eTOX
Computational prediction of *in vivo* toxicities

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on behalf of the eTOX Consortium
Present science and technology allow the development of reliable predictive systems on the basis of a wide consideration of relevant previous experience.
Benefits of early *in silico* prediction of *in vivo* toxicities

- 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
Current gaps in computational prediction of *in vivo* toxicities

- 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**).
Opportunity for better toxicity predictions

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

High Quality Tox Data Repository

Buried in toxicology archives

High Quality
ICH conform
Broad chemical space
Multiple endpoints

Pharmacology
Different species
Integrative approaches in predictive modelling
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)
Rationale of the eTOX project

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.
Scientific approach of the eTOX project

Integrated DB in honest broker

Protection of sensitive (structural) information

Incorporation of various databases:
- Pharma company 1
- Pharma company 2
- Pharma company n
- Biomed. literature
- Public DBs

Ontologies & text mining

Molecular descriptors
- Chemistry-related toxicity
- Ligand similarity
- Anti-targets docking
- Transporters & metabolism
- Functional & comparative genomics
- QSAR modelling

Integrative expert systems & meta-tools

Iterative validation & improvement process
Project achievements

- 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.
The developed method integrates simulations at three levels:

- **Simulation of ion channels blockade**
- **Simulation of the cardiomyocyte electrophysiology**
- **Simulation of the electrical propagation through a model of ventricular tissue, obtaining an ECG**
Multi-scale prediction of cardiotoxicity

The input is the 2D structure of a possible drug

The output is the possible ECG alteration

Ferran Sanz – GRIB
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.

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