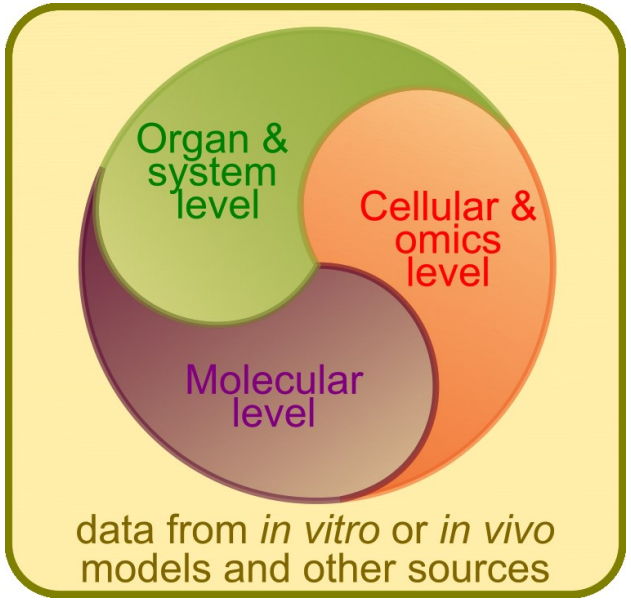
Multiscale Modelling of Drug Safety



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OpenTox 2019

Roche *pRED*

The parabole of blind men and an elephant

Six blind men were asked to inspect an elephant.

They are asked to identify the object before them which they cannot see.

One man, feeling the elephant's leg, thinks he is touching a tree trunk.

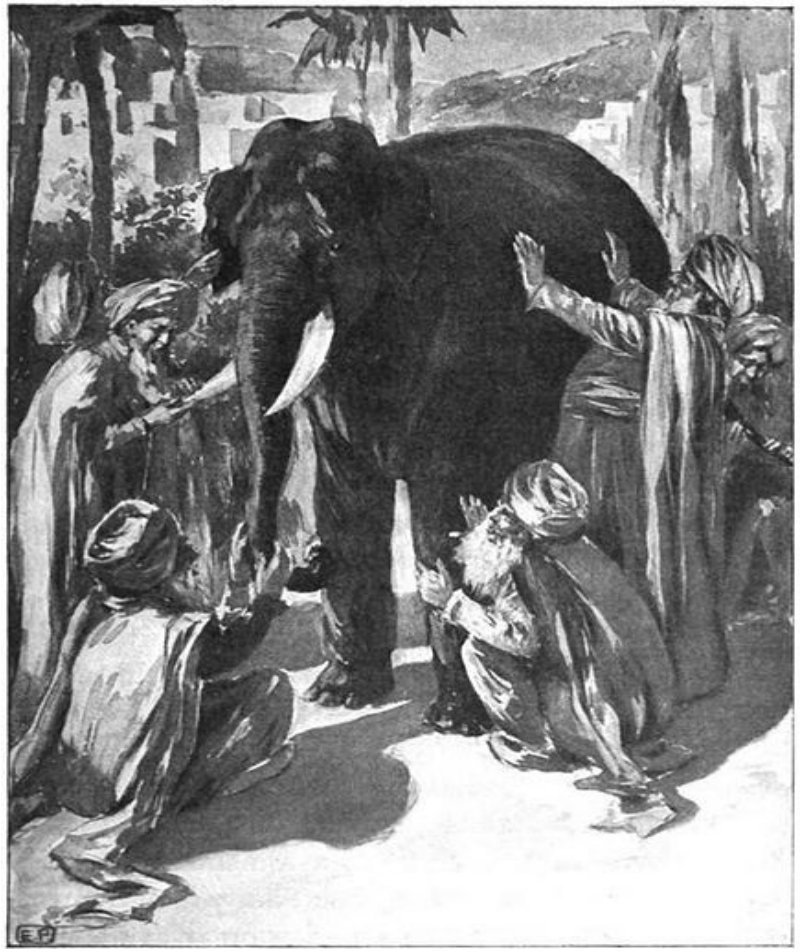
Another, grasping the elephant's trunk, thinks he is holding a snake.

A third, standing near the moving ear, thinks it is a large, feathered fan.

And so it goes for the other men touching the tusk, the side, and the tail.

Each man gave a different description of the same object.

But none was correct.



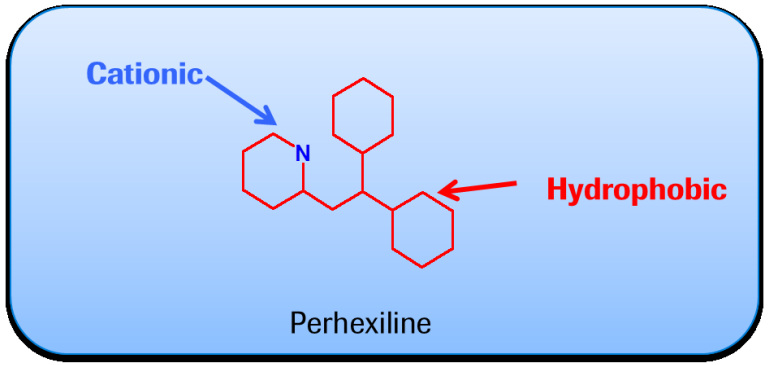
The drawing, *Blind men and an elephant,* is cited from *The Heath readers by grades,* D. C. Heath and Company (Boston). It is in the public domain in the United States and downloaded from wikimedia. The text was adapted from *Modeling Biological Systems: Principles and Applications* (2nd edition) by James W. Haefner.

Case study of molecular modelling

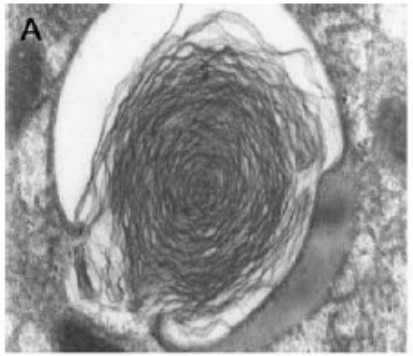
An *in silico* assay for assessing phospholipidosis potential of small druglike molecules

Drug-induced phospholipidosis is correlated with amphiphilicity

- Phospholipidosis is a lysosomal storage disorder characterized by the excess accumulation of phospholipids in tissues.
- *Drug-induced* phospholipidosis is caused by cationic amphiphilic drugs and some cationic hydrophilic drugs.



