



Innovative Medicines Initiative

# eTOX – Data integration for *in silico* toxicity prediction

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efpia\*

# General information

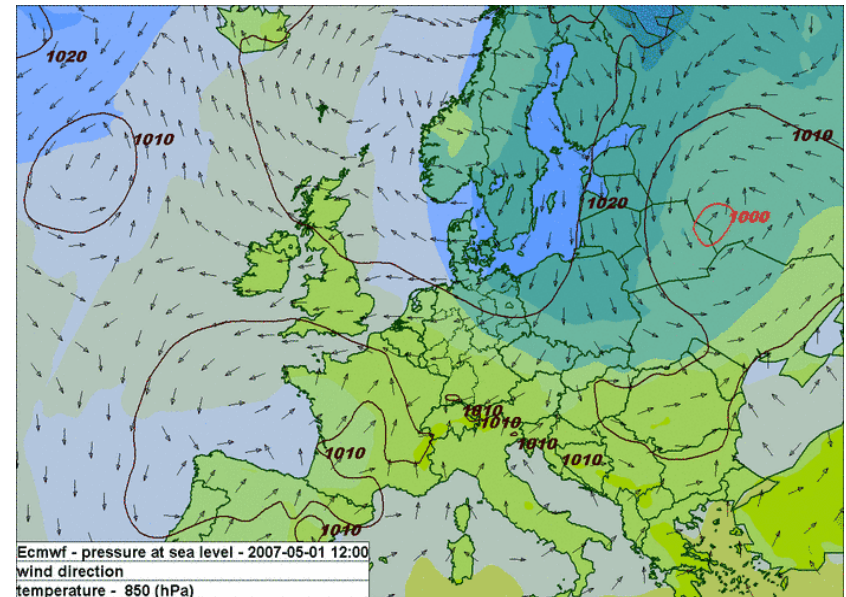
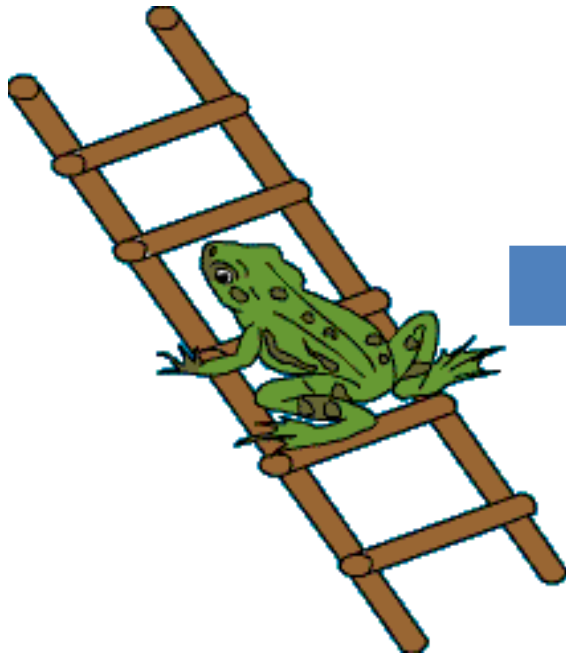
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- Project kick-off : **January 2010**
- Duration: **5 years**
- Consortium composition: **13 pharma companies + 7 academic institutions + 5 SMEs**
- Total budget: **13.9 M€**
- In kind contribution from EFPIA companies: **7.9 M€**
- IMI-JU funding: **4.7 M€**
- SME and Academia contribution: **1.3 M€**



# From mere guess to prediction



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

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- 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



# Current limitations in computational prediction of *in vivo* toxicities

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- Toxicological data from public sources is often **biased towards toxic effects** (negative toxicological data is usually not published).
- The data **quality of toxicological data** in the public domain can hardly be assessed and is sometimes **questionable**.
- The chemical space of published toxicological data is dominated by industrial or household chemicals (**pharmaceuticals are underrepresented**).
- Predictive models are mostly directed to pure chemical approaches (**integration of pharmacodynamic and DMPK data is lacking**).



# Opportunity for better toxicity predictions



Tremendous wealth of high quality toxicology data in the archives of the pharmaceutical companies, not yet leveraged!

