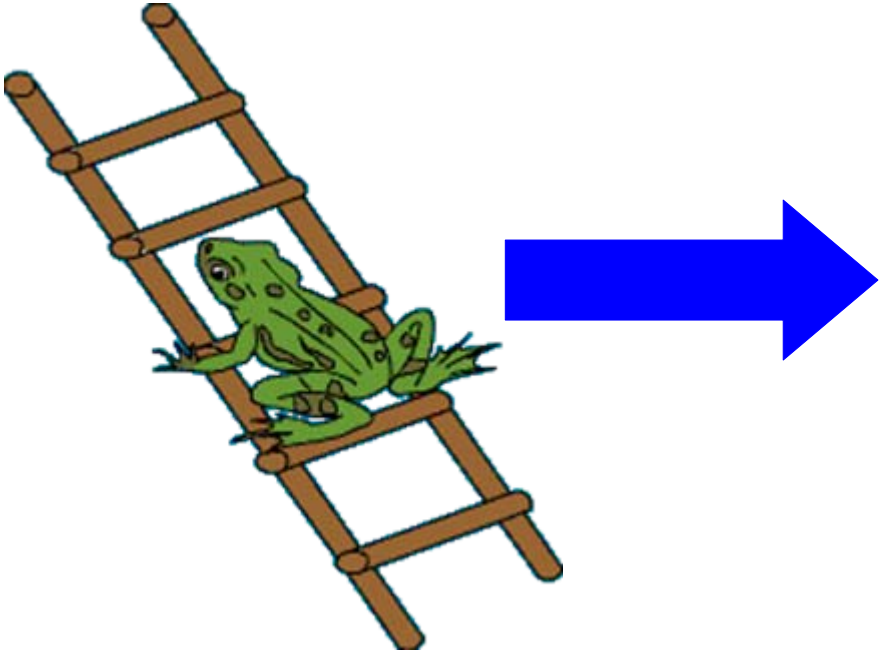
eTOX

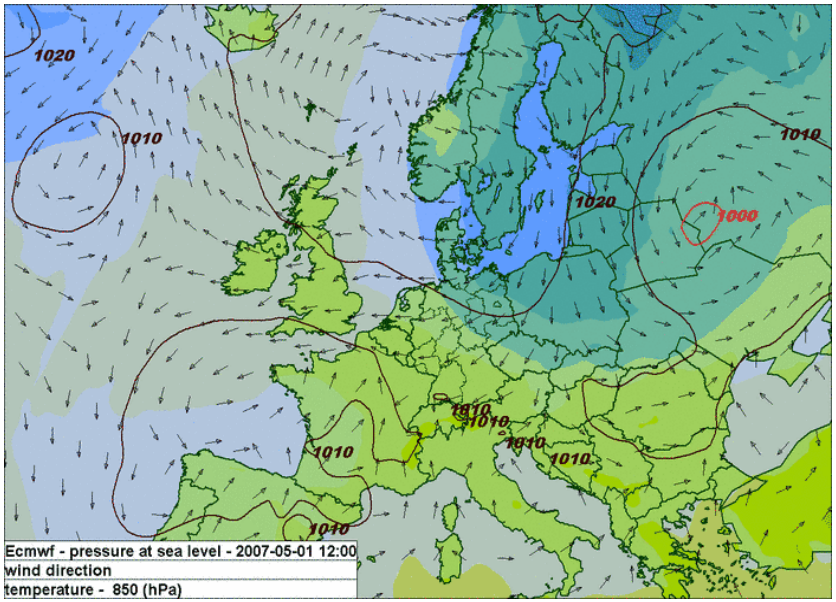
Computational prediction of toxicities

Ferran Sanz (GRIB, *Fundació IMIM - UPF)*
