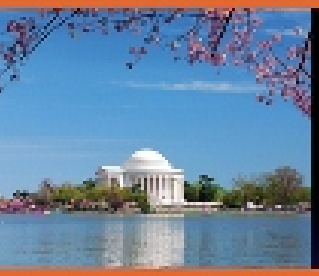


Nonclinical Topics Working Group
Industry Insights

eTOX & eTRANSAFE

Data Exploitation

Phil Drew

What is eTOX

The eTOX consortium/project has developed a huge drug safety database from pharmaceutical industry legacy toxicology reports and from publicly available toxicology data. It has also developed innovative in silico strategies and novel software tools to better predict the toxicological profiles of small molecules in early stages of the drug development pipeline.

This IMI project is devoted to large-scale sharing, data-basing and mining of industry legacy tox reports and includes predictive models and has a central tool for database querying and running the predictive models. Furthermore, a series of purpose-fit ontologies were developed which are supported by the OntoBrowser (a project deliverable).

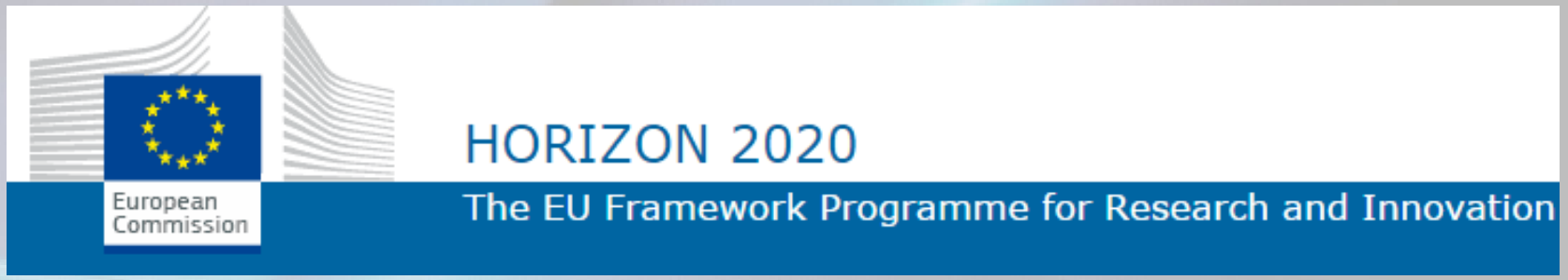
There is significant collaboration (partnering and shared funding) with ‘efpia’ Companies:

