



Innovative Medicines Initiative

# eTOX

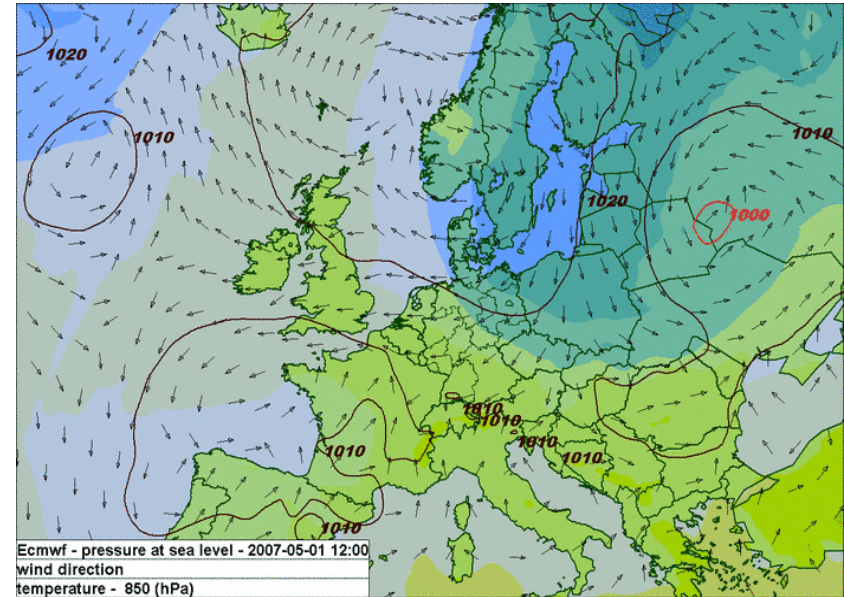
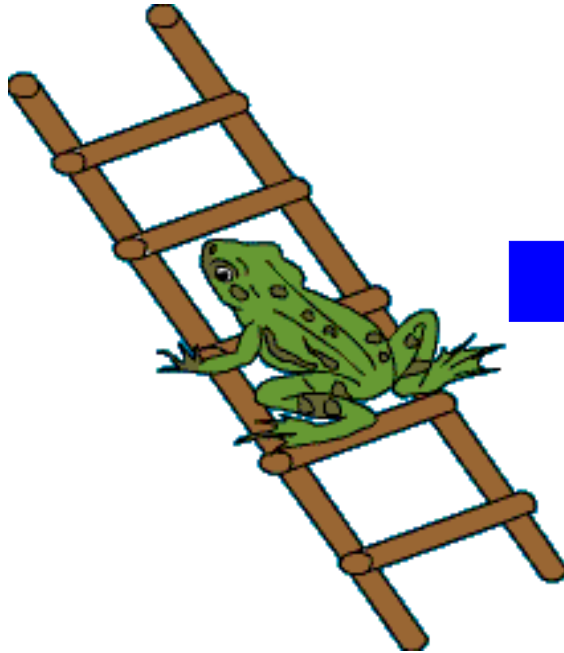
Computational prediction of *in vivo* toxicities

Ferran Sanz (GRIB, *Fundació IMIM - UPF*)  
on behalf of the **eTOX Consortium**

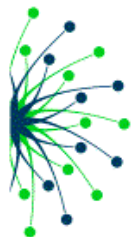


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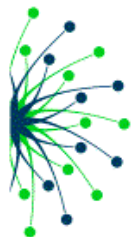
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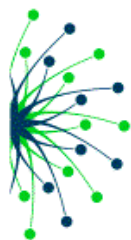
Present science and technology allow the development of reliable predictive systems on the basis of a wide consideration of relevant previous experience



