In This Issue

Have a look at the eTOX predictive system's prototype: the eTOXsys

Gathering the data (public and legacy reports) and providing it to the modelers for the development of predictive tools are tasks which have to be organized on the backbone of a sophisticated IT architecture.

The prototype design for eTOXsys is now available.
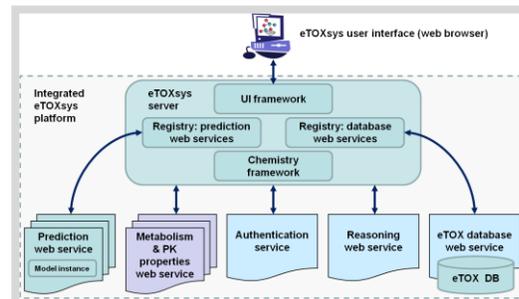
PROJECT NEWS

eTOX extension and collaboration with other initiatives

The ongoing eTOX activities are unveiling new opportunities for incorporating additional data types in the project database, as well as considering more sophisticated modeling strategies for developing the predictive system. Currently, to complement the feeding of the eTOX database with information from public sources, a synergistic collaboration is devised with Open PHACTS, another IMI-funded project that is applying the semantic web technology to create a knowledge management framework with the aim to facilitate the extraction and integration of biomedical information from heterogeneous sources.

Towards the eTOX predictive system

A meeting was held in Basel in January 2012 to discuss the functionalities of the predictive system (eTOXsys). Representatives of the EFPIA companies had prepared several use cases to illustrate what they desire from a predictive system and how it will be used in daily drug development. This approach effectively aligned the needs of the users with the technical procedures of the programmers, therefore such meetings will be held on a regular basis to take key decisions regarding the design of the system, such as parameters for prediction or complex query design.

KEYNOTE

Prophecy or Prediction ?

Message from the Project Coordinator: **Dr. François Pognan**

The previous keynote was rightfully entitled: "Present Challenges in the Prediction of Toxic Effects". Indeed, a good half of the eTOX endeavour is to 'predict' untoward events in animals treated with drug candidates. Let's look more closely at this key word 'predict'. According to the Webster dictionary, it means 'to declare or tell in advance'. And this is what the eTOX consortium is committed to achieve; tell in advance what might be the main toxicity issues to be expected before having actually tested a compound.

Now, the Webster also tells us that 'prophecy' is synonymous to 'prediction', but takes care to differentiate the terms. 'To prophesy usually means to predict future events by the aid of divine or supernatural inspiration', while 'To predict is usually to foretell with precision of calculation, knowledge or shrewd inference from facts or experience'. Clearly, eTOX pertains to the second one, even if sometimes toxicologists somehow rely on their intuition to interpret events, which in a way is a prediction of the past. It can be argued however that intuition is the unconscious use of shrewd inference of multiple past experiences. In the recent eTOX meetings, it clearly appeared that experienced toxicologists underestimated the necessity and difficulties of the 'precision of calculations' based on hard facts and numbers, while modelers overestimated the 'knowledge or shrewd inference from facts' available in the hands of these experienced toxicologists. Many assumptions were present within all stakeholders in the early days of eTOX. Discovering and tackling them along the way is a very healthy sign of good progress. It is pleasing to see how much improvement is being made into the understanding of hurdles and limitations we are all facing. This learning process has not helped the initial speed for concrete achievements but is the necessary warrant of our success. Thanks to this awareness, one can in the end prophesize that the foreseen robust quality of eTOX will grant a broad acceptance and usage of the eTOX system.

For more information, visit us at http://www.etoxproject.eu

- The prototype of the eTOX predictive system, eTOXsys, developed by MN includes the eTOXsys server and communicates to the first prediction web services developed by several partners, focusing on CYP450, Ph II enzymes, some antitargets, pharmacology and Phospholipidosis and Cardiotoxicity prediction; and provides access to the eTOX database (hosted by LL) for searching the database including full structure, substructure and similarity searches as well as searching for chemical names and registry numbers.

- Ontologies and controlled vocabularies are under development to allow mapping of the terms that have evolved over time, across all the different companies' reports and in the literature. The ClinPath ontology is completed and mapped to the vocabulary used by SEND, the CDISC format for clinical data storage. The HistoPath ontology is under review by Novartis pathologists and will be available to members of the consortium via the internet thanks to a new web-based ontology curation tool, the OntoBrowser (hosted by LL).

- A chemogenomics platform, ChOX, has been developed by EMBL partner to collect and curate publicly available toxicology data (compound interactions with toxicologically-related target proteins, drug metabolizing enzymes and transporters as well as pharmacokinetic and *in vivo* data), prioritizing compilation of data related with Phospholipidosis, Cardiotoxicity and Hepatotoxicity, the first endpoints to tackle toxicity prediction. ChOX 1.0 contains: 384 toxicology-linked targets, 153,520 distinct compounds and 415,051 activities gathered from 9,101 publications.

- A curation tool developed by CNIO partner currently supports the examination of the annotations extracted from the EPA reports and the literature. Its web interface enables the user to view summarized reports of a different nature (a list of all entities or relationships found in a document or in a collection of documents), with the possibility of easily examining the relevant section of a text.

- A visualization network tool, Tox-PPI, has been recently launched by DTU partner to facilitate the navigation through a biology network on proteins associated to toxicity events defined by a controlled vocabulary. This tool aims to help in the identification and the understanding of disease-causing genes and toxicity-causing genes, and to explore the molecular mechanisms of drug toxicity.
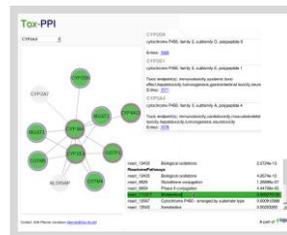
REPORT-O-METER 2040

The eTOX database will contain *in vivo* tox reports data from EFPIA companies. After overcoming the legal IP issues, settling the database schema, defining the ontologies, and solving other challenges, the database and the process of data extraction is now in place and data availability is rapidly gaining momentum.

EFPIA companies have now identified 2040 reports which are currently being extracted by CROs and their corresponding data will be available for the modelers in the eTOX database progressively with the next Vitic Nexus database releases.

PUBLICATIONS

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

- ARTICLE-(LL, FIMIM, Novartis, BHC, MN): Inroads to predict *in vivo* toxicology – An Introduction to the eTOX Project. Briggs K., et al. *Int. J. Mol. Sci.* 2012, 13, 3820-3846.
- ARTICLE-(DTU): The impact of network biology in pharmacology and toxicology. Panagiotou G., et al. *SAR QSAR Environ Res*. 2012 Feb 22.
- ARTICLE-(DTU, EMBL): Toxicogenomics Investigation under the eTOX Project. Taboureau O., et al. *J Pharmacogenom Pharmacoproteomics.* 2012, S7:001.

UPCOMING EVENTS

- **7-11.5.12 |** SafeSciMET course: *In Silico* ADME & Predictive Toxicology, University of Copenhagen (Denmark). Information: http://www.biohealthcluster.lu/Events/SafeSciMET-course-In-silico-ADME-and-Predictive-Toxicology

- **17-20.6.12 |** EuroTox 2012, Stockholm (Sweden). Information: http://www.eurotox2012.org/

- **2-6.7.12 |** Hands-on training at EBI – Joint EMBL-EBI and Welcome Trust Resources for Computational Drug Discovery, EMBL-EBI, Hinxton, Nr Cambridge, CB10 1SD (UK). Information: http://www.ebi.ac.uk/training/handson/course_120213_smallmols.html