efpia
European Federation of Pharmaceutical Industries and Associations

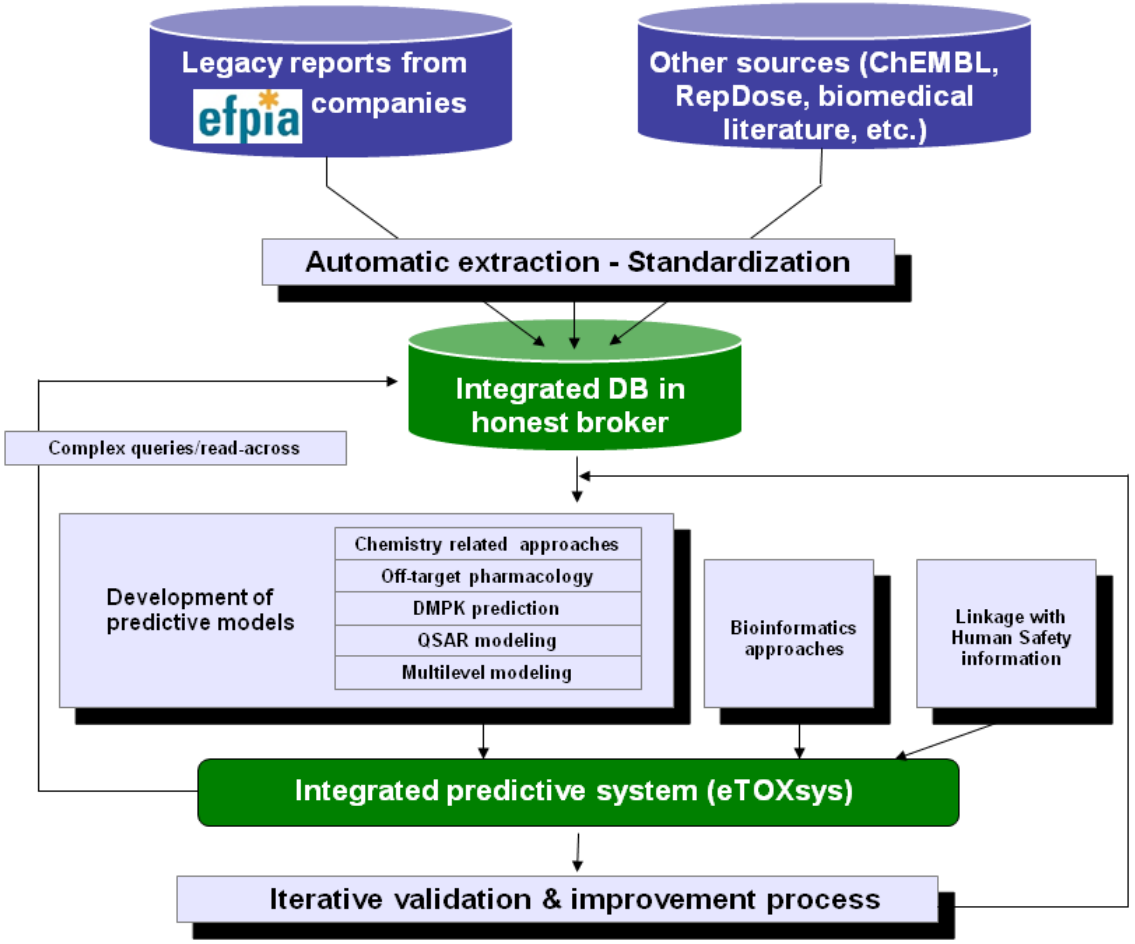
What is IMI

Innovative Medicines Initiative:

Part of the €3.2BN EU Horizon 2020 Project:



eTOX Roadmap

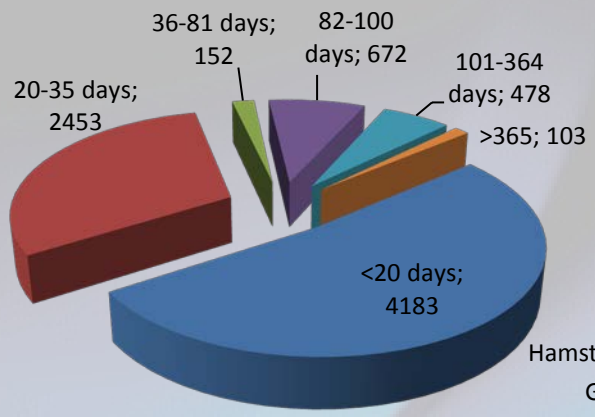


Predict more complex toxicity endpoints by:

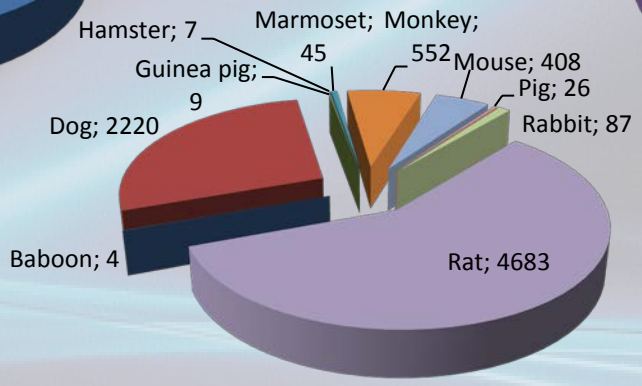
- Sharing high quality proprietary toxicity **data** previously accessible for modelling only by the owning company
- Development of several **models** representing the different components in the mechanism leading to a toxic effect
- Integrated overall decision making **tool - eTOXsys**

Highly Relevant Proprietary Data

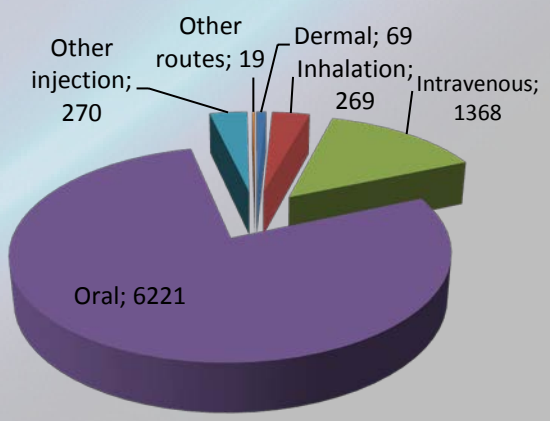
Non-Confidential Structures	Confidential Structures	Non-Confidential Studies
1,464	483	8,047