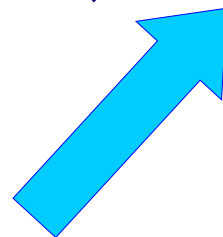
- Improved **selection/exclusion of candidate compounds**, lowering attrition in later phases
- Safety assessment of chemicals in the context of REACH policy of **replacing, refining and reducing *in vivo* studies** (3Rs)
- Development of **more targeted *in vivo* testing** strategies
- Better **predict human toxicities** and/or safer starting doses



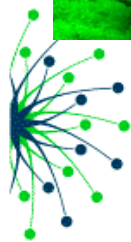
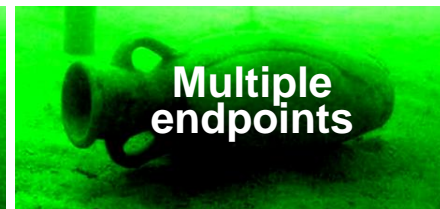
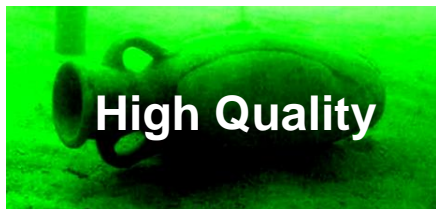
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- Toxicological data from public sources is often **biased towards toxic effects** (negative tox data is usually not published).
  - The data **quality of tox reports** in the public domain can hardly be assessed and is often **questionable**.
  -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



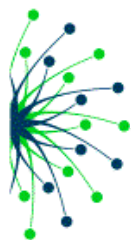
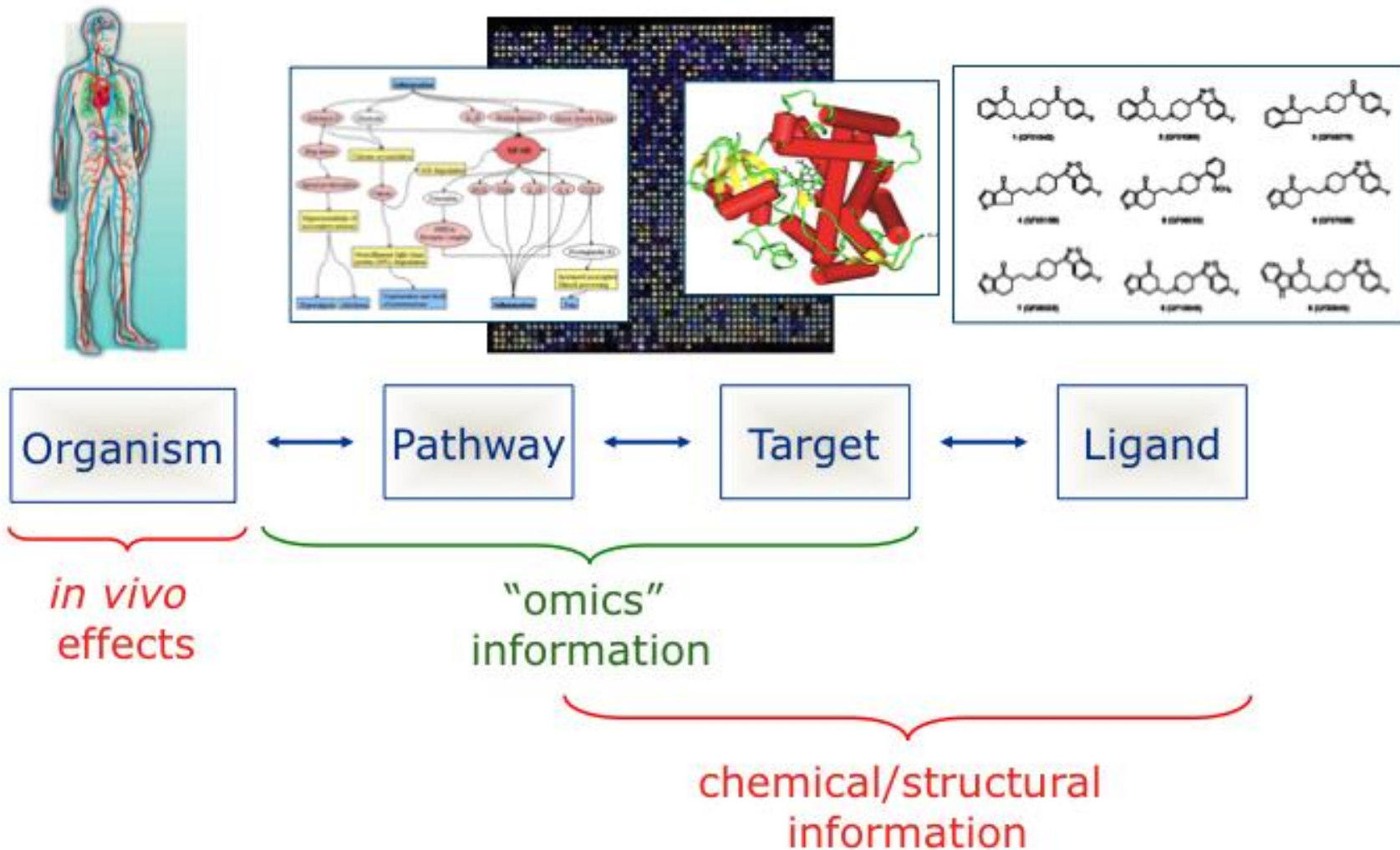
Tremendous wealth of high quality toxicology data in the archives of the pharmaceutical companies, not yet leveraged!



