
# *In silico* prediction of *in vivo* toxicity. The eTOX project

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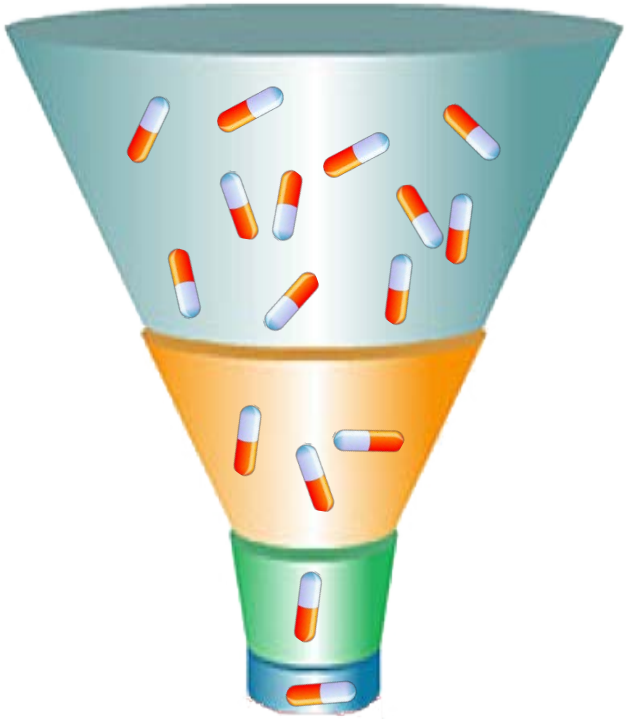
# The need of toxicity prediction

The efficiency of the drug R&D process depends critically on the identification of toxic effects in the early phases of the pipeline



Early Discovery

Late Discovery

Preclinical

Clinical

*Any toxic effect must be detected here, where several candidates are under investigation and the lead compounds can still be modified*

Fail fast!

# General information

- **Project vision:** to develop innovative strategies and novel software tools to better predict the potential side-effects of new drug candidates on the basis of integrative approaches.
- Total budget: **18.7 M€**
- EC funding: **6.9 M€**
- In kind contribution from EFPIA companies: **10.1 M€**
- Duration: **7 years** *(from 1/2010 till 12/2016)*
- **13 EFPIA companies**: Novartis, Bayer, AstraZeneca, Boehringer, Esteve, GSK, Janssen, Lundbeck, Pfizer, Roche, Sanofi-Aventis, Servier, UCB.
- **11 academic institutions**: FIMIM, EBI, Erasmus Medical Center, CNIO, ITEM, Universities of Leicester, Liverpool and Vienna, Free University of Amsterdam, Danish Tecnical University, Polytechnic University of Valencia.
- **6 SMEs**: Chemotargets, Intel:ligand, Lhasa, LMD, MN, Synapse

