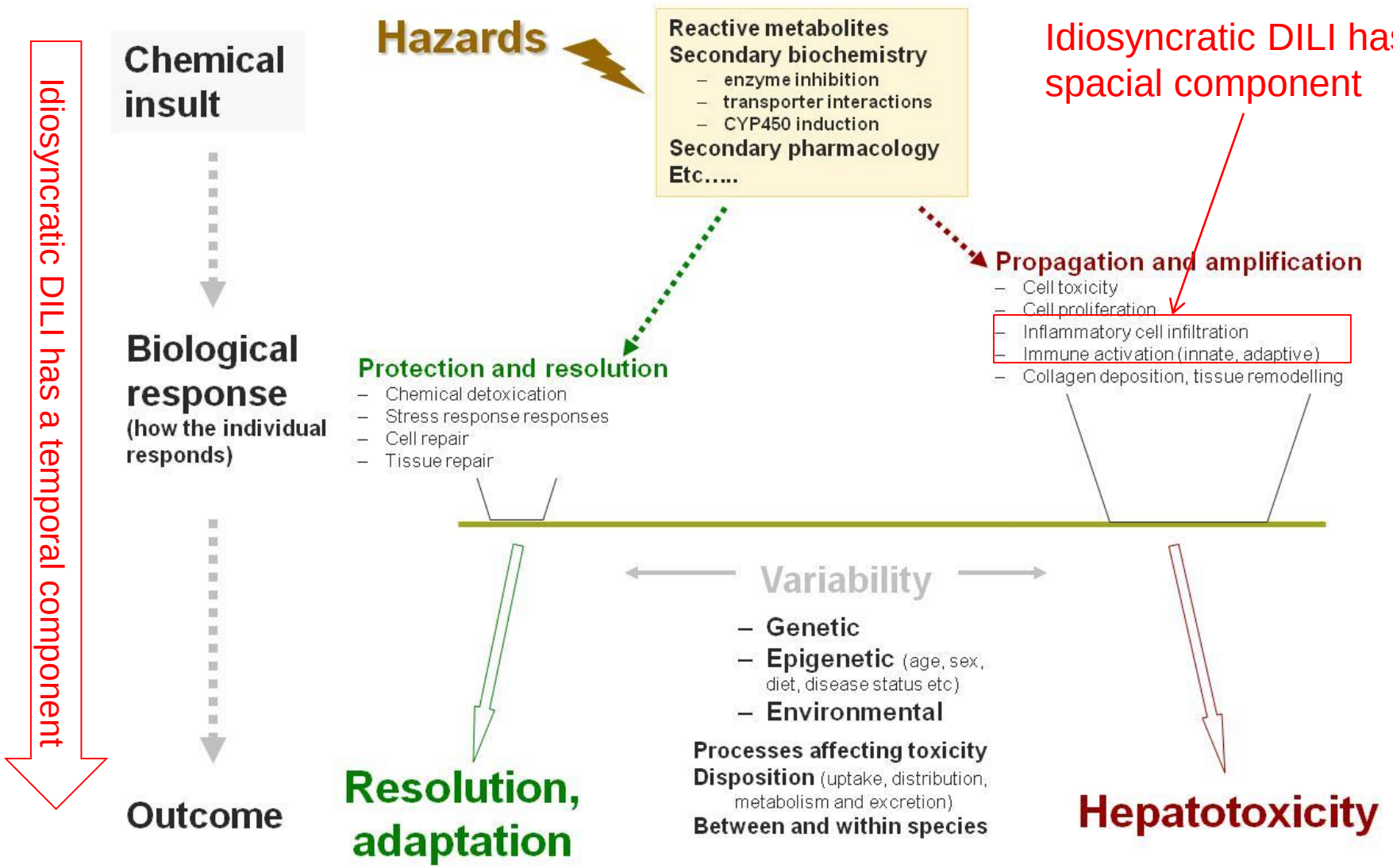
- QSAR modelling for compounds with CV toxicity
  - Molecules with similar properties are plotted close together
  - Plot of withdrawn compounds overlaid on all compounds in DrugBank
- No clear structural bias of compounds with CV toxicity beyond a tendency towards lipophilic molecules (shared with most withdrawn compounds)
  - Cannot predict CV liability solely based on molecular structure

