eTOX: Computational prediction of *in vivo* toxicities

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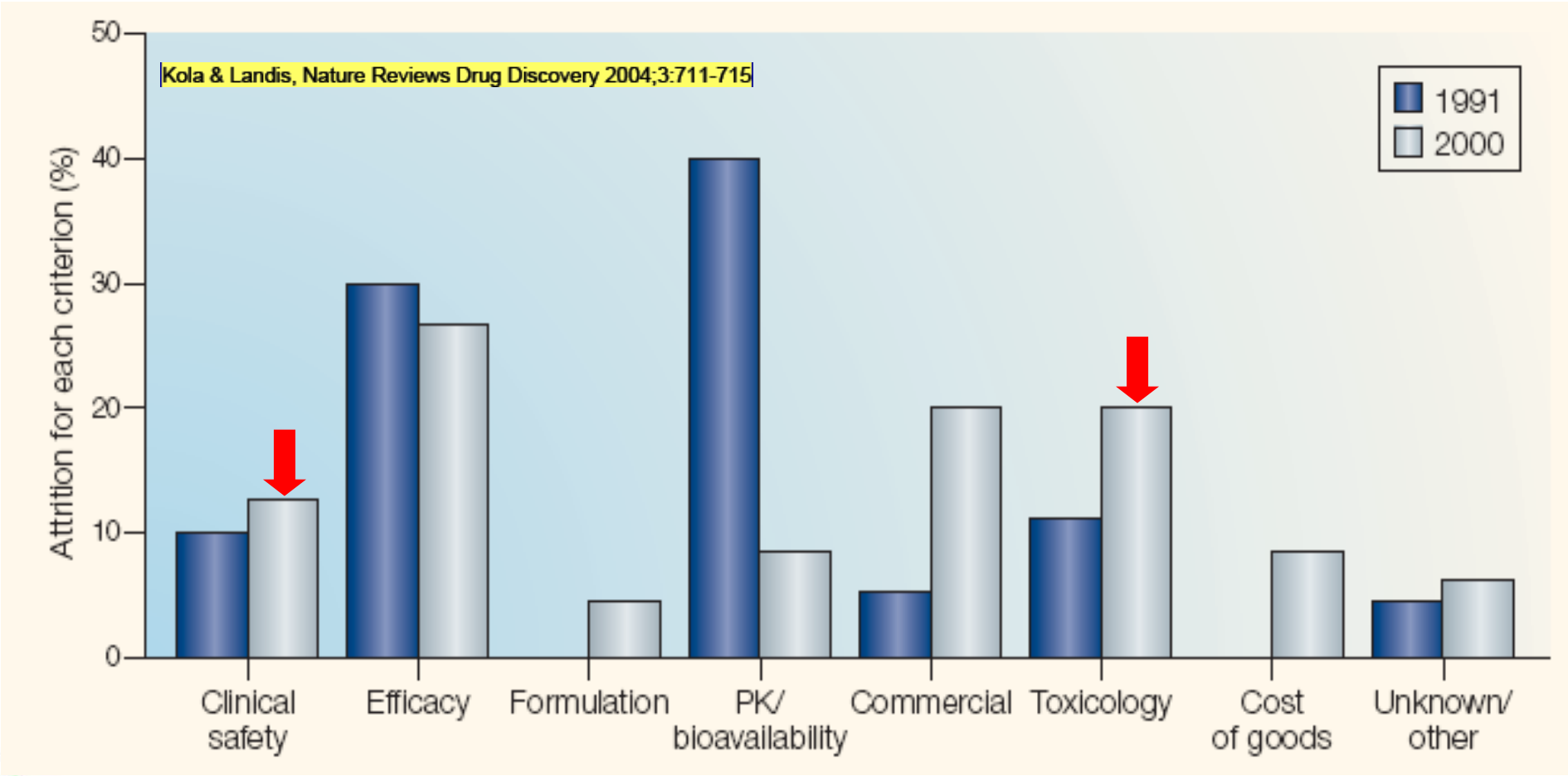
on behalf of the eTOX Consortium