# Project rationale

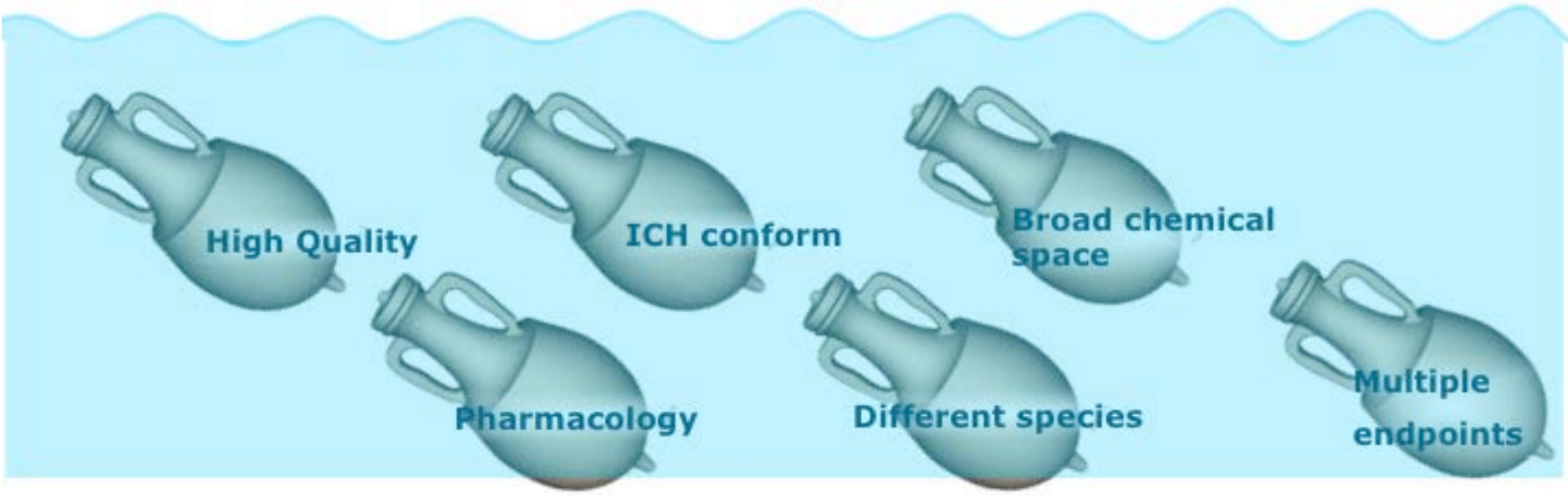
## Opportunity for better toxicity predictions

The wealth of high quality toxicology data in the archives of pharmaceutical companies is not yet leveraged.