on behalf of the **eTOX Consortium**

efpia

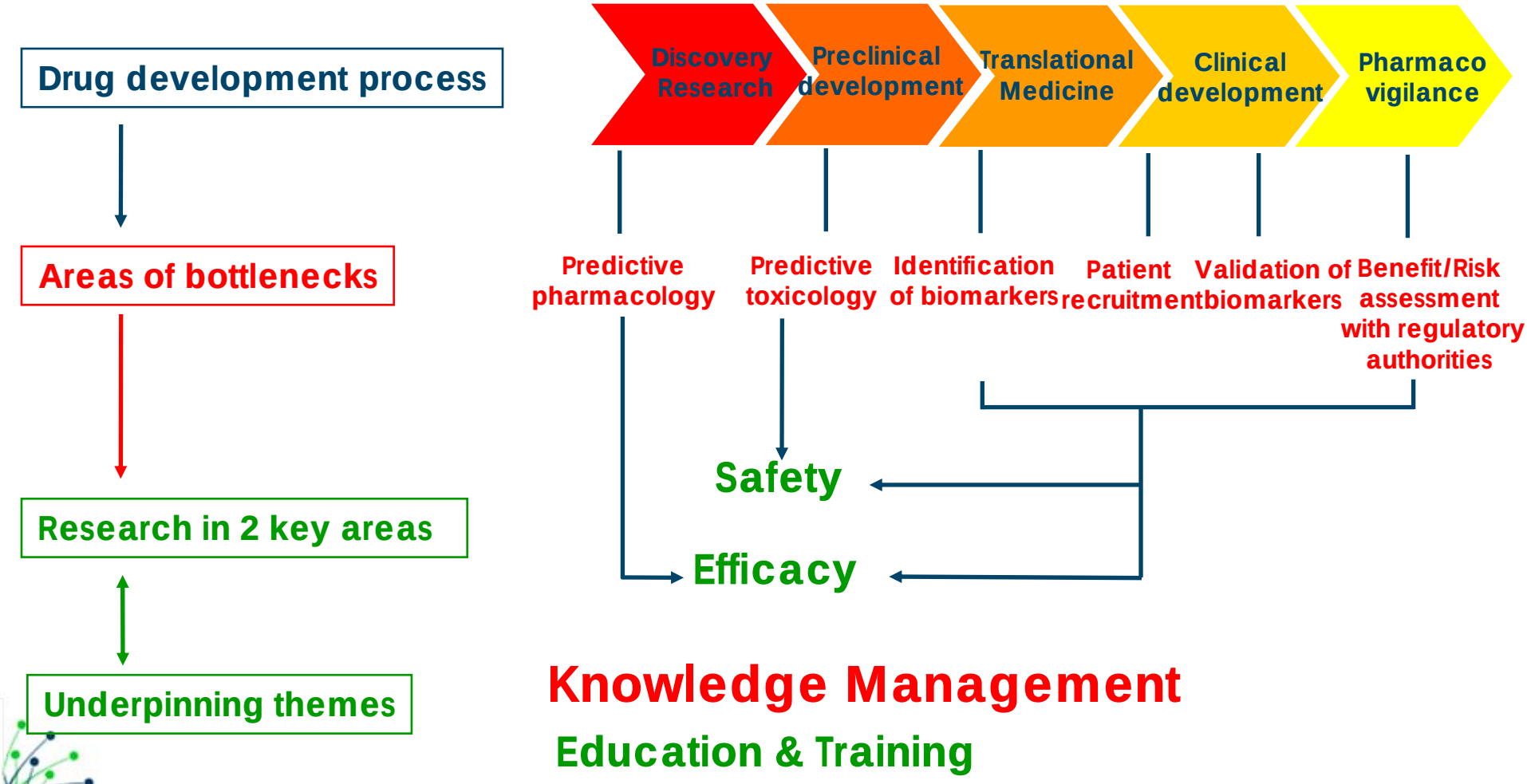
From divination to prediction



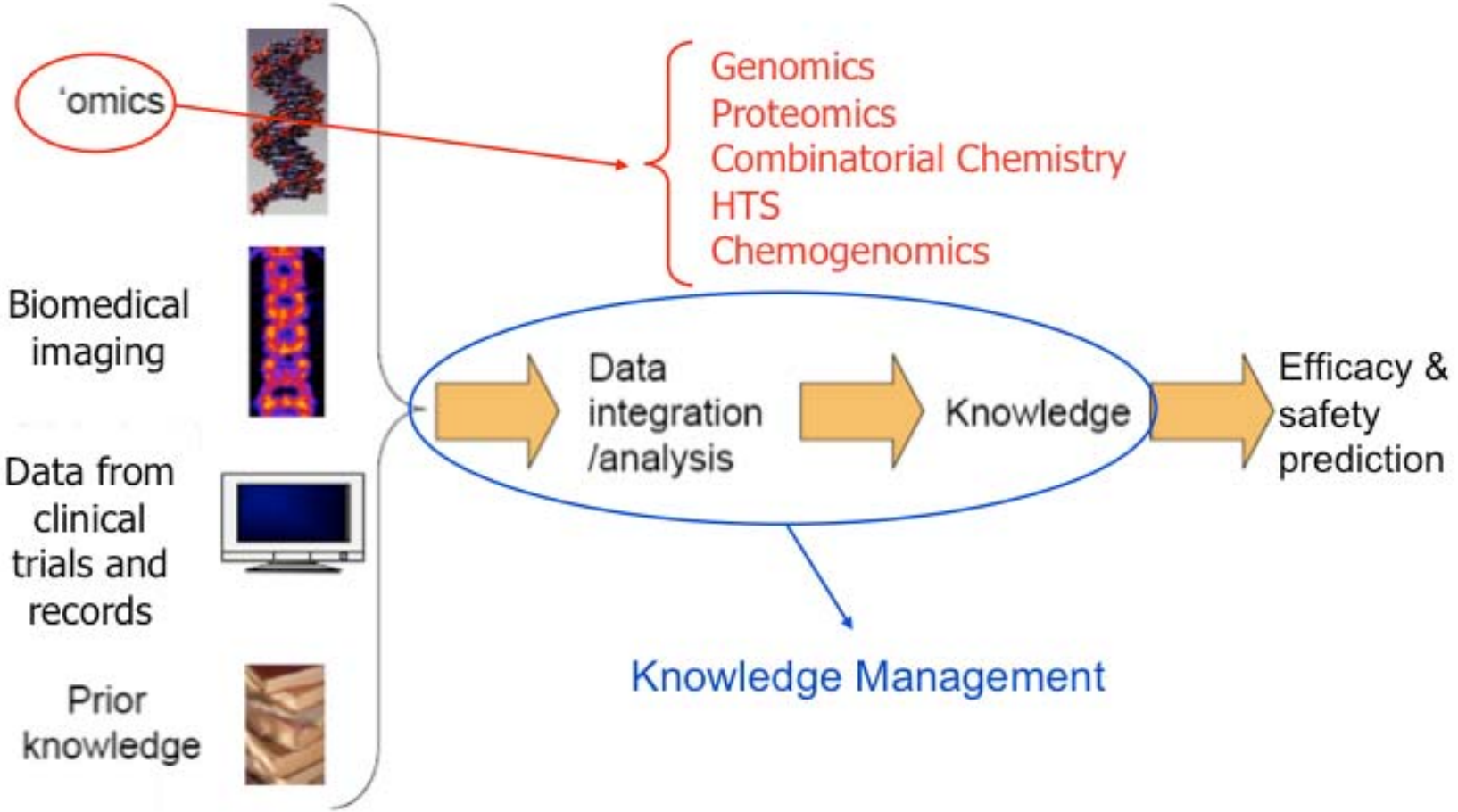


Present science and technology allow the development of reliable predictive systems on the basis of a wide consideration of relevant previous experience

