eTOX

Newsletter

In This Issue

We are pleased to announce the launch of the eTOX-Newsletter, which will be delivered on a quarterly basis (next March 2012).

In order to inform a broader audience and to promote collaboration with other ongoing projects, we will with this newsletter continuously provide updates on our project achievements. We will strongly appreciate feedback from our audience to enforce scientific advances and knowledge creation in the field of toxicity prediction field.

Welcome to eTOX!

The *eTOX* Project
(2010 - 2014)

The "*Integrating bioinformatics and chemoinformatics approaches for the development of expert systems allowing the in silico prediction of toxicities*" project aims to develop a drug safety database from the pharmaceutical industry legacy toxicology reports and public toxicology data, and 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 (see Objectives section or visit us at http://www.etoxproject.eu).

To carry out the present project a consortium that includes top experts in data management, bioinformatics, chemoinformatics, biostatistics and software development, with a wide experience in international partnerships and industry-academia collaborations, has been gathered (see Consortium section).

This project belongs to the call *Development of expert (QSAR) systems for in silico toxicity prediction* topic, and 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).

KEYNOTE

Present challenges in the Prediction of Toxic Effects
Message from the academic coordinator: **Prof. Ferran Sanz**

The reliable prediction of toxic effects of human relevance with the help of computational systems, be it with QSAR or rule-based systems, is currently mainly restricted to the endpoints mutagenicity and carcinogenicity and, to a lesser extent, (skin) sensitisation.

The reason for this focus is twofold: first the mechanisms leading to these toxic effects are relatively well-characterized and of a limited complexity (in the case of carcinogenesis this is mainly true for genotoxic carcinogens); secondly, there is abundant data in the public domain for such endpoints, which can be used to construct expert rule or quantitative-structure activity relationships.

"eTOX Project will facilitate as much as possible the accessibility to the resulting non-confidential part of the database and the predictive systems by the broader scientific community"

There have been several attempts to model and predict more complex toxic endpoints on the basis of available *in vivo* toxicity data (e.g. MTAs or CRADAs within the US Food and Drug Administration [FDA] and different software providers such as MDL QSAR, Leadscope, Multicase, etc. However, no major breakthrough has been discernable up to now, i.e. there is no broad acceptance and usage of these systems or models.

The *eTOX* Consortium

EFPIA partners:
· Novartis Pharma *AG (project leader)*
· AstraZeneca AB
· Bayer HealthCare *(deputy project leader)*
· Boeheringer Ingelheim International GmbH
· Esteve
· GlaxoSmithKline Research and Development LTD
· Janssen Pharmaceutica NV
· H. Lundbeck A/S
· Pfizer Limited
· F. Hoffmann-La Roche AG
· UCB Pharma SA
· Sanofi-Aventis Deutschland GmbH
· Institut de Recherche Internationales Servier

ACADEMIA partners:
· Fundació Institut Mar d'Investigacions Mèdiques
  (project management and coordination of public partners)
· Fundación Centro Nacional de Investigaciones Oncológicas Carlos III
· European Molecular Biology Laboratory
· Liverpool John Moores University
· Technical University of Denmark
· Universität Wien
· VU University Amsterdam

SME partners:
· Inte:Ligand GmbH
· Lhasa Limited
· Molecular Networks GmbH
· Chemotargets SL
· Lead Molecular Design SL

OBJECTIVES

The **eTOX** proposed strategy includes a synergetic integration of innovative approaches in the following areas:

- Database building and management, including procedures and tools for protecting sensitive data.
- Ontologies and text-mining techniques, with the purpose of facilitating knowledge extraction from legacy preclinical reports and biomedical literature.
- Chemistry and structure-based approaches for the molecular description of the studied compounds, as well as of their interactions with the off-targets responsible of polypharmacology.
- Prediction of DMPK features due to their relationship with toxicological events.
- Systems biology approaches in order to cope with the complex biological mechanisms which govern in vivo toxicological problems.
- Computational genomics to afford the inter-species and inter-individual variabilities that complicate the interpretation of experimental and clinical outcomes.
- Sophisticated statistical analysis tools required to derive the inevitably highly-multivariate QSAR models.
- Development and validation (according to the OECD principles) of QSARs, integrative models, expert systems and meta-tools.

PUBLICATIONS

A full list of publications is available on http://www.etoxproject.eu

- ARTICLE-(CT, IL, LMD, MN): Shaping the future of safer innovative drugs in Europe. Mestres J, Bryant SD, Zamora I, Gasteiger J. *Nat Biotechnol.* 2011; 29: 789–790.

- ARTICLE-(LJMU): A review of the electrophilic reaction chemistry involved in covalent protein binding relevant to toxicity. Enoch SJ, Ellison CM, Schultz TW and Cronin MTD. *Crit Rev Toxicol.* 2011; 783-802.

- ARTICLE-(DTU): Application of computational systems biology to explore environmental toxicity hazards. Audouze K, Grandjean P. *Environ Health Perspect.*

UPCOMING EVENTS

- **5-6.12/11 |** Innovation Convention, European Commission, Brussels (Belgium).
  Information: http://ec.europa.eu/research/innovation-union

- **5-6.01/12 |** Drug discovery: a job too complex for academia or industry alone? Oxford (United Kingdom).
  Information: http://www.thesgc.org/events/symposia/DrugDiscov2012

- **13-16.02/12 |** QSAR application toolbox training workshops, Barcelona (Spain)
  Information: http://tinyurl.com/cvttpnr

- **12-13.03/12 |** International Transporter Consortium Workshop Two, Maryland (USA).
  Information: http://www.ascpt.org