High Quality Tox Data Repository



Buried in toxicology archives



# Rationale of the eTOX project

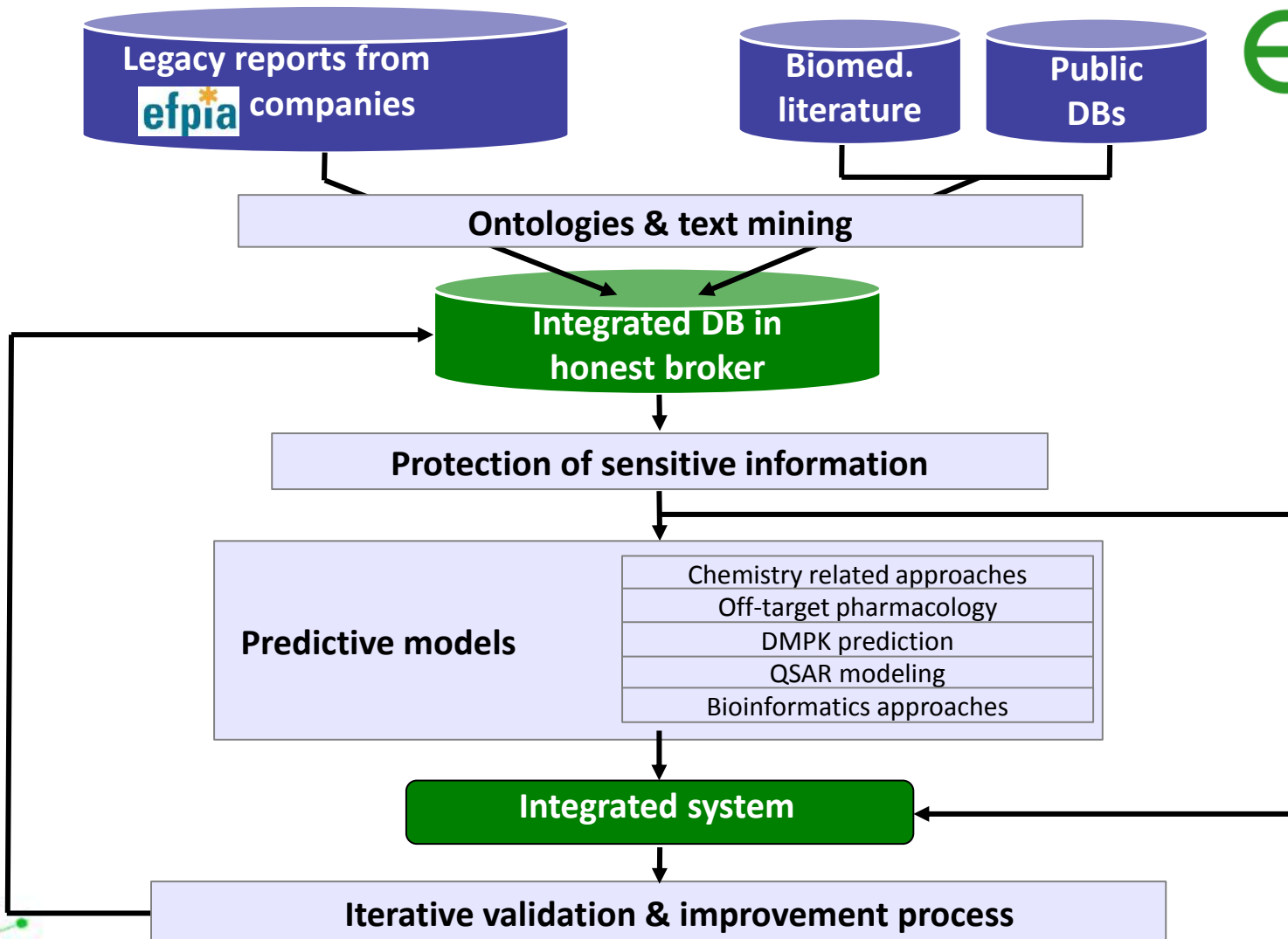
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1. **Data sharing**: Exploit legacy preclinical reports from the pharmaceutical industry.
2. Establishment of a **toxicological database** with high quality structural, *in vitro* and *in vivo* data. This repository will facilitate the development of better predictive models for *in vivo* toxicity.
3. The development of the models will take advantage of an **integrative** application of state-of-the-art **computational, chemoinformatic and bioinformatic approaches**.
4. **Validation** of the new predictive models. The validation exercises will be shared between companies and regulators.