efpia

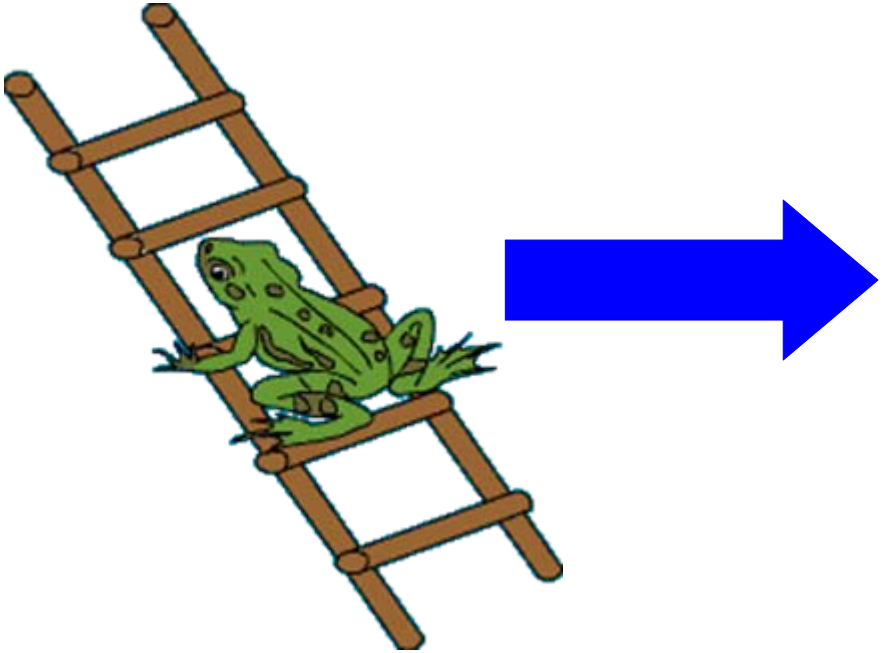
Toxicology + clinical safety: major concern in drug development

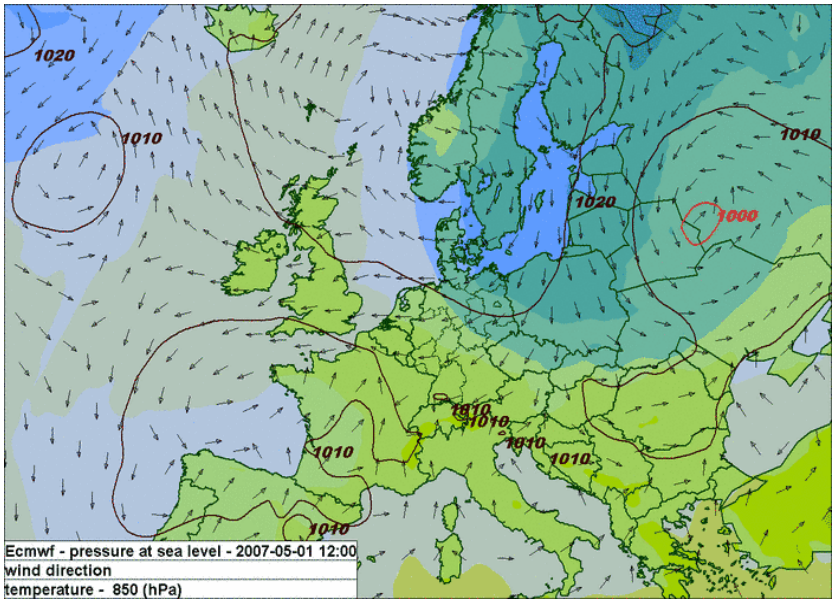


Benefits of computational prediction of *in vivo* toxicities

- Early selection/exclusion of drug candidates, lowering attrition in later phases
- Safety assessment of potential drugs in the context of REACH policy (replacing, refining and reducing *in vivo* studies) (3Rs)

From divination to prediction





Current computer sciences allow the development of reliable predictive systems, given that a wide and representative spectrum of previous experience is available for system training

Current gaps in computational prediction of *in vivo* toxicities

- Toxicological data from public sources is often biased towards toxic effects (negative toxicological data is usually not published).
- Data quality of tox reports in the public domain can hardly be assessed and is often questionable.
- Chemical space of published toxicological data is dominated by industrial or household chemicals (pharmaceuticals are underrepresented).
- Prediction models are mostly directed to pure chemical approaches (e.g., integration of pharmacodynamic and DMPK data is lacking).