The four IMI pillars

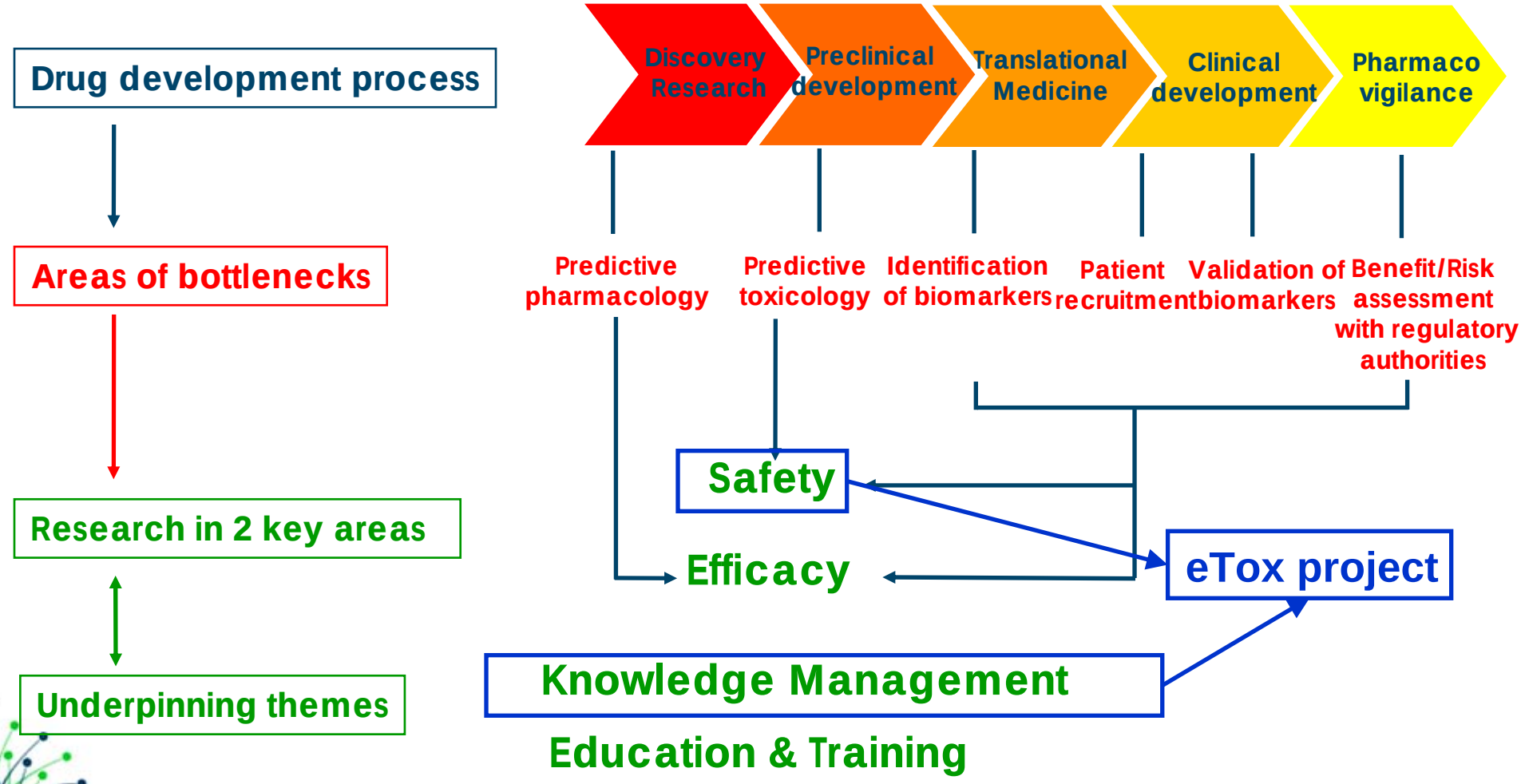


Integrative knowledge management in



Adapted from a presentation of Ian Ragan. EFPIA. 2006.

The four IMI pillars



The eTOX IMI project

- Project kick-off : **January 2010**
- Duration: **5 years**
- Total budget: **13.9 M€**
- In kind contribution from EFPIA companies: **7.9 M€**
- IMI-JU funding: **4.7 M€**

Benefits of early *in silico* prediction of *in vivo* toxicities

- 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
- Better predict human toxicities and/or safer starting doses