Lüllmann *et al.*, Drug Induced Phospholipidosis, *Crit. Rev. Toxicol. 4, 185, 1975*



Anderson and Borlak, Drug-Induced Phospholipidosis,. *FEBS Letters* 580, Nr. 23 (2006): 5533–40.

$$\vec{A} = \sum_i d \cdot \vec{\alpha}_i$$

Fischer *et al.* (Chimia 2000) discovered that it is possible to predict the amphiphilicity property of druglike molecules by calculating the amphiphilic moment using a simple equation.

$\vec{A}$: Caculated amphiphilic moment

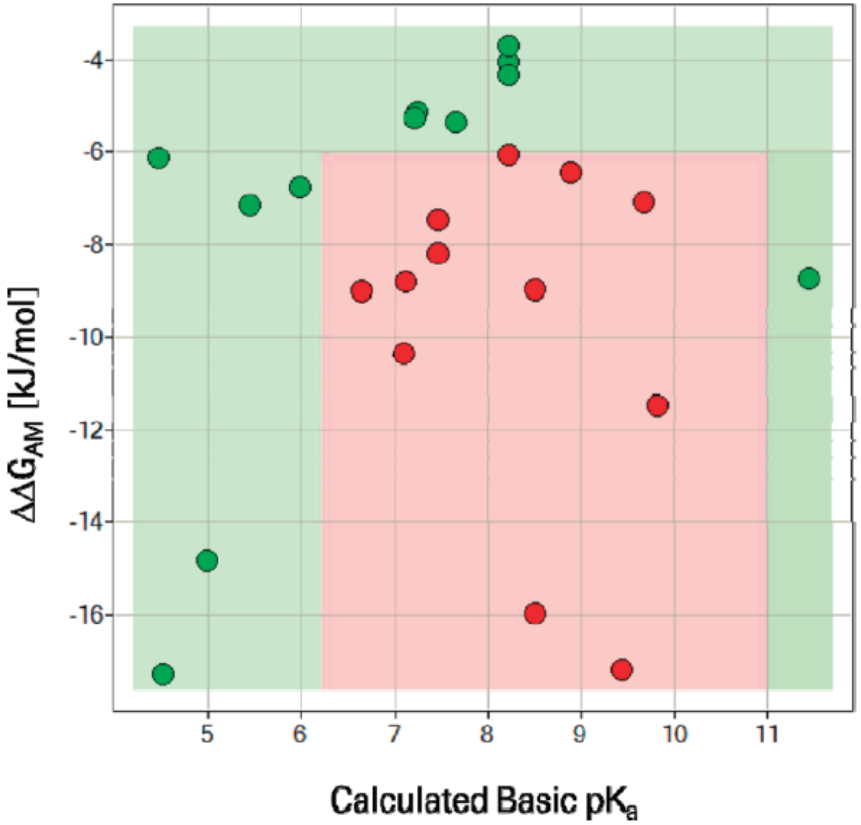
d: distance between the center of gravity of the charged part of a molecule and the hydrophobic/hydrophilic remnant of the molecule

$\vec{\alpha}_i$: the hydrophobic/hydrophilic contribution of atom/fragment *i*

***In silico* calculation of amphiphilicity property may be used to predict phospholipidosis induction potential**

In silico phospholipidosis prediction

Model Validation from 1999-2004



Plot of amphiphilicity ($\Delta\Delta G_{AM}$) versus calculated basic pK_a for the training set of 24 compounds. The red area defines the region where a positive PLD response is expected, and the green area defines where a negative response is expected according to the tool.

in vitro/ in vivo	in silico/ in vivo	Exp. PC/ in vivo	In silico/ in vitro	n=36
94%	81%	89%	89%	

in vitro/in silico			n=422
Accuracy [(TP+TN)/ (P+N)]	**Sensitivity [True Positive Rate]**	**Specificity [True Negative Rate]**	**Precision [TP/(TP+FP)]**
86%	80%	90%	84%

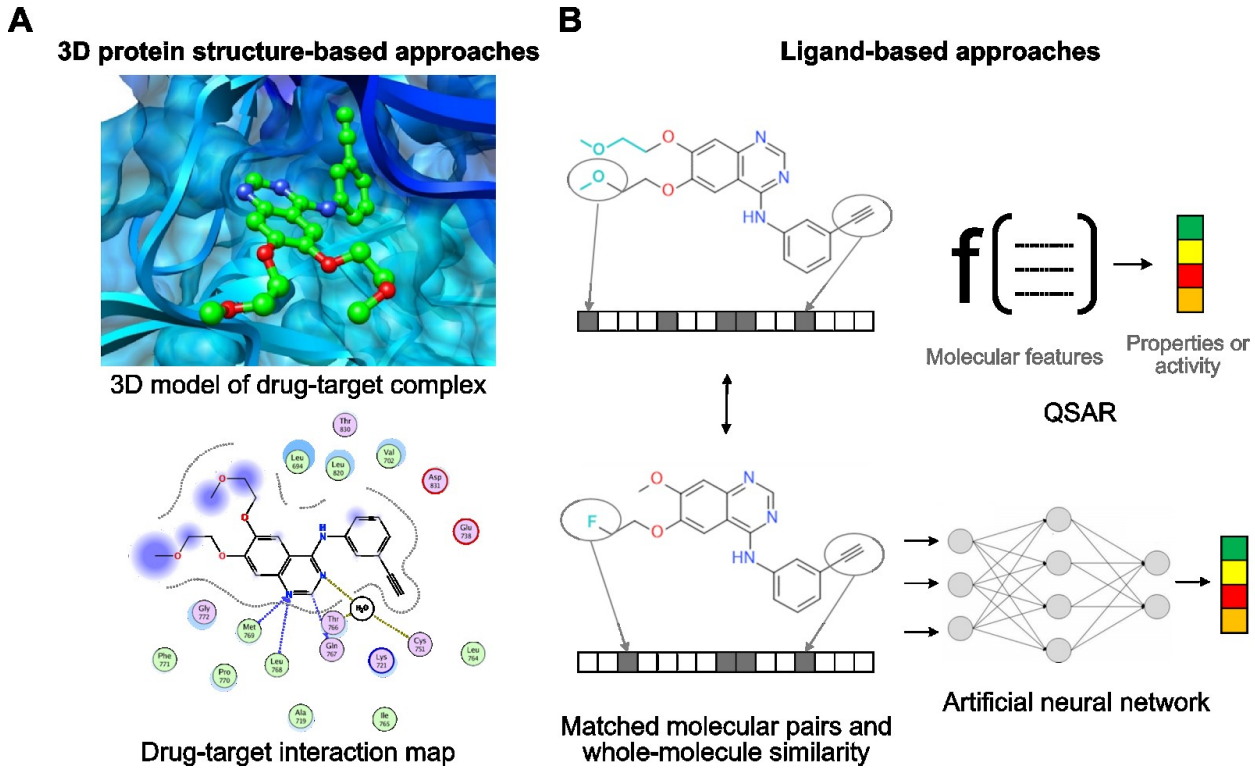
Fischer et al., *J. Med. Chem, 55 (1), 2012*

We gained mechanistic insights of phospholipidosis induction by cationic amphiphilic drugs with the model

Phospholipidosis: lessons learned

- Cationic amphiphilic properties of a molecule is an early marker for safety in drug discovery and early development.
- Extreme basic amphiphilic properties should be avoided because of a higher risk of PLD, QT-prolongation, mitochondrial toxicity.
- However, basic compounds with moderate amphiphilic properties are still a preferred scaffold for many therapeutic areas (especially CNS).