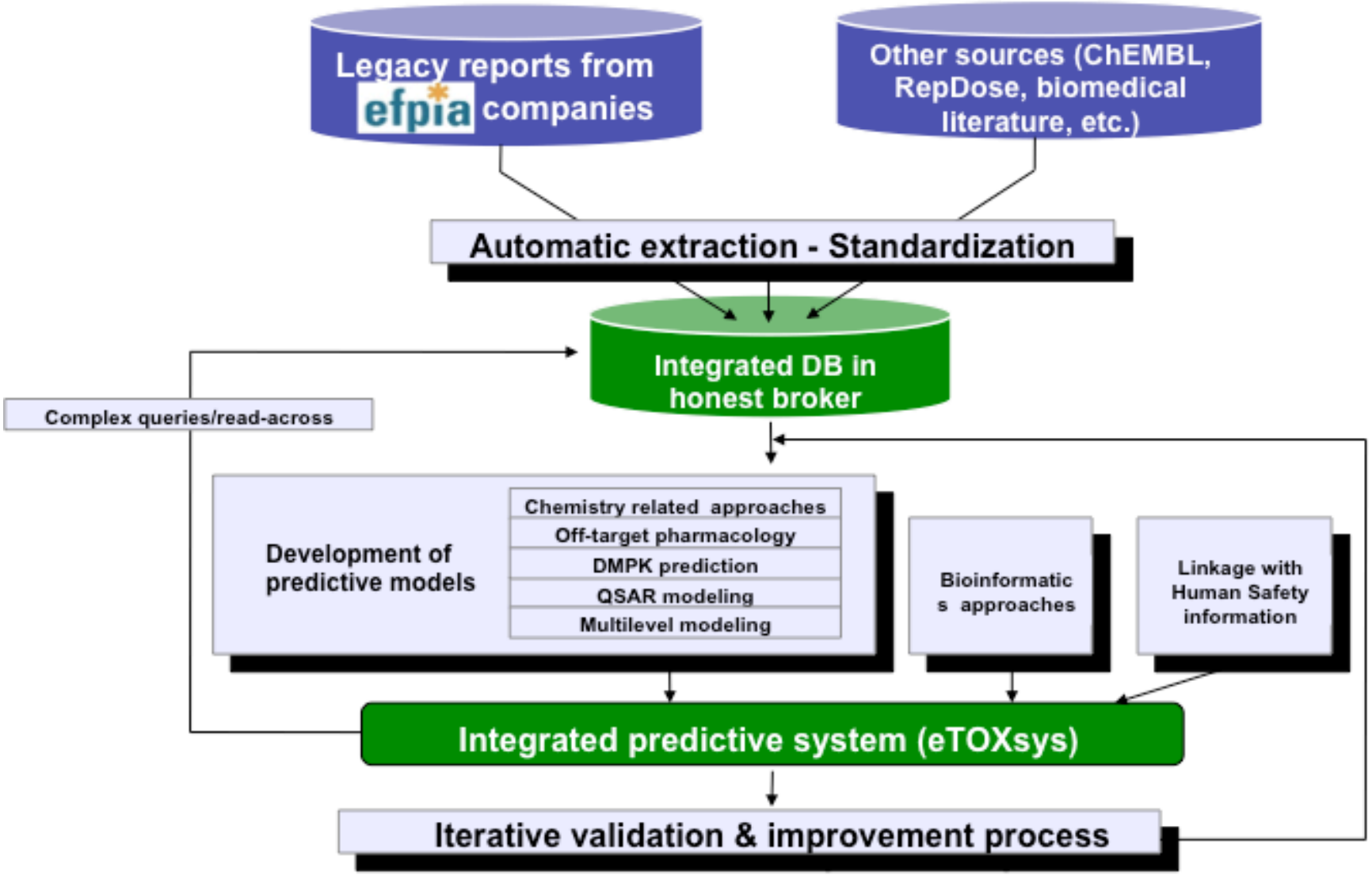
High Quality Tox Data Repository

efpia

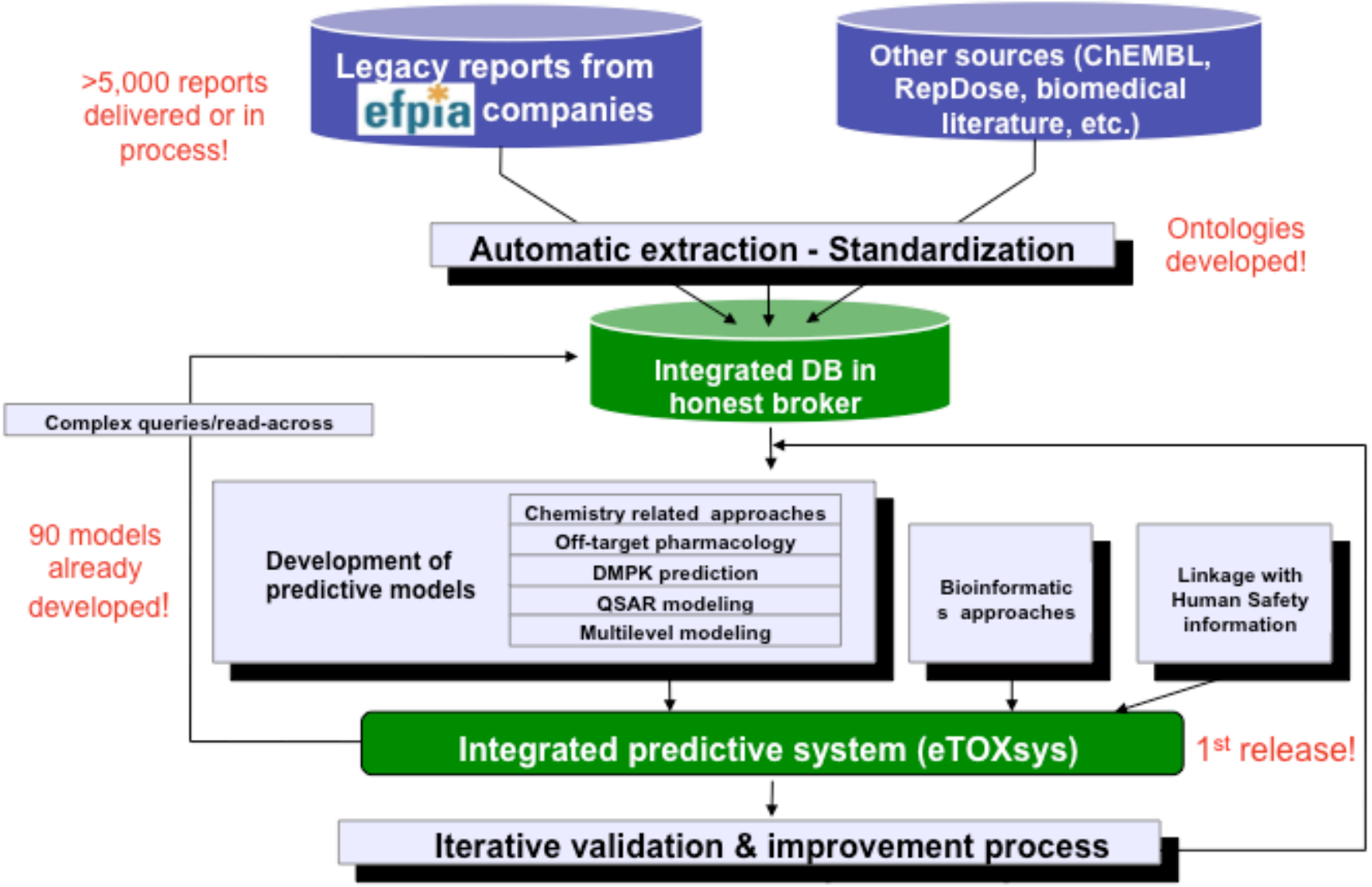
Buried in toxicology archives



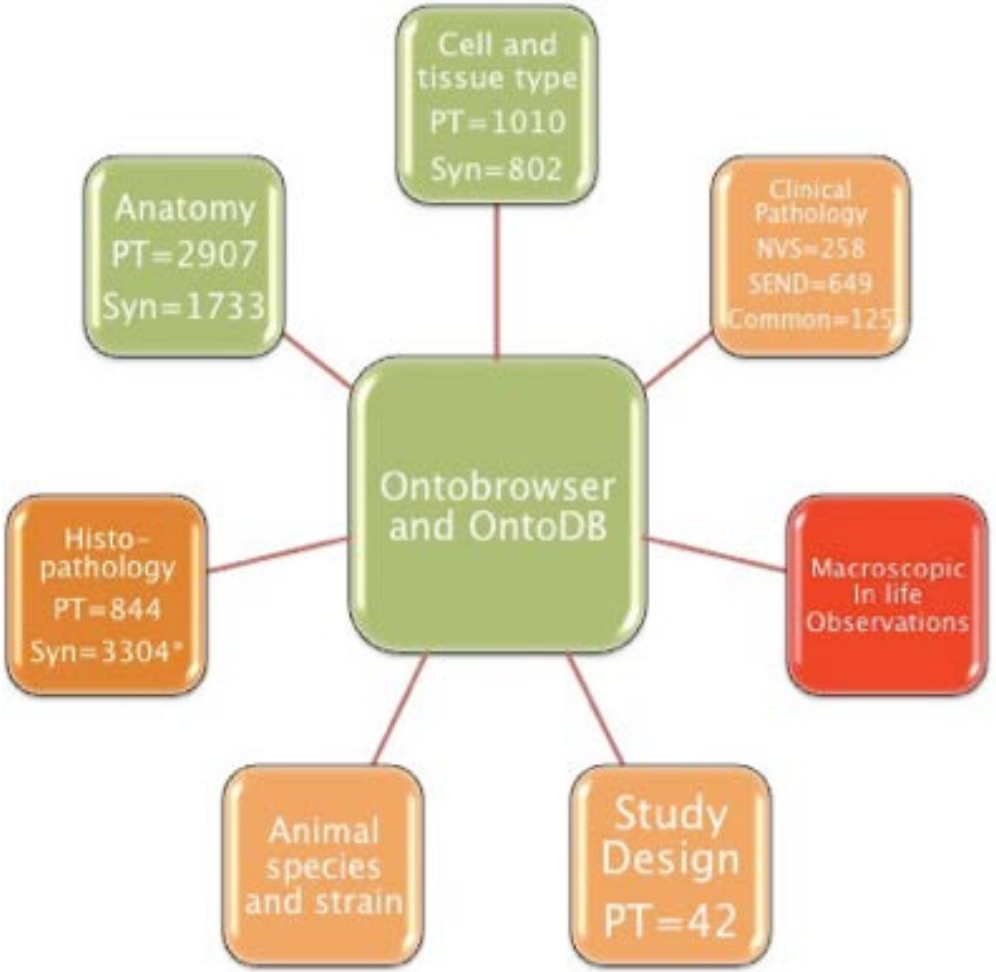