Opportunity for better toxicity predictions

Tremendous wealth of high quality toxicology data in the archives of the pharmaceutical companies, not yet leveraged!

Buried in toxicology archives

- High Quality
- ICH conform
- Broad chemical space
- Multiple endpoints
- Pharmacology
- Different species

The eTOX IMI project

- Project kick-off : **January 2010**
- Duration: **5 years**
- Total budget: **13.9 M€**
- In kind contribution from EFPIA companies: **7.9 M€**
- IMI-JU funding: **4.7 M€**

EFPIA partners (13)

- **Novartis Pharma (François Pognan)**
- **Bayer Schering Pharma (Thomas Steger-Hartmann)**
- AstraZeneca
- Boehringer Ingelheim
- Esteve
- GlaxoSmithKline
- Janssen Pharmaceutica
- Lundbeck
- Pfizer
- Hoffmann-La Roche
- UCB Pharma
- Sanofi-Aventis
- Servier

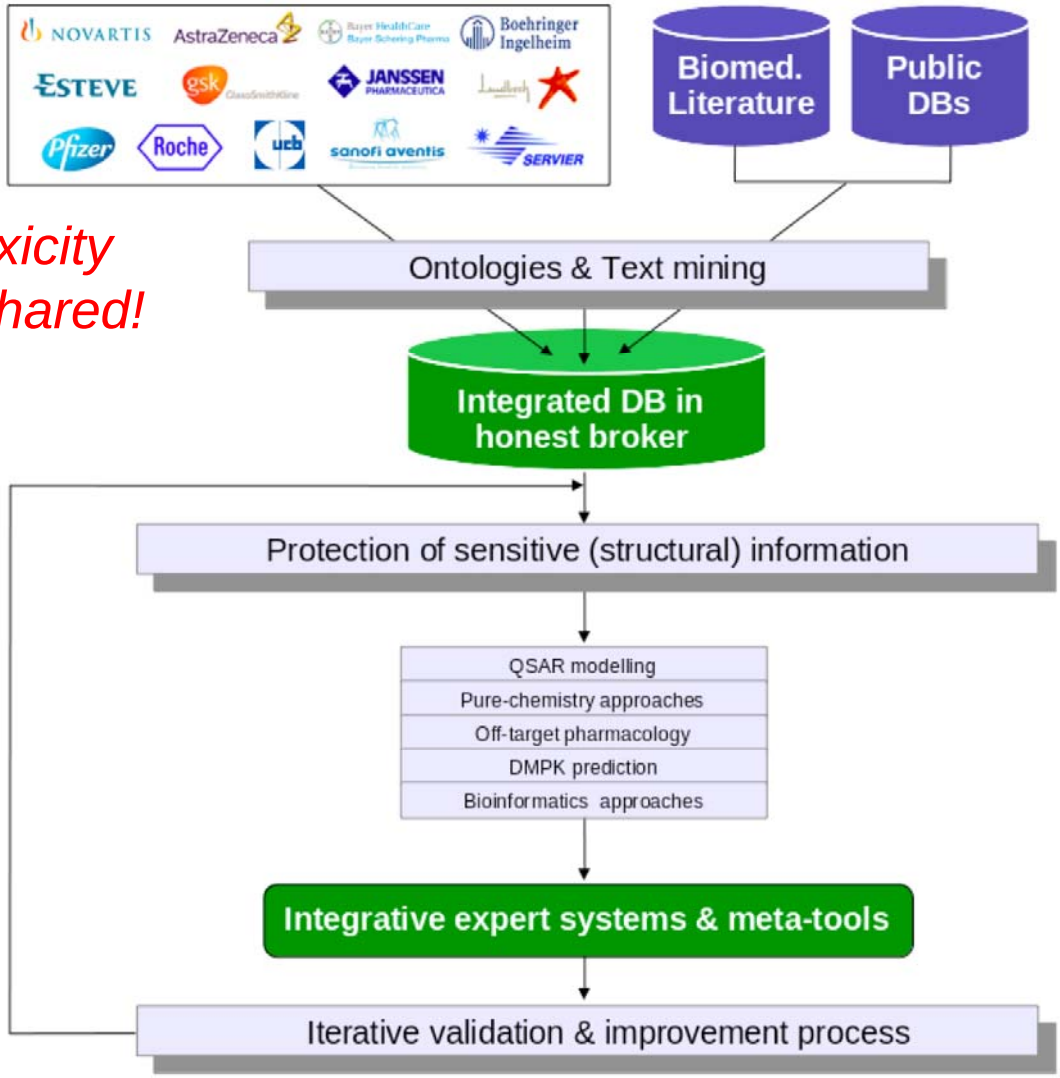
Academic partners (7) **and SMEs** (5)