- **Generally, some safety liabilities, despite complex underlying biological and chemical mechanisms, can be predicted by molecular modelling well, sometimes with surprisingly elegant models!**

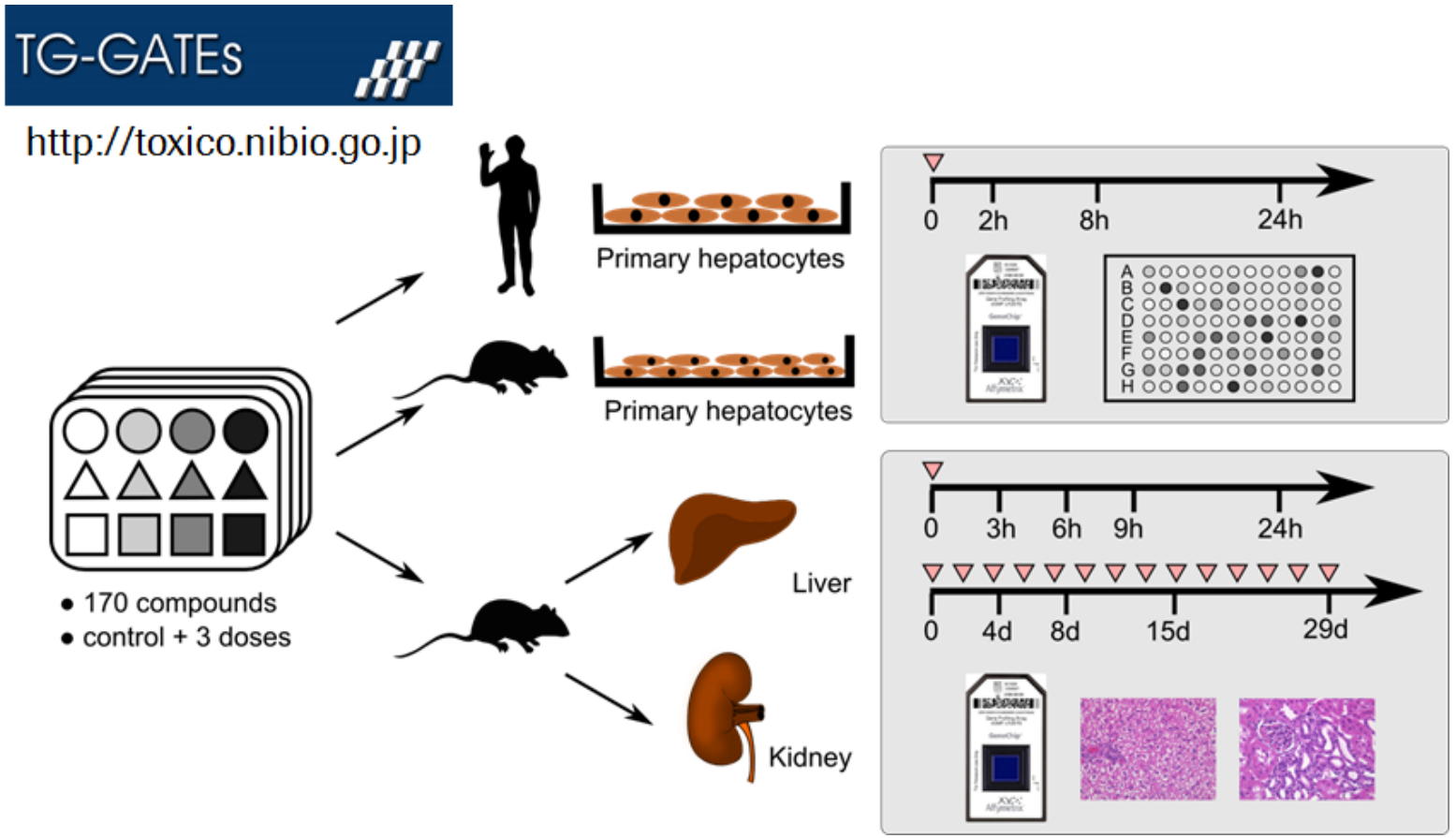


Overview of molecular-level modelling techniques

Case study of cellular & omics modelling

Understanding TG-GATEs data with gene networks and neural networks

Open TG-GATEs: Toxicogenomics Project-Genomics Assisted Toxicity Evaluation system