# Project overview



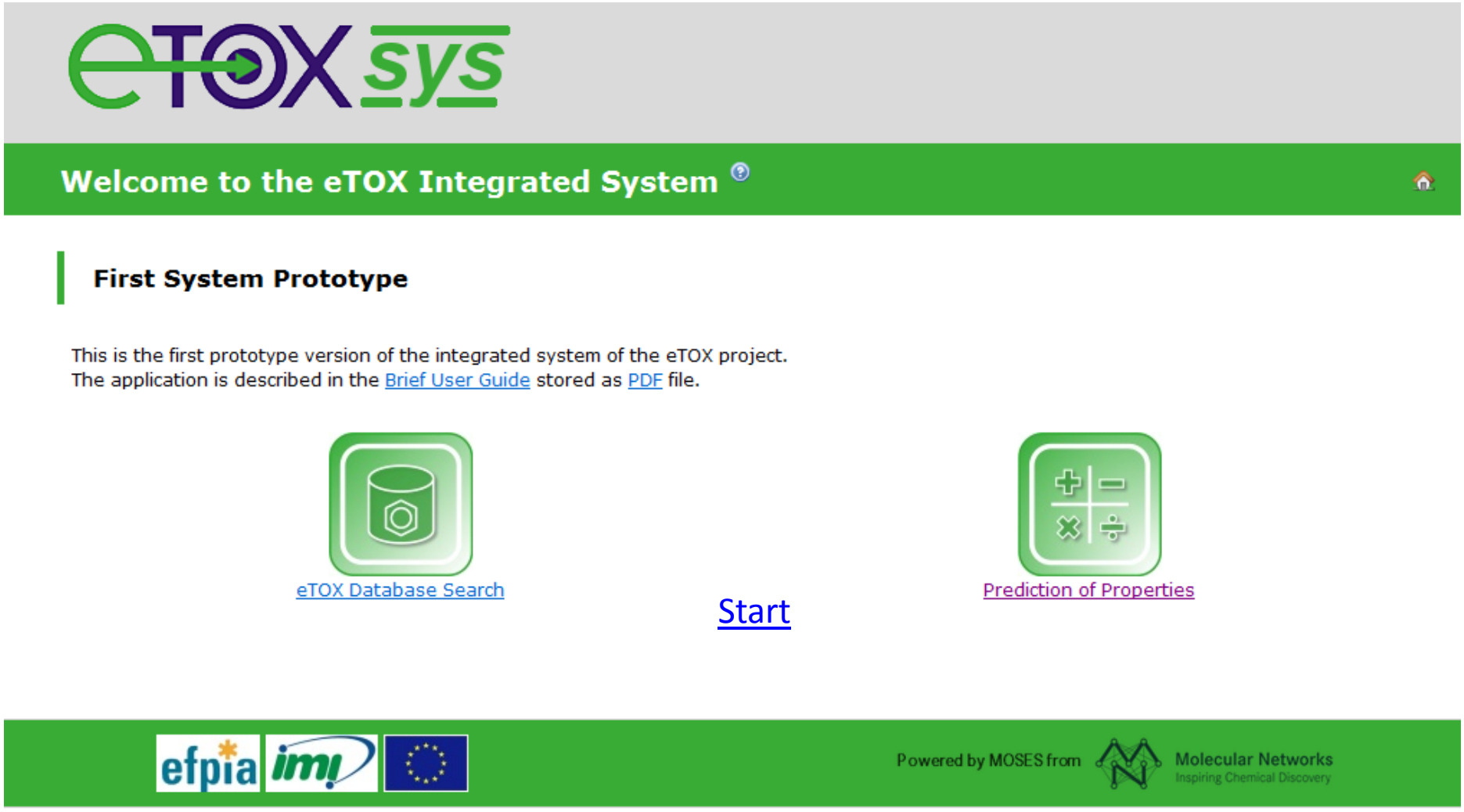
# Project achievements



# Ontologies developed

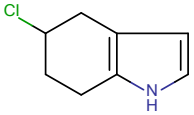


# eTOXsys combines read-across and prediction

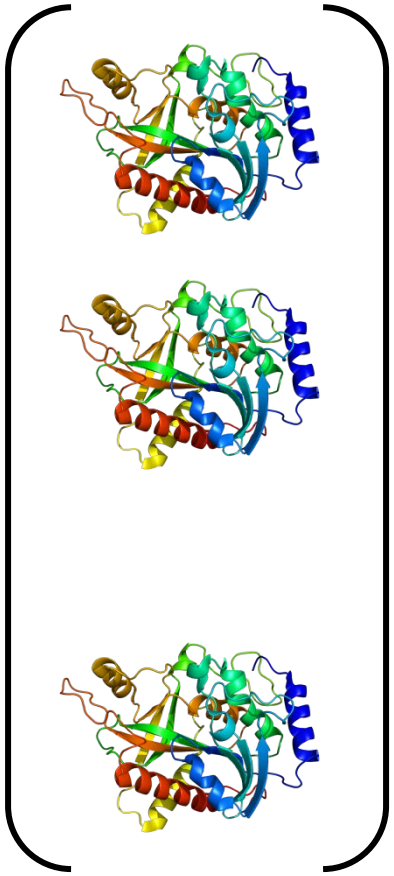