- **Fundació IMIM (E)**
- Centro Nacional de Investigaciones Oncológicas (UK)
- European Bioinformatics Institute (EMBL) (UK)
- Liverpool John Moores University (UK)
- Technical University of Denmark (DK)
- Universität Wien (A)
- Vrije Universiteit Amsterdam (VUA) (NL)

- Inte:Ligand GmbH (A)
- Lhasa Ltd (UK)
- Molecular Networks GmbH (D)
- Chemotargets SL (E)
- Lead Molecular Design SL (E)

Scientific approach of the eTOX project

12000 *in vivo toxicity studies will be shared!*



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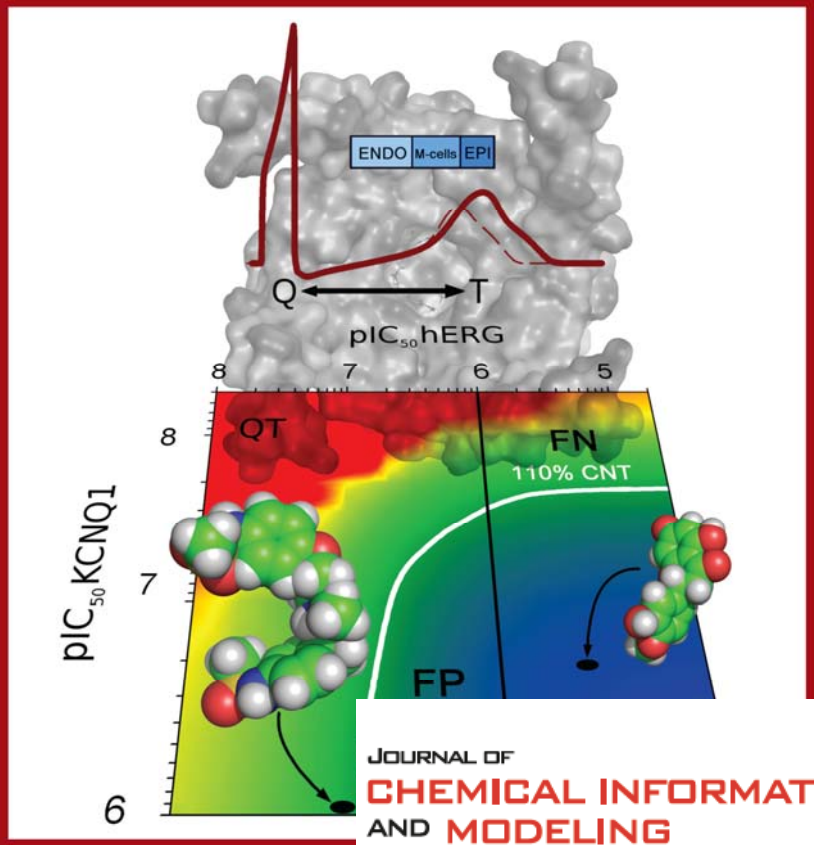

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ACS Publications
MOST TRUSTED. MOST CITED. MOST READ.