170
Compounds

>2000
Cellular assays

>12000
Pathology records

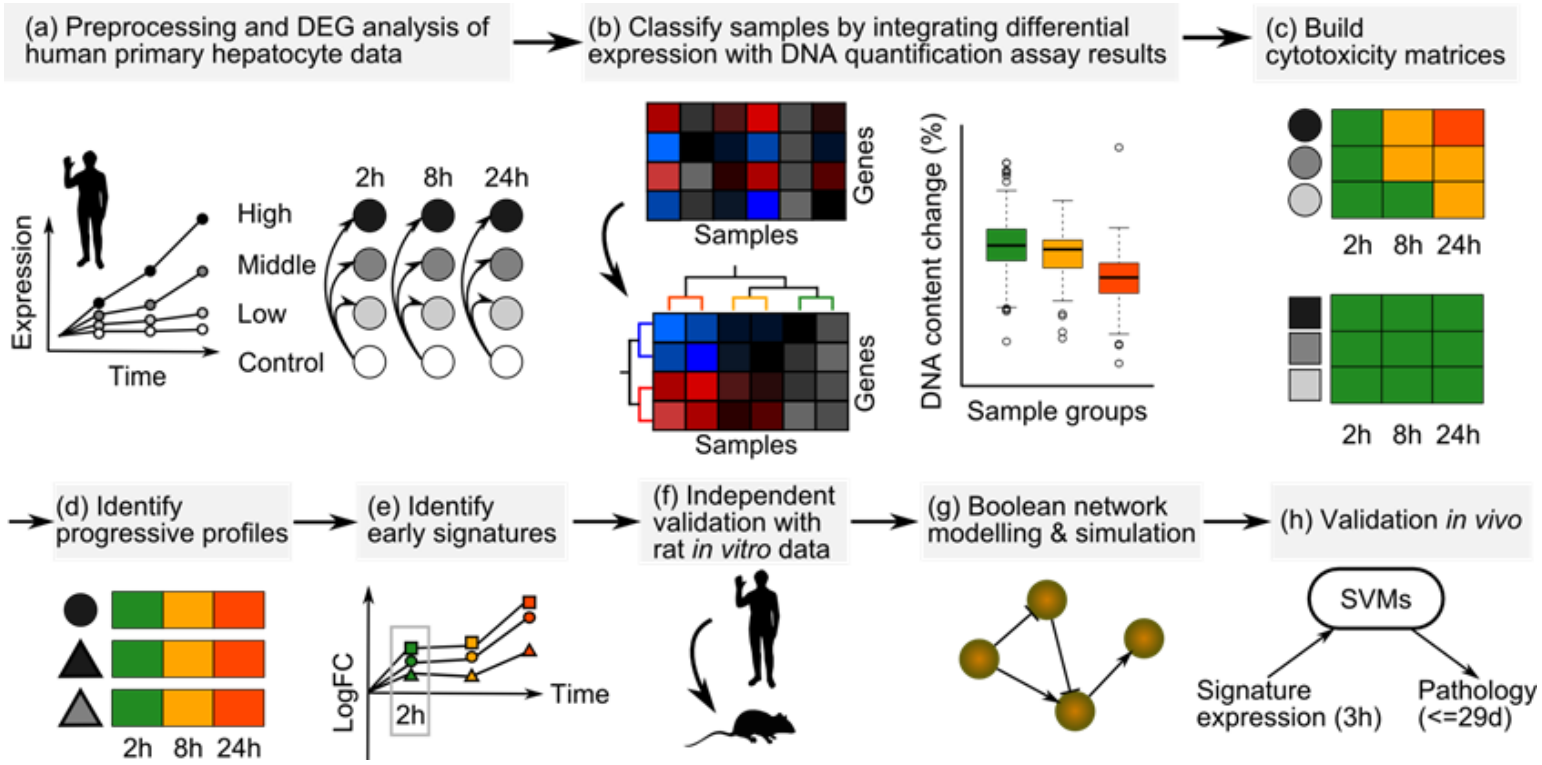
>24000
Expression profiles

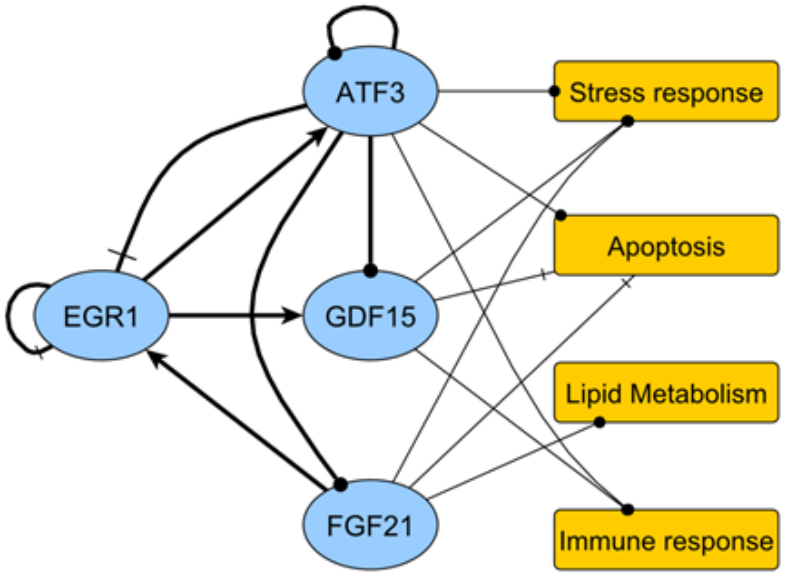
TG-GATEs is a rich resource to help the community to better understand drug-induced histopathology

We built a computational pipeline to mine the data, and identified a four-gene network predictive of toxicity

Analysis pipeline

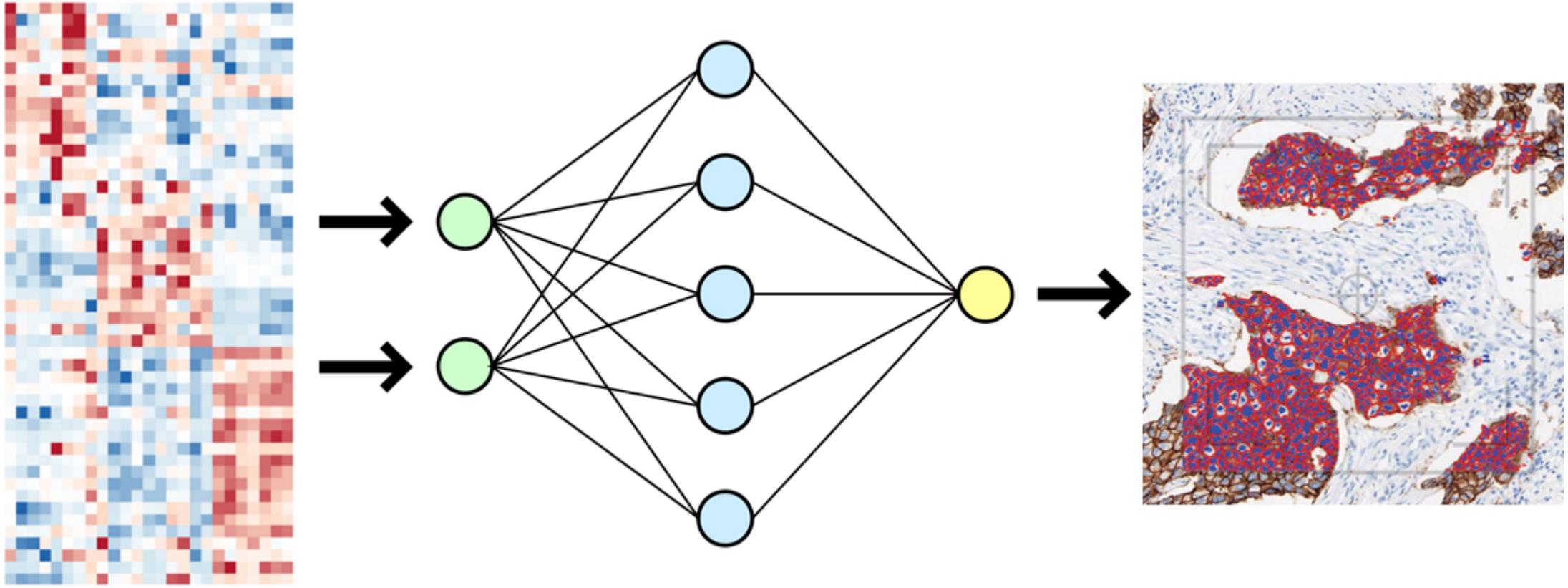
Zhang *et al.*, J. Pharmacogenomics, 2014