- ***Despite data complexity, too much "biology" for this approach to work***
- ***Biological understanding is lacking: what are the molecular mechanisms?***
- ***Need to improve the basic science before we can develop further models***

Dynamic modelling: Focus on idiosyncratic DILI

- Drug-induced liver injury (DILI)
  - Intrinsic: predictable, dose dependent e.g. acetaminophen
  - Idiosyncratic: unpredictable, dose independent (?)
- For pharmaceuticals, idiosyncratic DILI accounts for a significant number of patient deaths annually
- These occur in a minority (by definition) of patients
- Occurs late in the clinical development phase or even post-marketing
  - Cost the industry $$$$$
- Regulators are demanding larger and larger trials, beyond that required to establish efficacy, in attempts to detect idiosyncratic drug reactions
  - Cost $$$$
  - Delays getting new medicines to patient
- Need new approaches to the early prediction of idiosyncratic DILI
  - Preclinical screens (in vitro, in vivo)
  - Early clinical trials (biomarkers)
- **People are not even a good model of people!**
- **Can dynamic modelling render the unpredictable, predictable?**

Idiosyncratic DILI is…well…complicated!



Idiosyncratic DILI is multi-factorial due to a "perfect storm" of factors

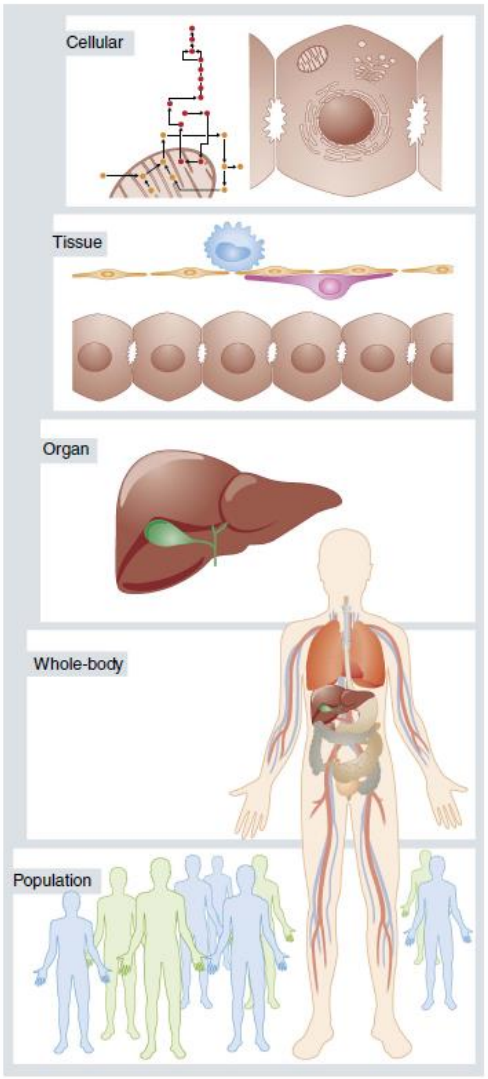

The DILI-sim Initiative
April 7, 2011
The UNC-Hamner Institute for Drug Safety Sciences
The Hamner Institutes for Health Sciences
Research Triangle Park, NC

