Computational prediction of toxicity
Connecting people, sharing know-how, speeding up health research

Join the partnership
What is IMI?

The European Union and the pharmaceutical industry have joined forces to make drug R&D processes in Europe more innovative and efficient.

2 billion Euro

1 billion Euro

Public

Partnership

Private

1 billion Euro

efpia
What is IMI?

• IMI created in February 2009

• IMI projects are focused on 4 areas
  – Predicting efficacy
  – Predicting safety
  – Knowledge Management
  – Education and Training

• More than 40 projects currently ongoing
  – Servier is engaged in 10 ongoing projects and 3 projects to be launched shortly
What is IMI?

- Objectives
  - World’s largest public-private initiative in life sciences
  - Supports collaborative research projects and builds networks of industrial and academic experts

- Missions
  - To boost pharmaceutical innovation in Europe
  - To speed up the development of better and safer medicines for patients
What is IMI?

- 595 Academic & research teams
- 108 SMEs
- 364 EFPIA teams
- 9 regulators
- 18 patient org
- €603 mln IMI JU cash contribution
- €600 mln EFPIA ‘n kind contribution

~ 4000 researchers
What is eTOX?

- Setup tool for prediction of toxicological endpoints starting from chemical structure
What is eTOX?

- Project kick-off: January 2010
- Duration: 5 + 2 years
- Total budget: 13.9 + 5 M€
- In kind contribution from EFPIA companies: 7.9 + 2.1 M€
- IMI-JU funding: 4.7 + 2.2 M€
- SME and Academia contribution: 1.3 + 0.7 M€
Participants

- EfpiA
- Academia
- SMEs
Present science and technology allows 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 toxicity outcomes

• Improved selection/exclusion of candidate compounds, lowering attrition in later phases

• Safety assessment of chemicals in the context of REACH replacing, refining and reducing *in vivo* studies (3Rs)

• Development of more targeted *in vivo* testing strategies

• Capturing knowledge for improved *in silico* predictions for use in safety assessment
Current limitations 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).
  - **Quality of tox reports** can hardly be assessed and is sometimes questionable.
  - Chemical space 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)*.
Contributions of EFPIA partners

- Provision of high quality data
  - Exploit legacy preclinical reports
  - Mostly GLP
  - From some days to long term studies
  - Different species
  - Multi endpoints
    - From systemic toxicity studies
    - From DMPK studies
    - From safety pharmacology studies (including ligand binding)
  - Broad chemical space
Contributions of academia and SMEs

• Expertise in bioinformatics and chemoinformatics, including software development in these fields

• Database development and hosting

• Development
  – New QSAR models
  – Expert systems
Prediction of in vivo toxicity outcomes

1. Data collection

   - Public databases

   - Bibliography

   - Pharma Reports

2. Data sharing and Integration

3. Building the models

4. Testing and Validation

   - Alerts

   - New structures

5. Refinement

   - New structures or limited early toxicity studies
Scientific approach of the project

Integration of DBs in honest broker

Protection of sensitive (structural) information

- QSAR modelling
- Pure-chemistry approaches
- Off-target pharmacology
- DMPK prediction
- Bioinformatics approaches

Integrative expert systems & meta-tools

Iterative validation & improvement process

WP0
WP1
WP2
WP3/4
WP5
WP6
WP7
WP8/9
WP0 - The major task

Searchable in a database

Chemical structures

Reports from EFPIA companies

Legacy reports from EFPIA companies
WP0 - The major task

- Selection of records within pharma companies and extracting information from them

Planned
Sum of cleared reports and those currently waiting for clearance

Cleared
Reports submitted to CROs or in-house facilities for data extraction

Extracted
Reports with processing by CROs or in-house facilities completed

eTox DB
Reports after quality checks, available at Vedic eTOX database

Planned: 5865
Cleared: 5430
Extracted: 3984
eTox DB: 2771
WP0 - The major task

Chemical structures

Biomed. literature

Public DBs

Public data

ChOX

WP0 - The major task

Biomed. literature

Public DBs

Public data

Chemical structures
WP0 - The major task

- Identification, selection and import of information from public sources
  - eTOX Protein Compilation
    - CYP450
    - TRANSPORTERS
    - ANTI-TARGETS
  - eTOX Datasets
    - Hepatotox
    - Phospholipidosis
    - Rat in-vivo, Human and cross-species PK
    - Cytochrome P450
    - Other DMPK datasets
    - TP-search
WP2 - Ontology

- Development of common ontology

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WP3/4 - Modeling

- Development and testing of predictive models

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WP6 – eTox Sys

- Development and testing of the predictive system architecture
WP6 – eTox Sys

- Development and testing of the predictive system architecture
• Development of a queried database
WP6 – eTox Sys

- Development of a queried database
• Development of a queried database
WP7 – Validation

- Models could be tested
- Regulatory Agencies aim to participate
Conclusion and perspectives

- World largest toxicity database

- Incorporation of data
  - To follow with EFPIA reports including new type of data

- Models
  - Improve models with EFPIA data
  - Validation of models
eTox team
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

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Merci pour votre attention