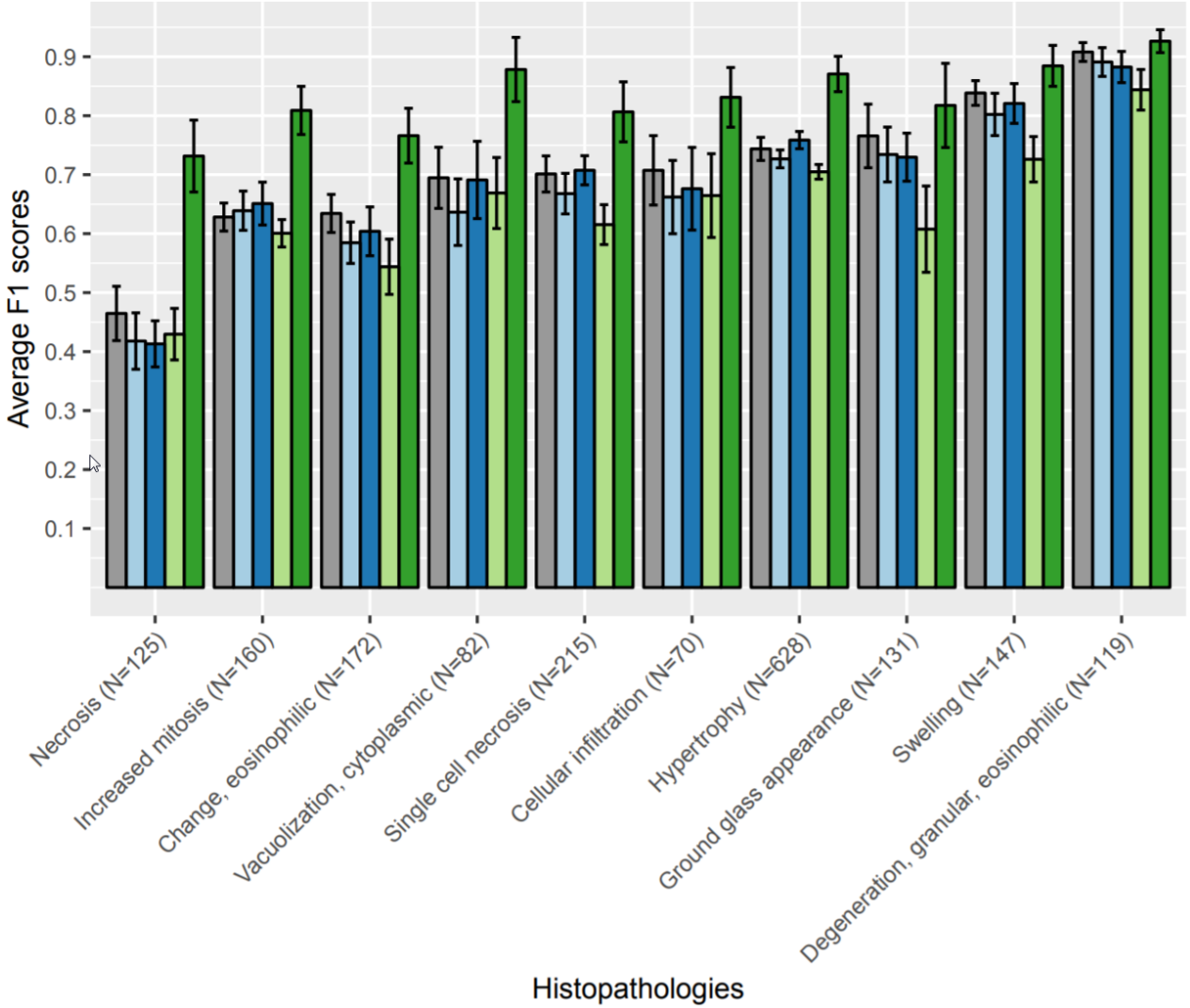
The model was built with unsupervised & supervised learning, network modeling, and integration of prior knowledge

Can we train deep-neural networks to predict drug-induced histopathology based on gene-expression?



Master thesis of Mr. Tao Fang (Roche BEDA alumni, currently at EBI)

Deep neural networks outperform other models for drug-induced liver histopathology prediction



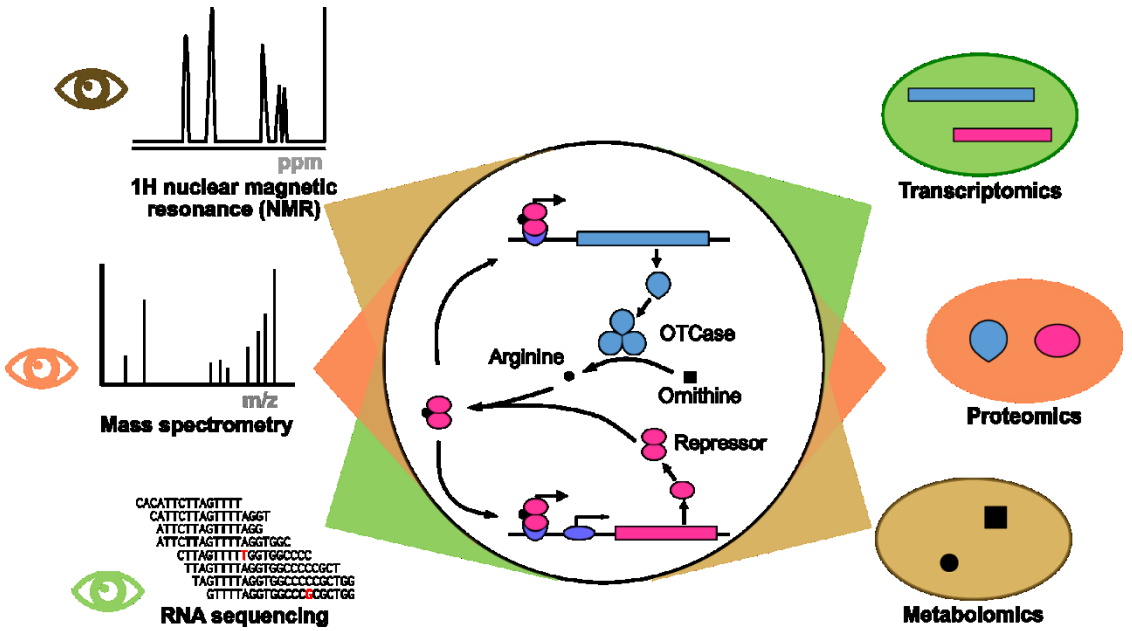
The data was split into 80% training and 20% validation data ten times. One model of each type was trained for each split. The average performance (F_1 score, the harmonic mean of precision and recall) and the standard deviation is reported.