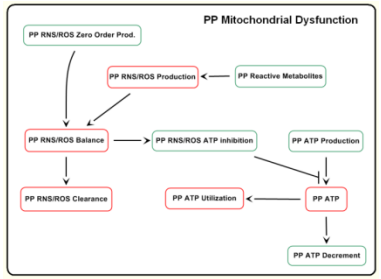
Goals of DILI-sim

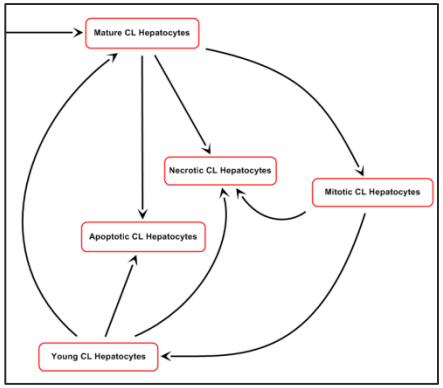
	Industry hepatotoxicity challenges	DILIsym™ model contributions
Nonclinical	• *in vitro* to *in vivo* extrapolation across mouse, rat, and dog • Animal to human translation • Identifying and/or evaluating DILI biomarkers **NEAR-TERM GOAL**	• *Predict in vivo hepatotox across species from minimal in vitro data inputs* • *Use simulations to propose candidate biomarker combinations and/or mechanistic links*
Phase II/III Clinical Trials and Post-Market Surveillance	• Interpretation of clinical liver signals: Due to drug or comorbidity? • Identifying and/or evaluating DILI biomarkers **LONGER RANGE GOAL**	• *Predict hepatotox response across wide range of patient types* • *Use simulations to propose candidate biomarker combinations and/or mechanistic links*

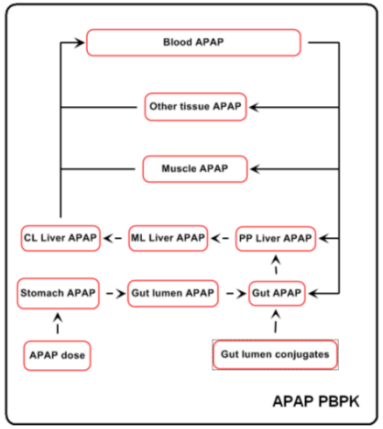
Aim is to provide tools that can help integrate and interpret structural, *in vitro* and *in vivo* data to predict likely hepatic responses in preclincal species and ultimately man

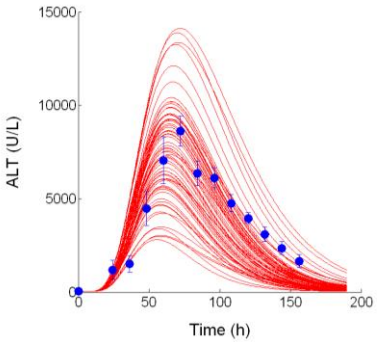
The DILI-sim Modeling Approach: Multi-Scale "Middle-out" approach







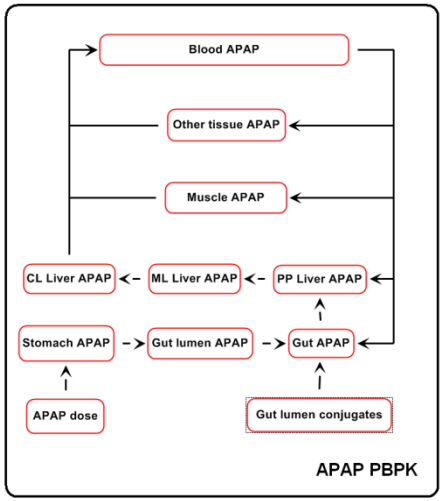




Kuepfer 2010, Molecular Systems Biology

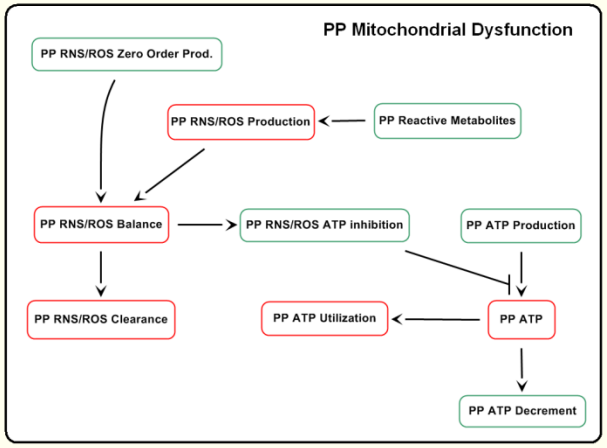
DILIsym™ Model v1.0 Sub-model Interactions:
Drug Metabolism, GSH, and Mito. Dysfunction