A Multiscale Simulation System for the Prediction of Drug-Induced Cardiotoxicity

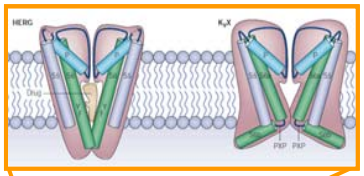
Cristian Obiol-Pardo,[†] Julio Gomis-Tena,[‡] Ferran Sanz,[†] Javier Saiz,[‡] and Manuel Pastor*[,†]

J. Chem. Inf. Model. 2011, 51, 483–492

Multi-scale prediction of cardiotoxicity

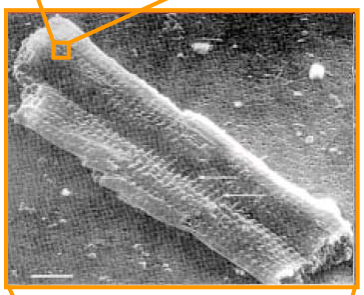
The developed method integrates simulations at three levels:

Molecular



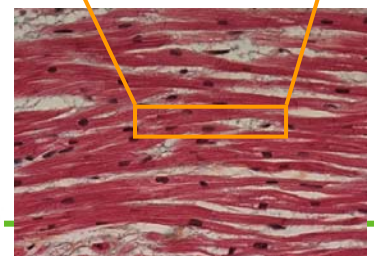
Simulation of ion channels blockade

Cellular



Simulation of the cardiomyocyte electrophysiology

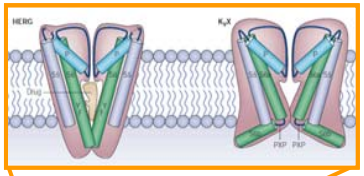
Tissular



Simulation of the electrical propagation through a model of ventricular tissue, obtaining an ECG

Multi-scale prediction of cardiotoxicity

Molecular



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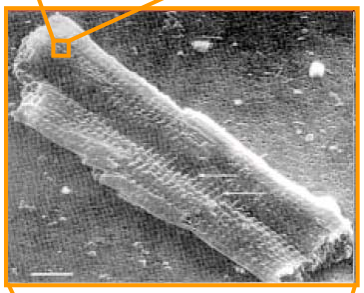

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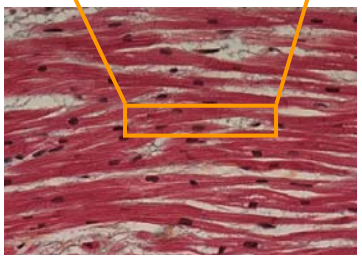
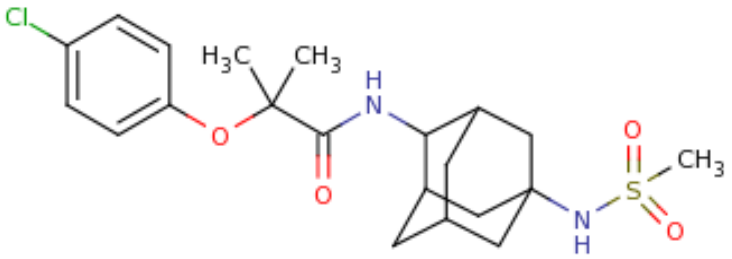
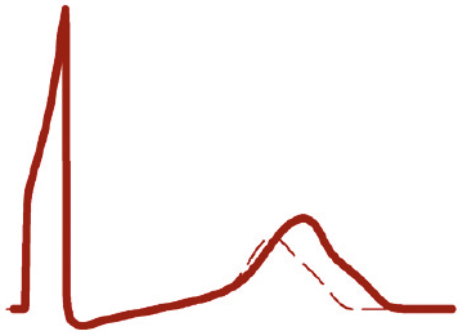




The input is the 2D structure of a possible drug



The output is the possible ECG alteration

Virtual Physiological Human network of excellence

More information at…

www.e-tox.net