LR = logistic regression
SVM = support-vector machines;
RBF = radial basis function kernel
DNN = deep neural networks
ml-DNN = multi-label DNNs.

Deep neural networks (DNNs) outperform other models in the task of gene-expression based histopathology prediction

TG-GATEs: lessons learned

- Gene expression profiling and more generally omics can be powerful for safety evaluation, especially when the safety issue can be caused by multiple factors and therefore becomes intractable using molecular modelling techniques only.
- We are working with advanced *in vitro* modelling systems, such as organ-on-a-chip and iPS-derived cells, as well as state-of-the-art profiling techniques, such as single-cell sequencing and imaging, to model preclinical safety profiles of drug candidates.
- **Some safety liabilities, especially phenotypes that converge at the downstream of diverse upstream mechanisms (such as drug-induced histopathology), may be predicted and modelled by omics and cellular level modelling. We strive at mechanistic and explanatory models whenever possible.**



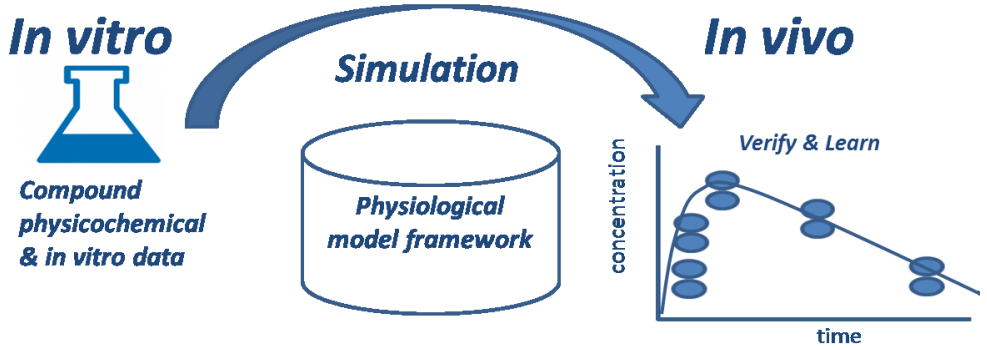
Omics data are projections of high-dimensional biological space. The inverse problem, *i.e.* to infer high-dimensional space from low-dimensional data, is very challenging, but it remains our goal to attain mechanistic and explanatory models whenever possible.

Case study of organ & system modelling

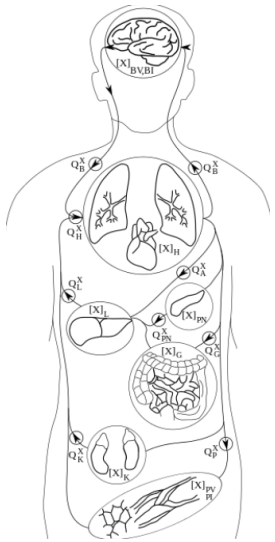
PBPK modelling and cardiac safety

Physiologically Based Pharmacokinetics (PBPK): an established and successful organ- and system-level modelling approach

- **PBPK**: A mathematical modeling technique for predicting the absorption, distribution, metabolism and excretion (ADME) of synthetic or natural chemical substances in humans and other animal species.



Verify in animal, predict in human



$$\frac{dC_{muscle}}{dt} = \frac{[C_{blood} - (C_{muscle} / R_{muscle})] \cdot Q_{muscle}}{V_{muscle}}$$

$$\frac{dC_{IS}}{dt} = \frac{[C_{blood} - (C_{IS} / R_{IS})] \cdot Q_{IS} + [k_{slow}(1-F)BW \cdot DOSE) + (k_{fast} F \cdot BW \cdot DOSE)]}{0.5}$$

$$\frac{dC_{liver}}{dt} = \frac{[C_{blood} - (C_{liver} / R_{liver})] \cdot Q_{liver}}{V_{liver}}$$

$$\frac{dC_{fat}}{dt} = \frac{[C_{blood} - (C_{fat} / R_{fat})] \cdot Q_{fat}}{V_{fat}}$$

A retrospective analysis in 2017, which covered more than 30 Roche projects in a 14-year time span, found that **accuracy of PBPK predictions confirmed with observed AUC within 2-fold in ~70% cases** (ref. 2). The study identified weak points and suggested actions taken to improve.

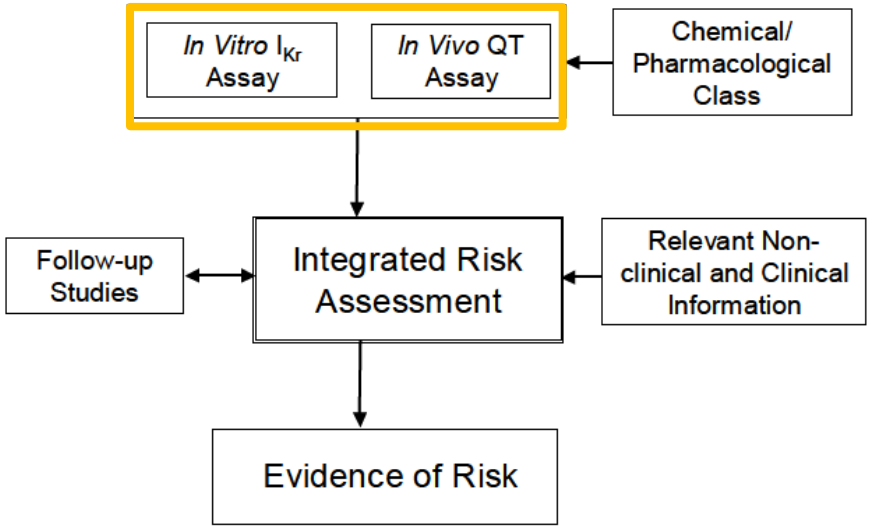
1. Jones, Hannah M., Neil Parrott, *et al.* „A Novel Strategy for Physiologically Based Predictions of Human Pharmacokinetics“. *Clinical Pharmacokinetics* 45, Nr. 5 (1. Mai 2006): 511–42.
2. Neil Parrot *et al.* „Physiologically-Based Pharmacokinetic Modeling Predictions for Entry into Human Studies. An Analysis of Small Molecule Development Candidates at Hoffmann-La Roche, 2003-2016“. ASCPT Annual Meeting 2017