Drug distribution & metabolism

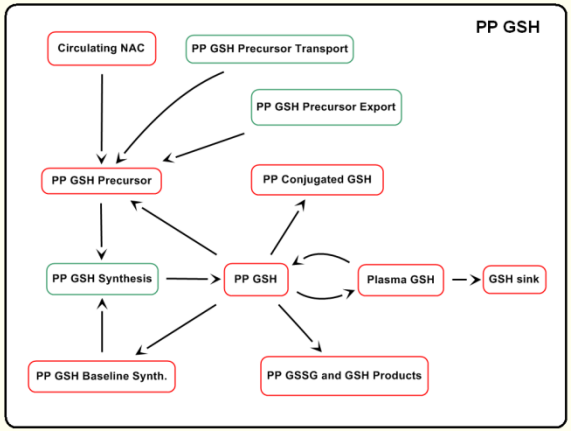


RM

Mitochondrial

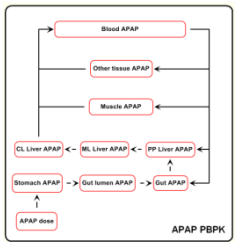


GSH depletion & recovery

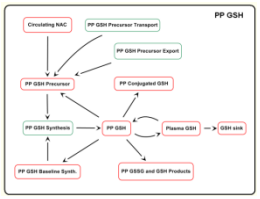


Form to Function Approach Links Dynamic Changes in Hepatocytes to Liver Function

Drug distribution & metabolism

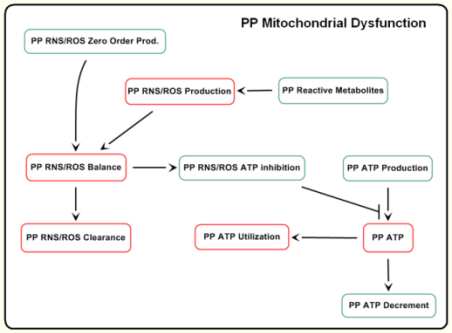


GSH depletion & recovery

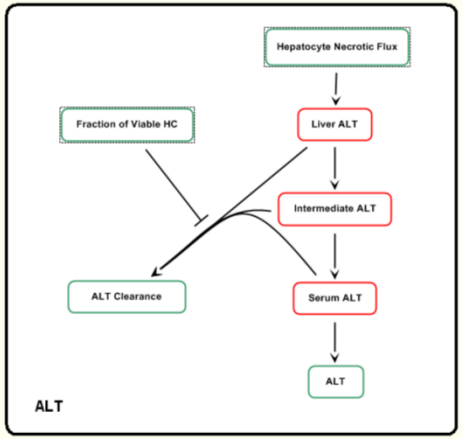


