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eTOX: Integrative Strategies for Predicting Drug Toxicities

Ferran Sanz Fundació IMIM. Universitat Pompeu Fabra. Barcelona

The eTOX project





Time: Start January 2010 (5+2 years project)Budget: 18.7 M€ over 7 years (including ENSO extension)



F. Sanz, GRIB (IMIM-UPF)



- Development of a framework for the sharing of legacy preclinical reports from pharmaceutical industry, complemented with information from the public domain
- Generation of a toxicological database with high quality structural, *in vitro* and *in vivo* data. This repository will facilitate read-across and development of predictive toxicity models
- Building of predictive models taking advantage of integrative application of computational, chemoinformatics and bioinformatics approaches
- Validation of the predictive models within companies and with regulators

Project workflow





Classification according to sensitivity







Status on Oct. 20th, 2014:

- Compounds: 1932 (1213 non-confidencial)
- **Reports: 4664** (4050 non-confidential)
- Studies: 7090 (6052 non-confidential)

Reports from EFPIA companies (systemic toxicity studies)



Top 10 organs affected by histopathology



Chemical coverage monitoring



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Project workflow: ontologies & Ontobrowser



OntoBrowser eTOX Ontology Browser



March 13th, 2014: 848 preferred terms 18,808 synonyms Cross ref to INHAND 10% Id: MC:0000541 Ontology: histopathology Term: bile duct hyperplasia Definition: nonneoplastic proliferation of bile duct epithelium Source: INHAND Reference Id: 7005 Comments: Created By: alessandro.piaia@novartis.com Status: APPROVED

Multilevel & multiscale modelling



Methods solely based on statistical methodologies (QSAR) are unlikely to yield robust models for predicting *in vivo* toxicity endpoints from chemical structure.



This multilevel strategy fits well with the Adverse Outcome Pathway (AOP) concept

Multilevel & multiscale modelling



The strategy implemented in eTOX is based on two-level modeling:

- 1. Build models for predicting first-order endpoints (e.g. hERG blockade)
- 2. Integrate first-order predictions and/or *in vitro* experimental data for predicting higher-order endpoints (*in vivo* toxicity, e.g. QT prolongation)













pubs.acs.org/jcim



A Multiscale Simulation System for the Prediction of Drug-Induced Cardiotoxicity

Cristian Obiol-Pardo,⁺ Julio Gomis-Tena,[‡] Ferran Sanz,[†] Javier Saiz,[‡] and Manuel Pastor^{*,†}

J. Chem. Inf. Model. 2011, 51, 483-492

FOX Virtual Physiological Human network of excellence

New approach for the predictive simulation of the long-QT syndrome in early stages of drug development. It integrates simulations at three levels:



Simulation of (several) ion channels blockade

Simulation of the cardiomyocyte electrophysiology

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







The input is the 2D structure of a possible drug



The output is the possible ECG alteration

Predictive models development



The last eTOX prototype already implements 74 models for diverse endpoints



- ADME
- Transporters
- Physicochemical Properties
- Carcinogenicity
- Genotoxicity
- Organ Toxicity
- Target Safety Pharmacology



The technologies used in eTOX simplify the model development and maintenance (eTOXlab) and the deployment of the predictive system behind firewalls (VM)



Int. J. Mol. Sci. 2014, 15, 21136-21154; doi:10.3390/ijms151121136

OPEN ACCESS

International Journal of

Molecular Sciences ISSN 1422-0067 www.mdpi.com/journal/ijms

Article

The eTOX Data-Sharing Project to Advance *in Silico* Drug-Induced Toxicity Prediction

Montserrat Cases ^{1,3}, Katharine Briggs ², Thomas Steger-Hartmann ³, François Pognan ⁴, Philippe Marc ⁴, Thomas Kleinöder ⁵, Christof H. Schwab ⁵, Manuel Pastor ¹, Jörg Wichard ³ and Ferran Sanz ^{1,*}

More information...



More information at: <u>www.e-tox.net</u>



Sign up for eTOX Newsletter at: editorial@e-tox.net

Some tips for a successful proposal



- Approach potential partners as soon as the topic is know (before the official call for proposals)
- Partners have to be internationally recognised experts in the field (you need the best)
- Excellent matching of the proposal with the description of the topic
- Innovative and feasible scientific contributions to the topic
- Optimal consortium design (total coverage of the required scope of expertise, avoiding unjustified duplication of partner profiles)
- Involvement of relevant SMEs
- Attractive presentation of the proposal (text and layout)
- Don't forget the managerial and "political" arguments