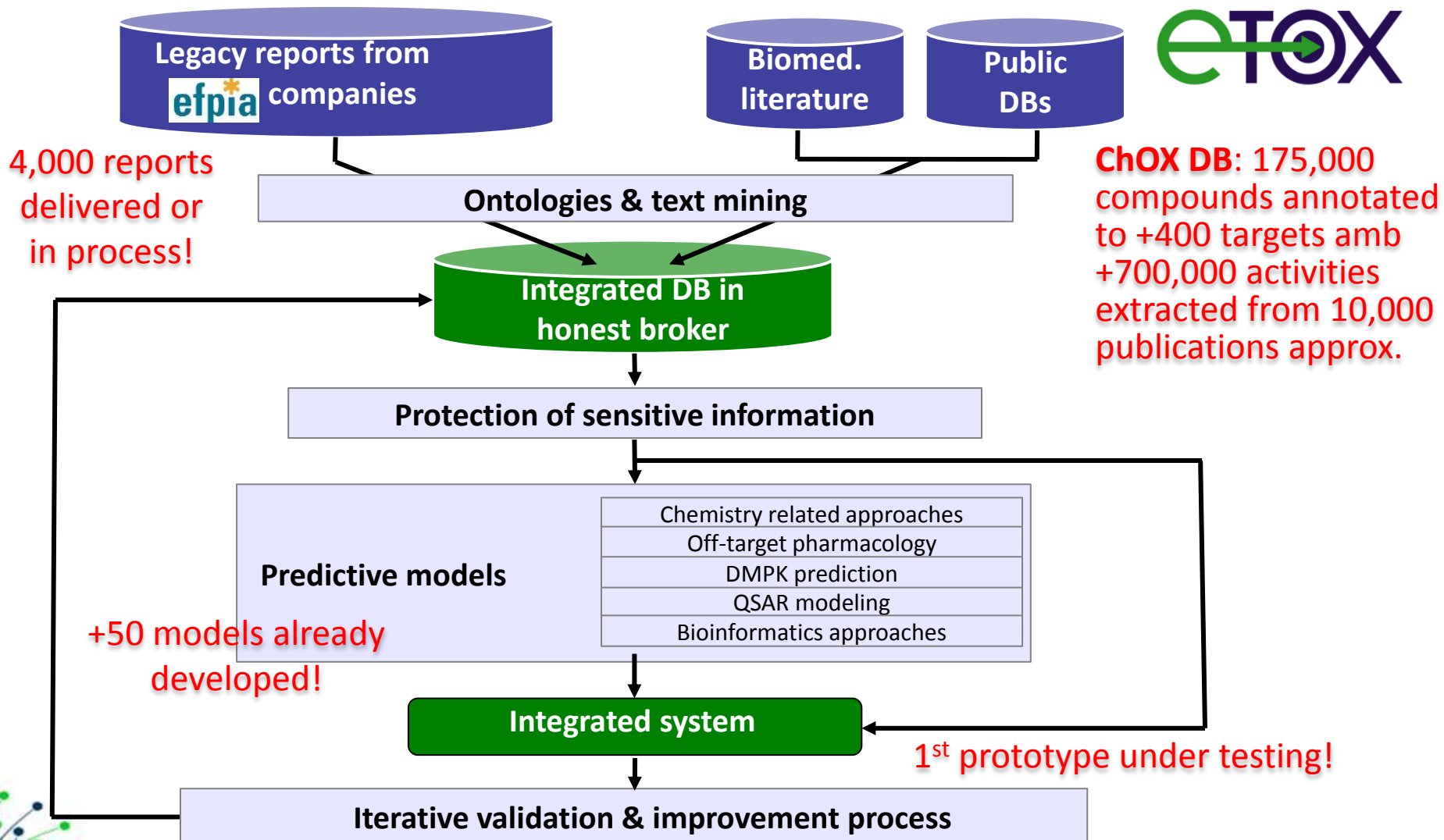


# eTOX project structure





# Some achievements

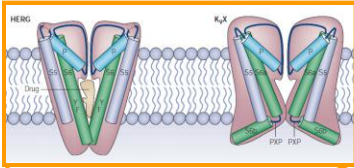


# Multi-scale prediction of cardiotoxicity



The developed method integrates simulations at three levels:

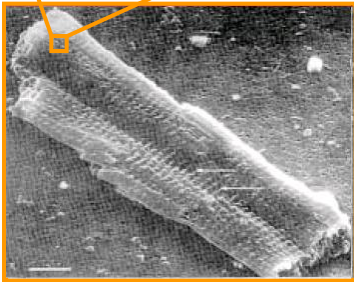
Molecular



Simulation of ion channels blockade



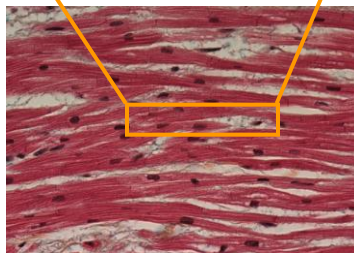
Cellular



Simulation of the cardiomyocyte electrophysiology



Tissular

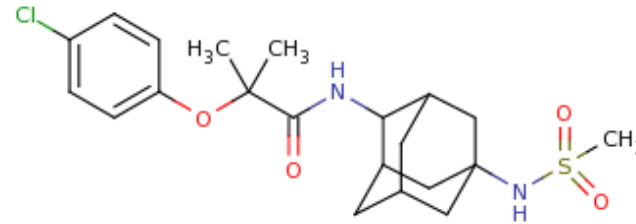
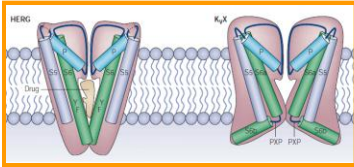


Simulation of the electrical propagation through a model of ventricular tissue, obtaining an ECG



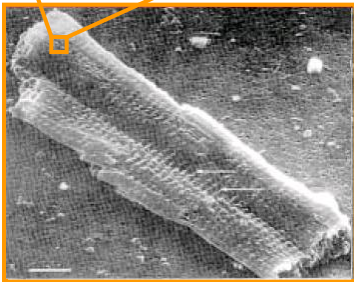
# Multi-scale prediction of cardiotoxicity

Molecular

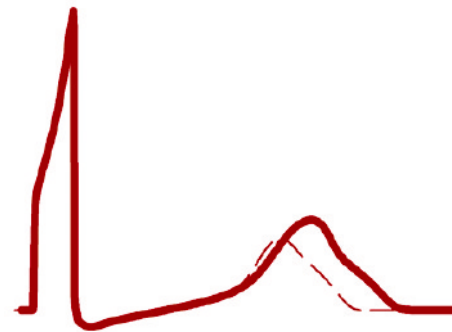
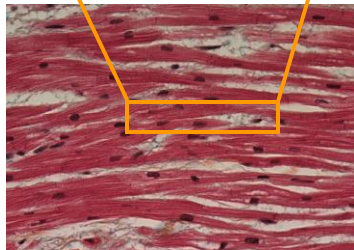


The **input** is the 2D structure of a possible drug

Cellular



Tissular



The **output** is the possible ECG alteration

# More information at...

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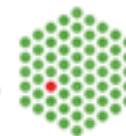
- [www.etoxproject.eu](http://www.etoxproject.eu)
- Briggs K, Cases M, Heard DJ, Pastor M, Pognan F, Sanz F, Schwab CH, Steger-Hartmann T, Sutter A, Watson DK, Wichard JD. Inroads to Predict in Vivo Toxicology - An Introduction to the eTOX Project. *Int J Mol Sci* 2012; 13: 3820-46.
- Obiol-Pardo C, Gomis-Tena J, Sanz F, Saiz J, Pastor M. A Multiscale simulation system for the prediction of drug-induced cardiotoxicity. *J Chem Inf Model* 2011; 51: 483-92.



# Thank you!



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