RM

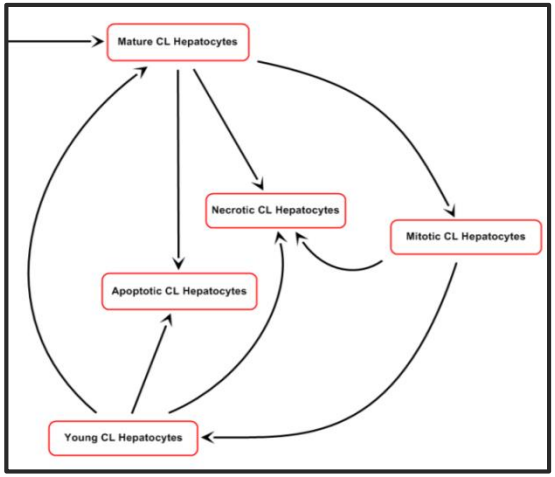
Mitochondrial dysfunction



Biomarkers



Hepatocyte life-cycle



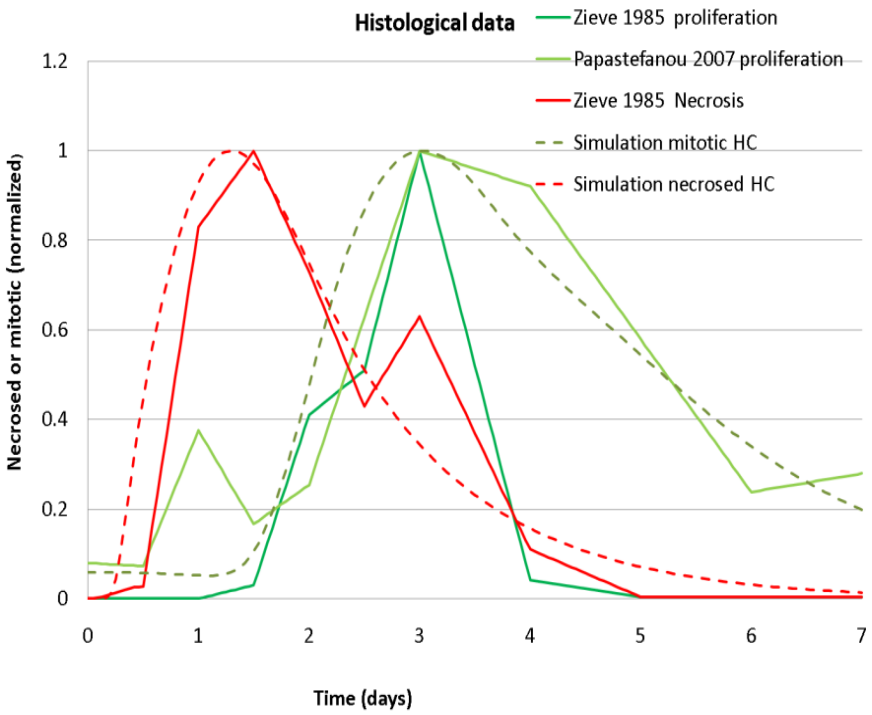
Immune mediators

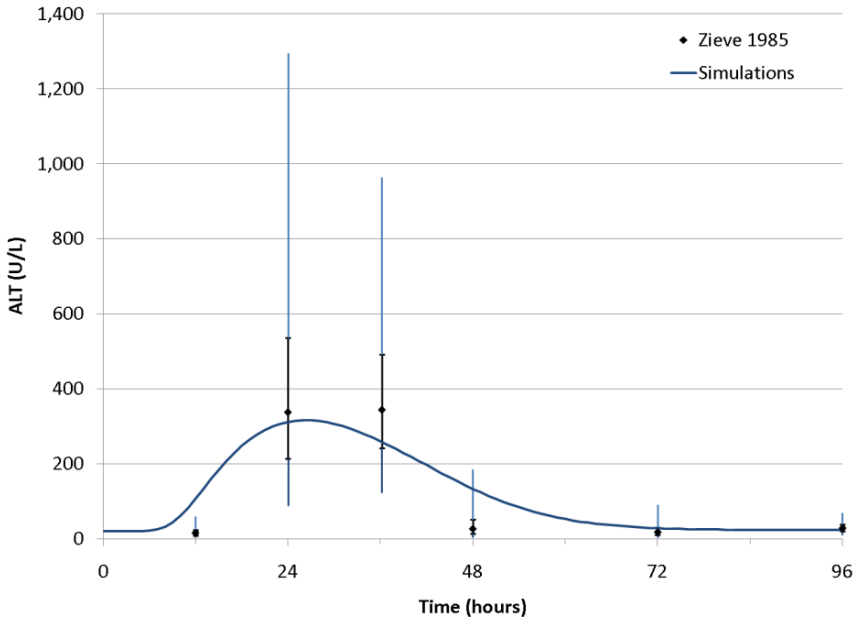
'Form to function'

THE HAMNER INSTITUTES FOR HEALTH SCIENCES

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

Good Agreement Between Simulations and Measured Data in Rats Following APAP Overdose