Current gaps in computational prediction of *in vivo* toxicities

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

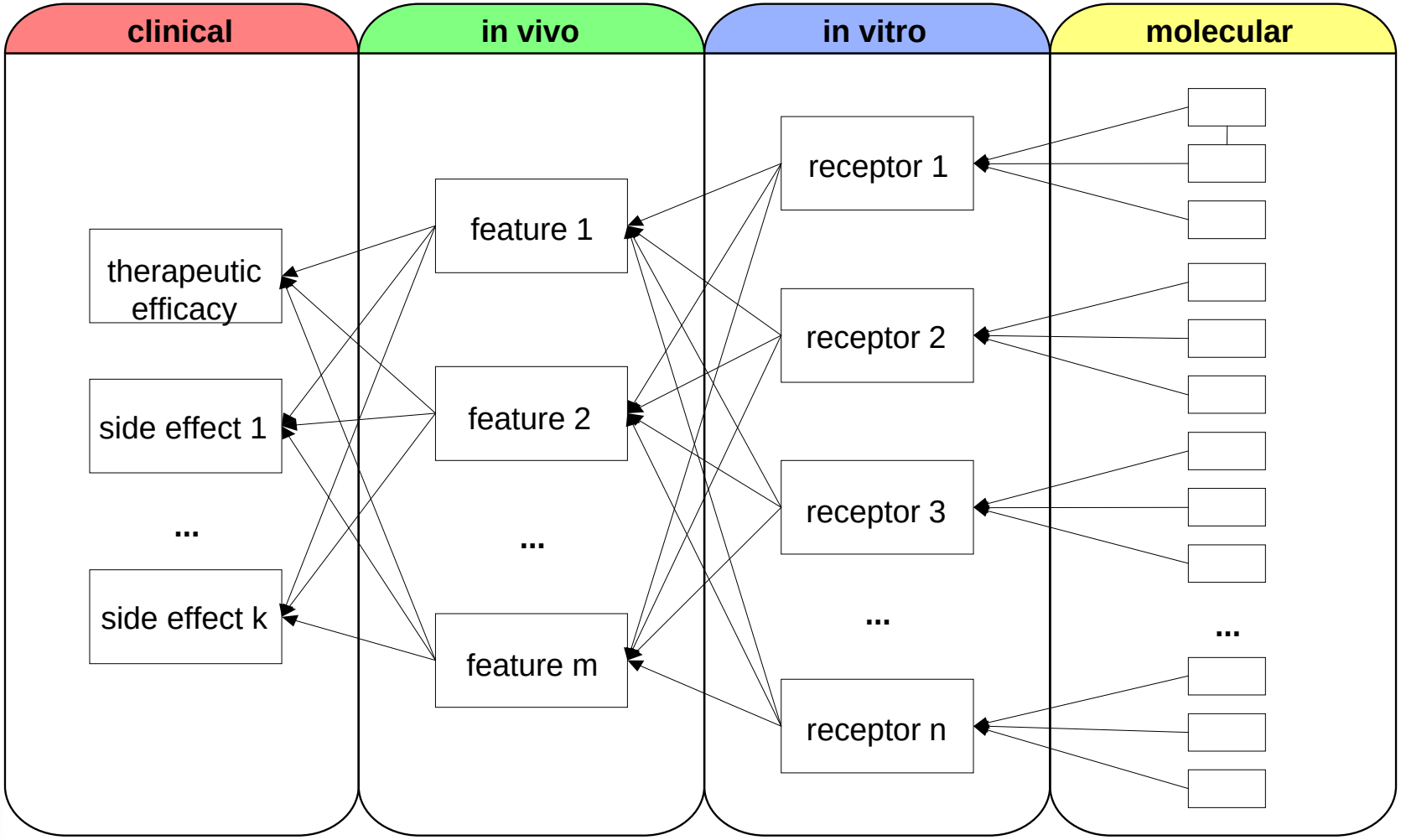
Opportunity for better toxicity predictions

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

Buried in toxicology archives

- High Quality
- ICH conform
- Broad chemical space
- Multiple endpoints
- Pharmacology
- Different species