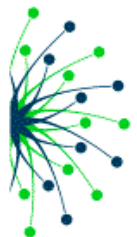
Buried in toxicology archives



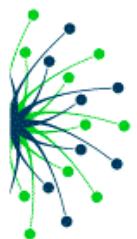




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- Project kick-off : **January 2010**
  - Duration: **5 years**
  - Total budget: **13.9 M€**
  - In kind contribution from EFPIA companies: **7.9 M€**
  - IMI-JU funding: **4.7 M€**

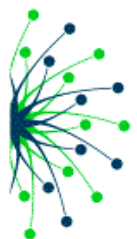


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- **Novartis Pharma (François Pognan)**
  - **Bayer Schering Pharma (Thomas Steger-Hartmann)**
  - AstraZeneca
  - Boehringer Ingelheim
  - Esteve
  - GlaxoSmithKline
  - Janssen Pharmaceutica
  - Lundbeck
  - Pfizer
  - Hoffmann-La Roche
  - UCB Pharma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

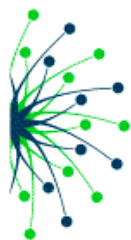


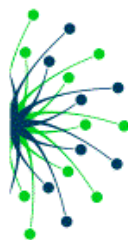
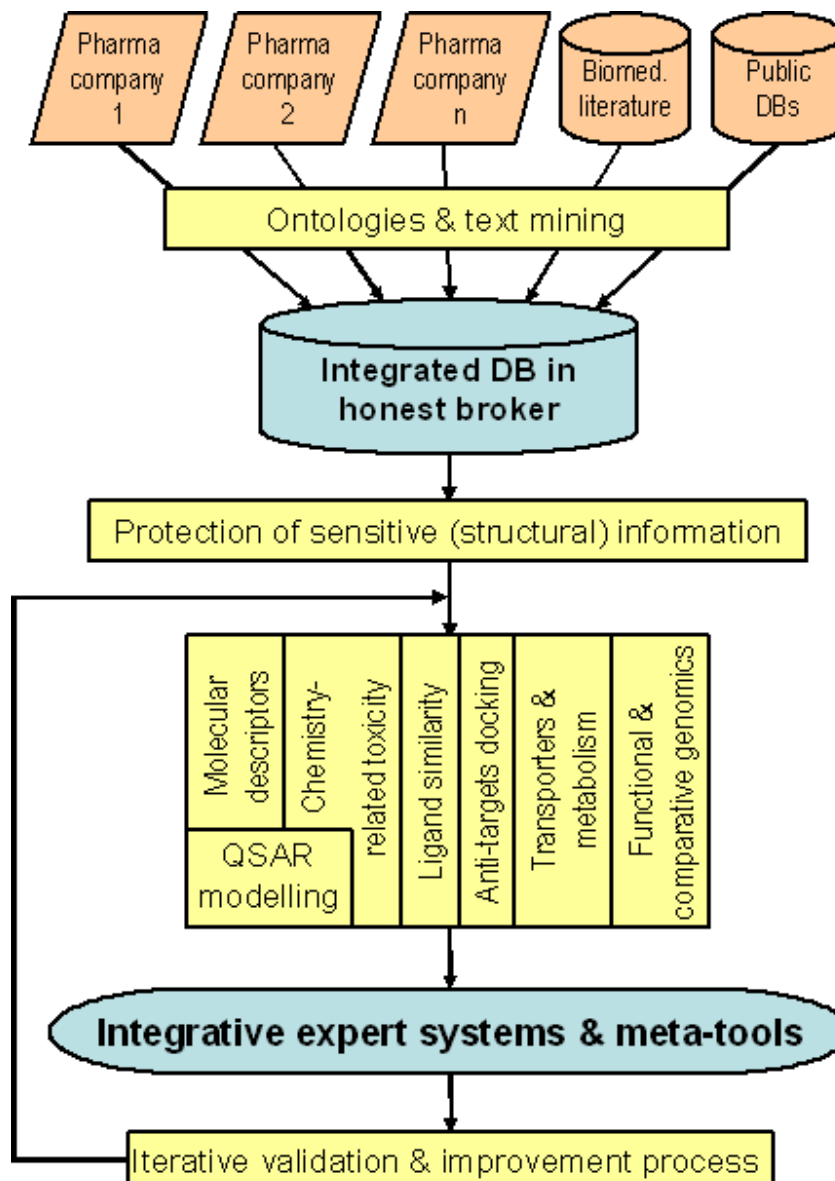


- **Fundació IMIM (E)**
- Centro Nacional de Investigaciones Oncológicas (UK)
- European Bioinformatics Institute (EMBL) (UK)
- Liverpool John Moores University (UK)
- Technical University of Denmark (DK)
- Universität Wien (A)
- Vrije Universiteit Amsterdam (VUA) (NL)
  
- Inte:Ligand GmbH (A)
- Lhasa Ltd (UK)
- Molecular Networks GmbH (D)
- Chemotargets SL (E)
- Lead Molecular Design SL (E)

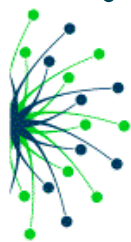


1. **Data sharing**: Exploit legacy preclinical reports from the pharmaceutical industry to link chemical features to pathology findings.