PBPK modelling examplifies how organ- and system-level modelling helps to study drug mechanism and safety

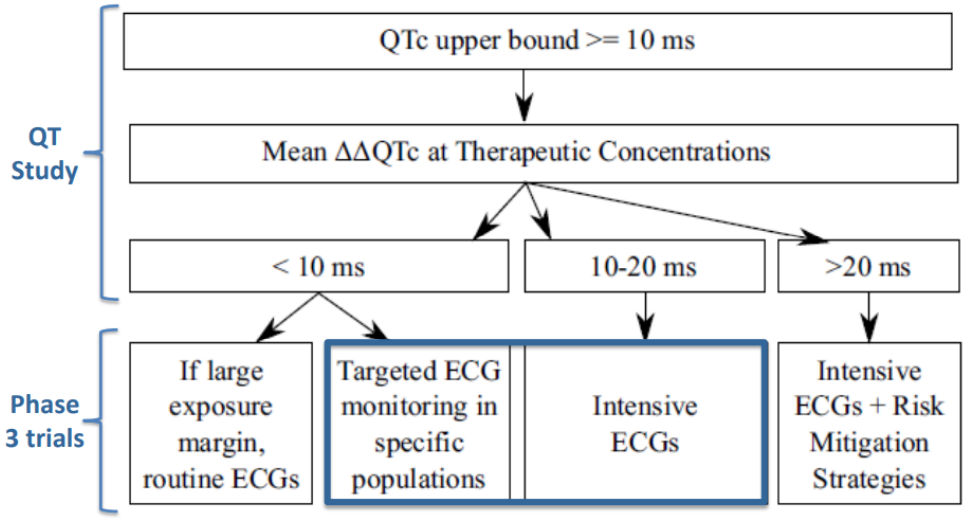
Current cardiac safety paradigm

Conservatively "safe", but very costly

The current ICH S7B



The current ICH E14

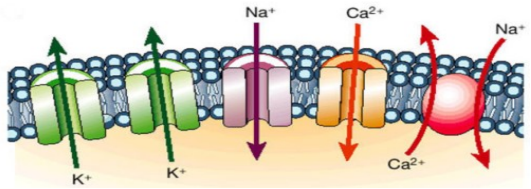


- Guidelines resulted in no new drugs with unrecognized torsade risk
- **But** the **lack of specificity** and the associated **significant cost** of unnecessary intensive ECG monitoring, black label and premature discontinuation of promising drug candidates was well recognized by the regulators
- **No clear "integration"** between S7B and E14 (identified in ICH assembly)

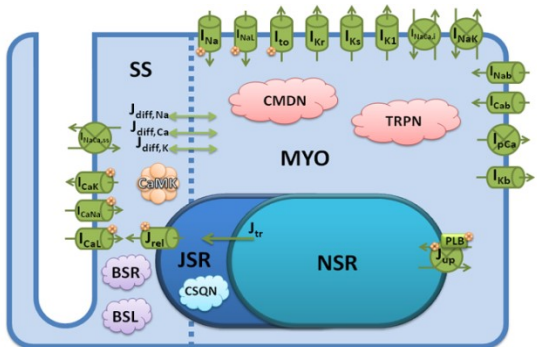
An integrative approach capturing comprehensively pro-arrhythmia mechanisms is needed

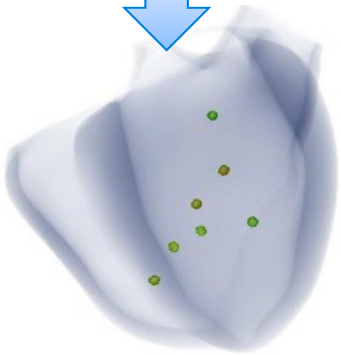
What is the new CiPA integrative approach?

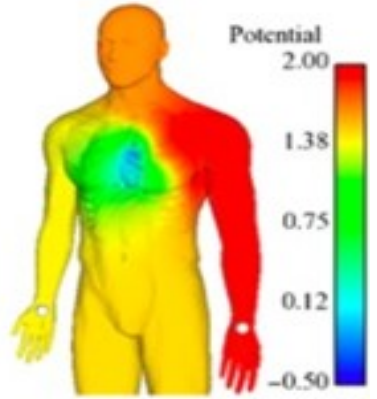
Technology innovation drives the change in the regulatory landscape



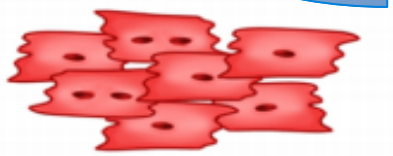
Key Ion Channels Assessment







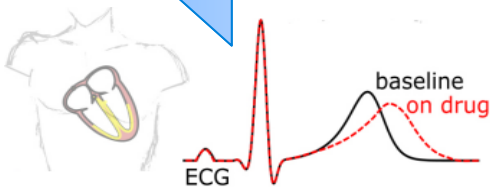
In Silico Cell, Heart, Patient



Cardiomyocyte assay

Confirm & Learn

Comprehensive Assessment of Pro-arrhythmic Risk



Phase I ECG Biomarker

See the blog post '*Three potassium channel modelling papers*' by Gary Mirams for some recent update