# Multi-level modelling

Avoid direct *in vivo* endpoint prediction




Molecular models



Pharmacological models

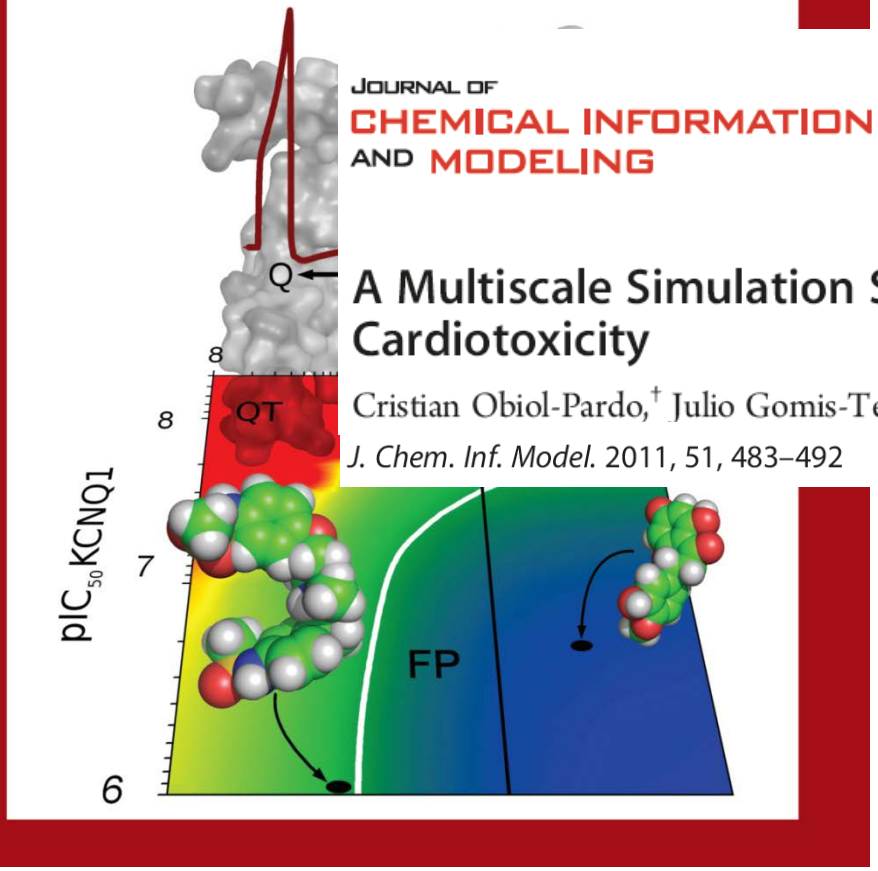
From MD to $K_d$/$IC_{50}$

From $K_d$/$IC_{50}$ to *in vivo*

Relevant (anti-)targets

# Multi-scale prediction of cardiotoxicity

JOURNAL OF CHEMICAL INFORMATION AND MODELING
February 2011
Volume 51
Number 2
pubs.acs.org/jcim