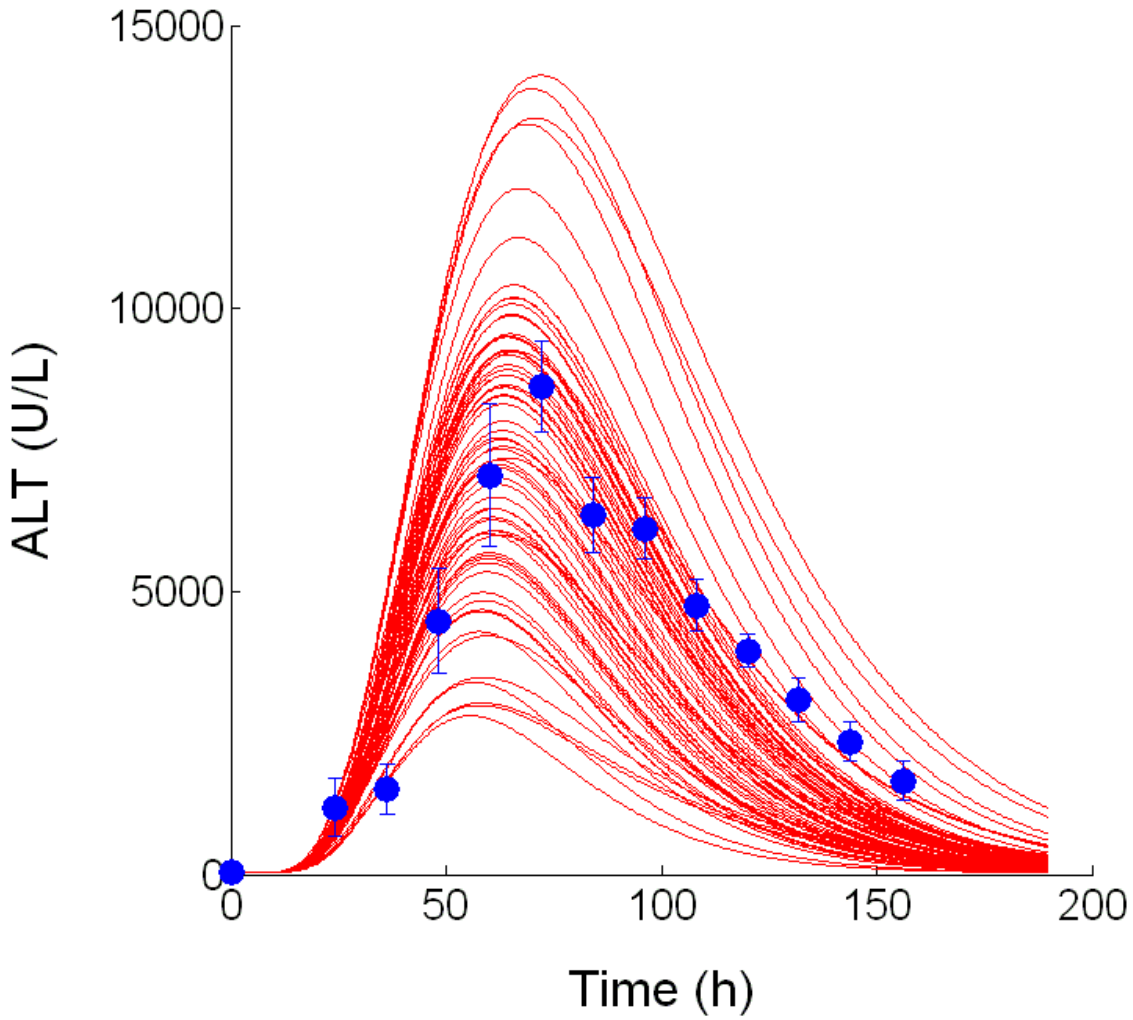


RATS

Inter Quartile Range &
95% Confidence Interval shown

Preclinical data and simulation results

Population Sample Generation – Humans



HUMANS

Schiodt 2001

39g mean APAP dose
34 hr mean NAC delay

n = 37

** Red lines indicate simulated humans*

Clinical data and simulation results

CONCLUSIONS

- Toxicology is intrinsically a problem in systems biology
  - “Pathology with numbers”
- Lots of data and information but often little knowledge
  - Understanding of key drives such as hERG and cardiac ion channels are not always known
- Mutlifactoral, temporal responses involving environmental and genetic factors
  - Understanding and prediction demands a quantitative approach
- First generation models are coming on line
  - Summarising and organizing information – knowledge repositories
  - May fail, but in organizing the data will help us understand gaps
- Investments in systems models for safety are easier to justify
  - Models have both longevity and breadth of application
    - Used for many projects over many years
  - Investments in large-scale approaches can be justified because of the nature of the problem, when it occurs and returns if successful
  - *Huge scope for pre-competitive working in this space*

Has Systems Biology finally found a true home in pharmaceutical R&D?

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