2. Establishment of a **toxicological database** with high quality structural, *in vitro* and *in vivo* data. This repository will facilitate the development of better predictive models for *in vivo* toxicity.
3. The development of the models will take advantage of an **integrative** application of state-of-the-art **computational, chemoinformatic and bioinformatic approaches**.
4. **Validation** of the new predictive models. The validation exercises will be shared between companies and regulators.



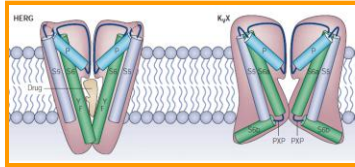


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- Creation of a complex framework of legal statutes and IT-technical provisions to overcome the hurdles of sharing proprietary data of EFPIA companies.
  - Development of a first version of a toxicity ontology for seamless data gathering, integration and exploitation.
  - Design and successful testing of strategies for the masking of sensitive structural information of compounds.
  - Design and setup of the first version of the eTOX central database.
  - Compilation and assessment of public data sources.
  - Agreement on the (modular) architecture of the eTOX predictive system.
  - Analysis and benchmarking of current models for toxicity prediction, and definition of quality criteria for method selection and development.
  - Development of an innovative multi-scale modelling strategy for the prediction of cardiotoxicity (J. Chem. Inf. Model. 2011; 51:483-92)
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The developed method integrates simulations at three levels:

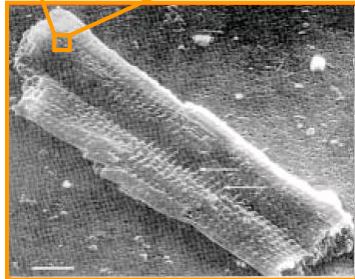
Molecular



Simulation of ion channels blockade



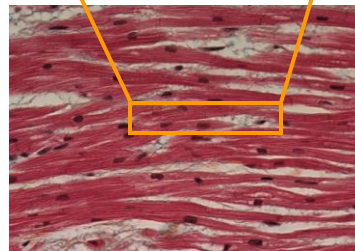
Cellular



Simulation of the cardiomyocyte electrophysiology

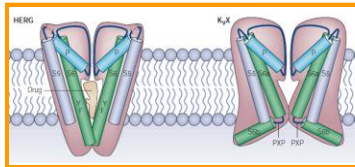


Tissular

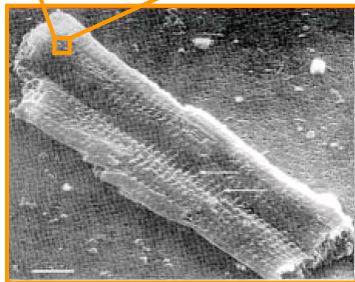


Simulation of the electrical propagation through a model of ventricular tissue, obtaining an ECG

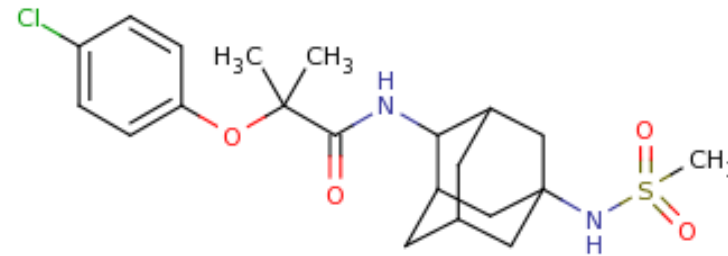
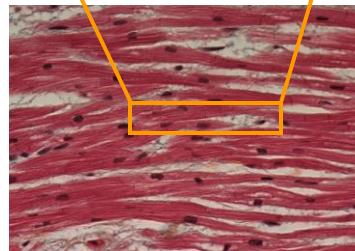
Molecular



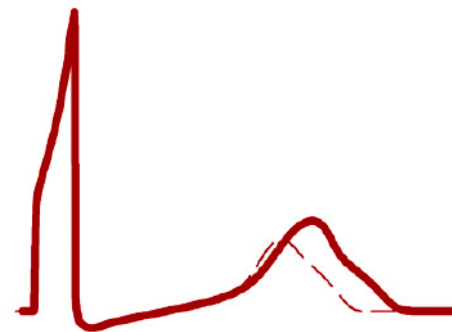
Cellular



Tissular



The **input** is the 2D structure of a possible drug



The **output** is the possible ECG alteration





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LAST NEWS

January 2010  
eTOX Kick off

The IMI JU Project eTOX kicked off on Monday 18th January 2010 when it held its first consortium meeting in Barcelona, Spain.

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## Welcome to the eTOX Website

### Objectives

The eTOX project aims to develop a **drug safety database from the pharmaceutical industry legacy toxicology reports and public toxicology data**; innovative in silico strategies and novel software tools to better predict the toxicological profiles of small molecules in early stages of the drug development pipeline

### Funding

eTOX, under Grant Agreement n°115002, is funded by the Innovative Medicines Initiative Joint Undertaking (IMI-JU), a unique partnership between the European Community and the European Federation of Pharmaceutical Industries and Associations (EFPIA).