JOURNAL OF CHEMICAL INFORMATION AND MODELING

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

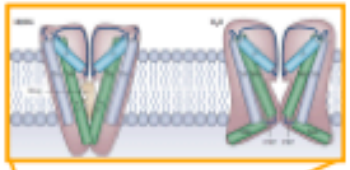
Cristian Obiol-Pardo,[†] Julio Gomis-Tena,[‡] Ferran Sanz,[†] Javier Saiz,[‡] and Manuel Pastor*[,†]

*J. Chem. Inf. Model.* 2011, 51, 483–492

# Multi-scale prediction of cardiotoxicity

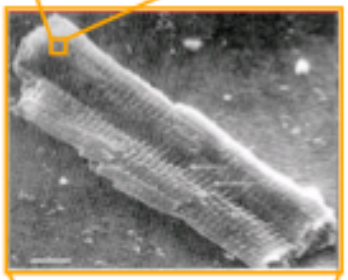
New approach for the predictive simulation of the long-QT syndrome integrating simulations at three levels:

Molecular



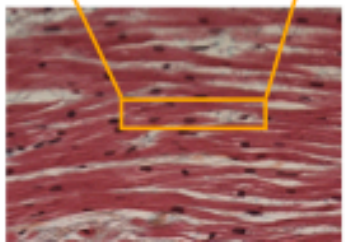
Simulation of (several) ion channels blockade

Cellular



Simulation of the cardiomyocyte electrophysiology

Tissular



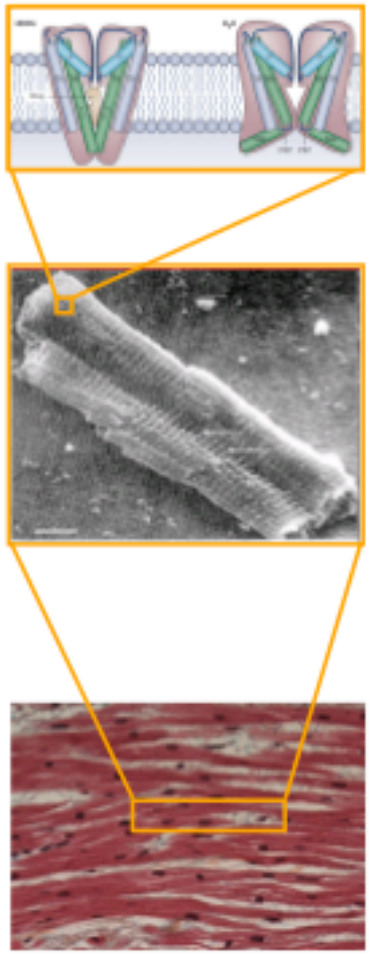
Simulation of the electrical propagation through a model of ventricular tissue, obtaining an ECG

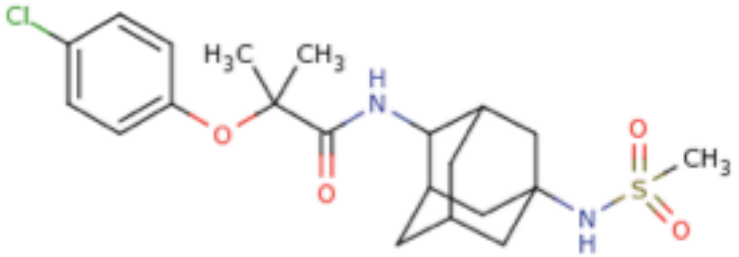
# Multi-scale prediction of cardiotoxicity