Opportunity for better toxicity predictions



Rationale of the eTOX project

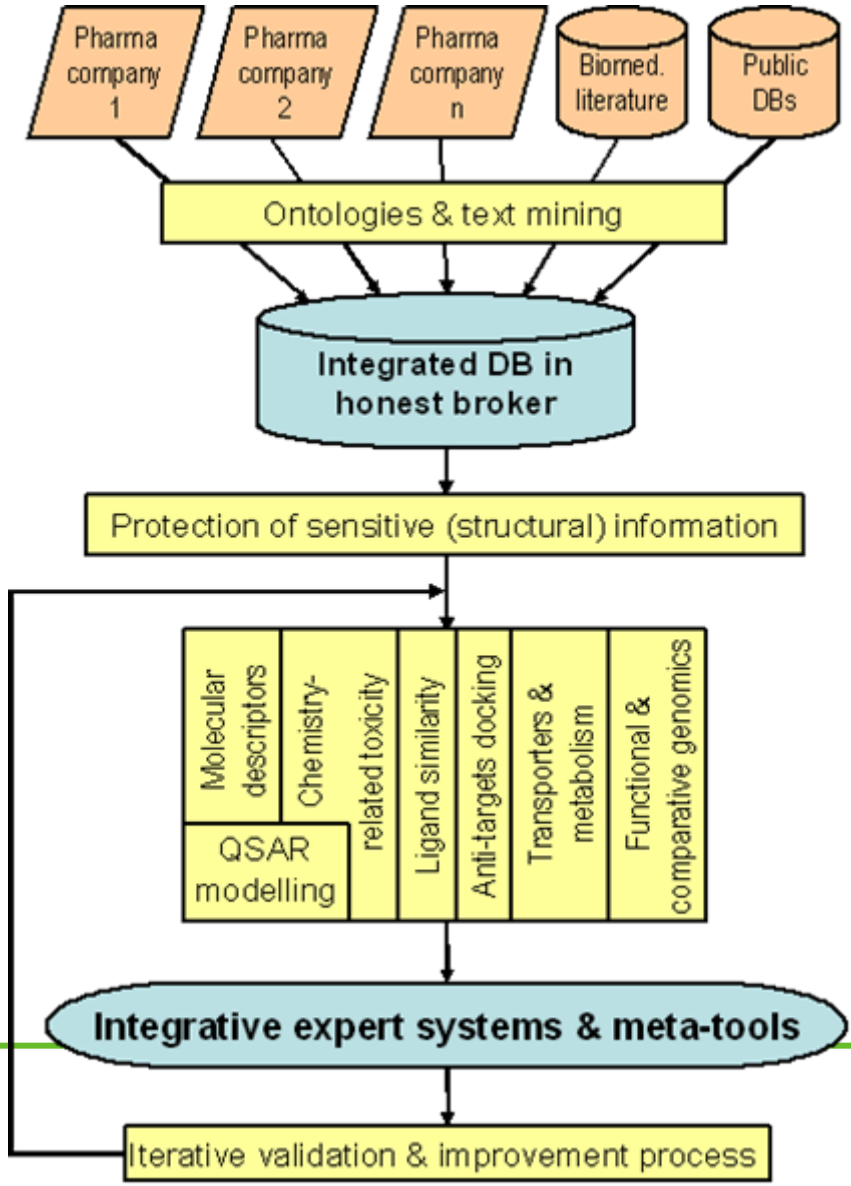
1. Data sharing: Exploit legacy preclinical reports from the pharmaceutical industry to link chemical features to pathology findings.

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 exercices will be shared between companies and regulators.

Scientific approach of the eTOX project



Data sharing and IP protection

Proposed strategy:

- Classification of data: confidential, non-confidential (structure and European Public Assessment Report (EPAR) in the public domain)
- Data transfer to “honest broker” bound by legal framework
- Masking of sensitive structural information by means of molecular descriptors and other procedures but keeping usefulness for developing predictive models
- Provision of IT infrastructure to prevent loss and illegal download of sensitive data

EFPIA partners

- **Novartis Pharma AG (François Pognan)**
- **Bayer Schering Pharma AG (Thomas Steger-Hartmann)**
- AstraZeneca AB
- Boehringer Ingelheim International GmbH
- Laboratorios del Dr Esteve SA
- GlaxoSmithKline Research and Development Ltd
- Janssen Pharmaceutica NV
- H. Lundbeck A/S
- Pfizer Ltd
- F. Hoffmann-La Roche AG
- UCB Pharma SA
- Sanofi-aventis
- Servier

Contributions of EFPIA partners

1. Provision of high quality data (mostly GLP) from systemic toxicity studies (different species), DMPK studies, and safety pharmacology studies (including ligand binding)

2. Data extraction from legacy reports (in-house or with external help)

3. Profound toxicological expertise

4. Expertise in the field of QSAR, pharmacophore modelling and ontologies

5. Contacts to regulatory authorities (including interfacing regulatory databases)

Academic partners and SMEs

- **Fundació IMIM (E)**
- Centro Nacional de Investigaciones Oncológicas (UK)
- European Bioinformatics Institute (EMBL) (UK)
- Liverpool John Moores University (UK)
- Technical University of Denmark (DK)
- Universität Wien (A)
- Vrije Universiteit Amsterdam (VUA) (NL)

- Inte:Ligand GmbH (A)
- Lhasa Ltd (UK)
- Molecular Networks GmbH (D)
- Chemotargets SL (E)
- Lead Molecular Design SL (E)

Contributions of academics and SMEs

1. Expertise in bioinformatics and chemoinformatics, including software development in these fields
2. Database development and hosting
3. Development of QSAR models and expert systems
4. DMPK modelling (CYP, transporters)
5. Validation methodology for predictive systems

Ongoing eTOX work

- Selection of records within pharma companies and development of semi-automatic procedures for extracting information from them
- Identification, selection and import of information from public sources
- Setup of the database infrastructure in the honest broker premises
- Development and testing of strategies for the masking of sensitive information
- Analysis and design of the predictive system architecture

More information at…

www.e-tox.net