We proffer Multiscale Modelling of Drug Mechanism and Safety

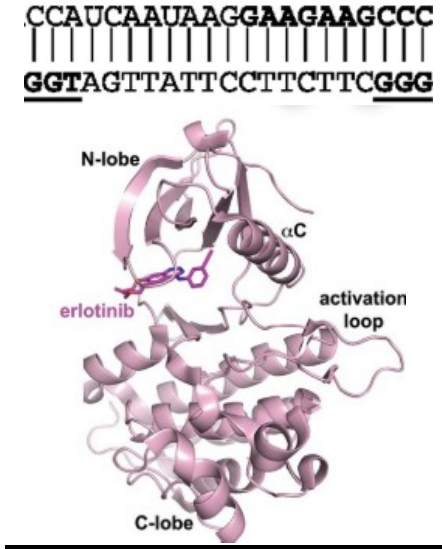




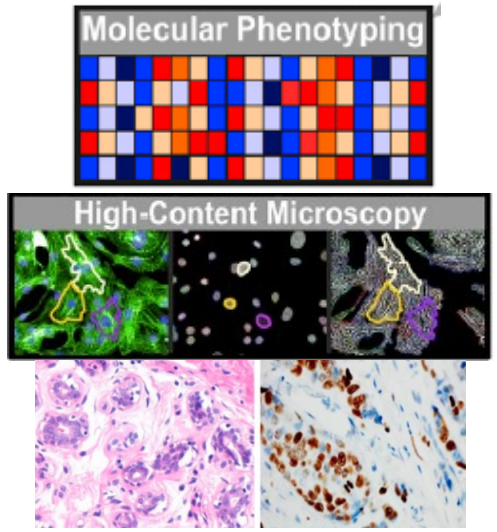
Jitao David Zhang[1], Lisa-Sach Peltason[1], Christian Kramer[1], Ken Wang[1], Martin Ebeling[1]

[1]Pharma Early Research and Development, Roche Innovation Center Basel, F. Hoffmann-La Roche, Grenzacherstrasse 124, 4070 Basel, Switzerland

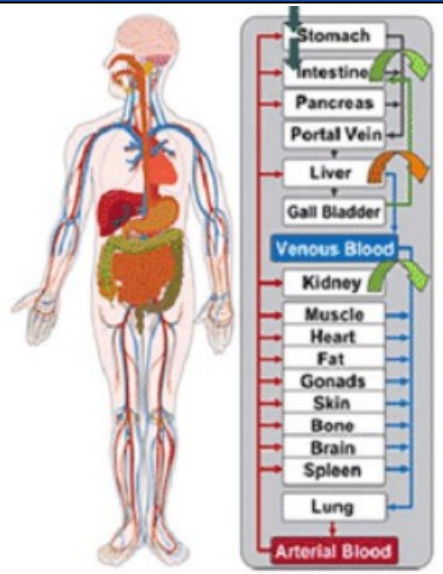
Forward translation



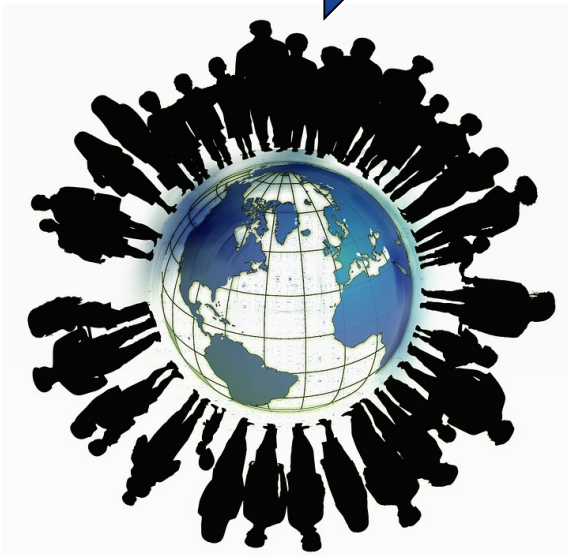
Molecular modelling



Omics & cellular modelling



Organ & system modelling



Populational modelling

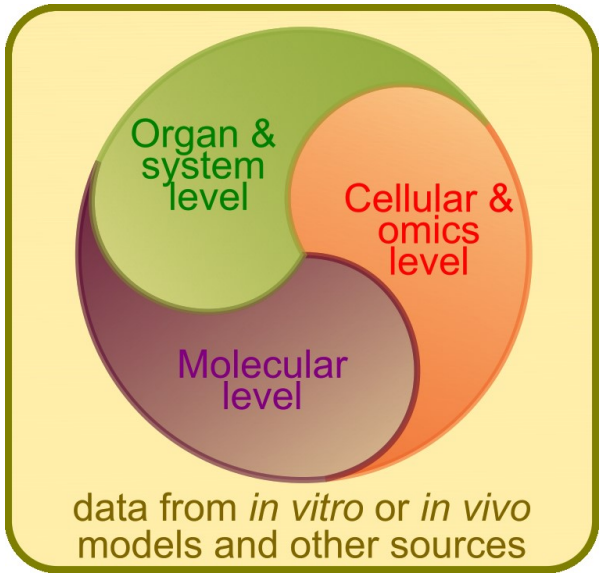
Reverse translation

Take-home messages

1. It is high-time to take a **multiscale modelling** approach to understand drug mechanism and safety.

2. **Mathematics** is the common language, **informatics** is the common tool, and a better understanding of **biology** is the common goal of all modelling approaches.

3. Three **case studies** of multiscale modelling of preclinical drug safety:
   - Drug-induced phospholipidosis
   - Drug-induced cytotoxicity and liver histopathology
   - Drug-induced cardiotoxicity



P.S. Our review, *Multiscale Modelling of Drug Mechanism and Safety*, is currently under revision. Interested audience can get a copy by mailing me at jitao_david.zhang@roche.com

Acknowledgement

- Lisa Sach-Peltason, Christian Kramer, Ken Wang, Martin Ebeling (Multiscale Modelling)
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- Students of the course *Applied Mathematics and Informatics in Drug Discovery* (AMIDD) WS 2019, for questions and inspiration.

Refine, Reduce, and Replace Animal Use: Chance and Challenge for Multiscale Modelling

https://www.sciencemag.org/news/2019/09/us-epa-eliminate-all-mammal-testing-2035

BEDA - Bioinformatics & Exploratory Data Analysis

Agile team of biostatistics and bioinformatics experts using data analytics to understand diseases and enable the transition of Roche molecules from early discovery to the clinic

pRED

PS

BiOmics & Pathology

- BEDA
- Genetics & Genomics
- Pathology
- Protein, Metabolite & Cell Sciences

Design of experiment & statistical modeling

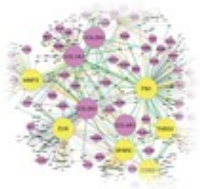
FAIR data

Genetics & genomics

Metagenomics & microbiomics

Transcriptomics

Proteomics & metabolomics



Networks and pathway analysis

Reverse translation & machine learning

Personalized safety

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Doing now what patients need next