Molecular

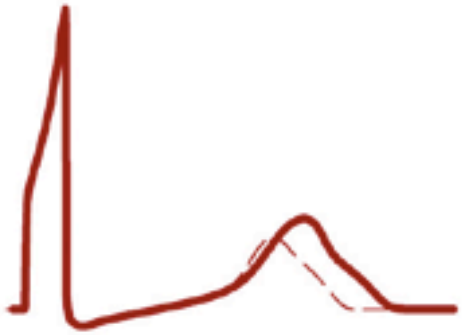
Cellular

Tissular





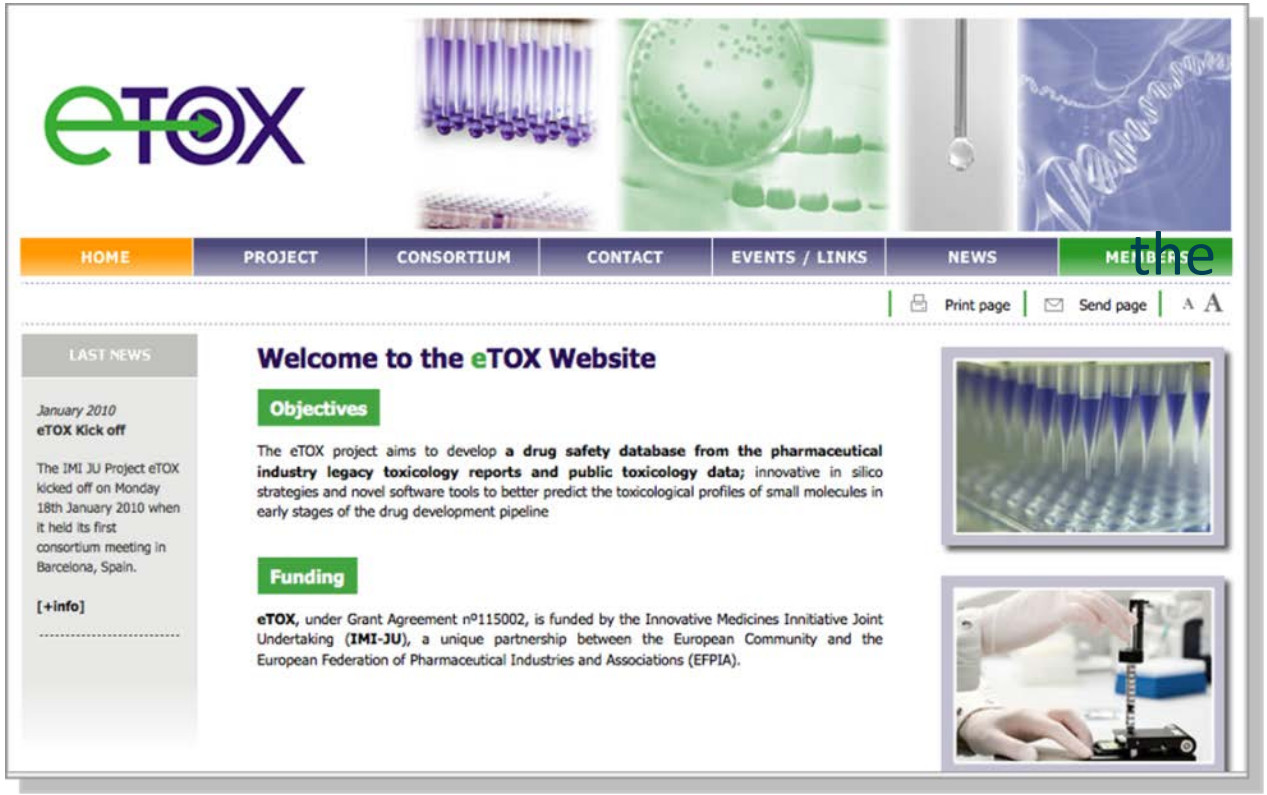

The input is the 2D structure of a possible drug



The output is the possible ECG alteration

# More information

Visit the project webpage: **www.etoxproject.eu**

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