Study Duration

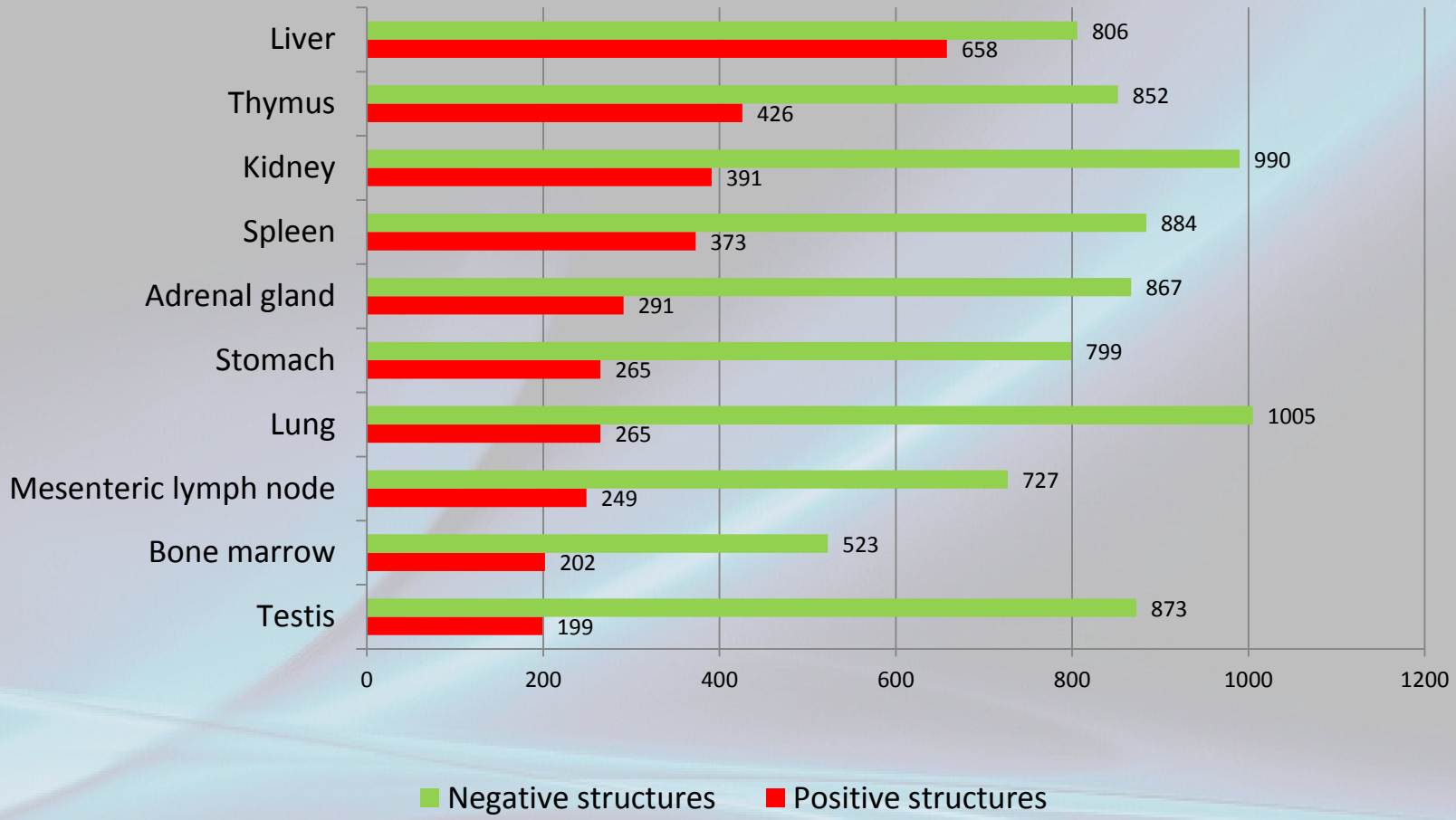


Species

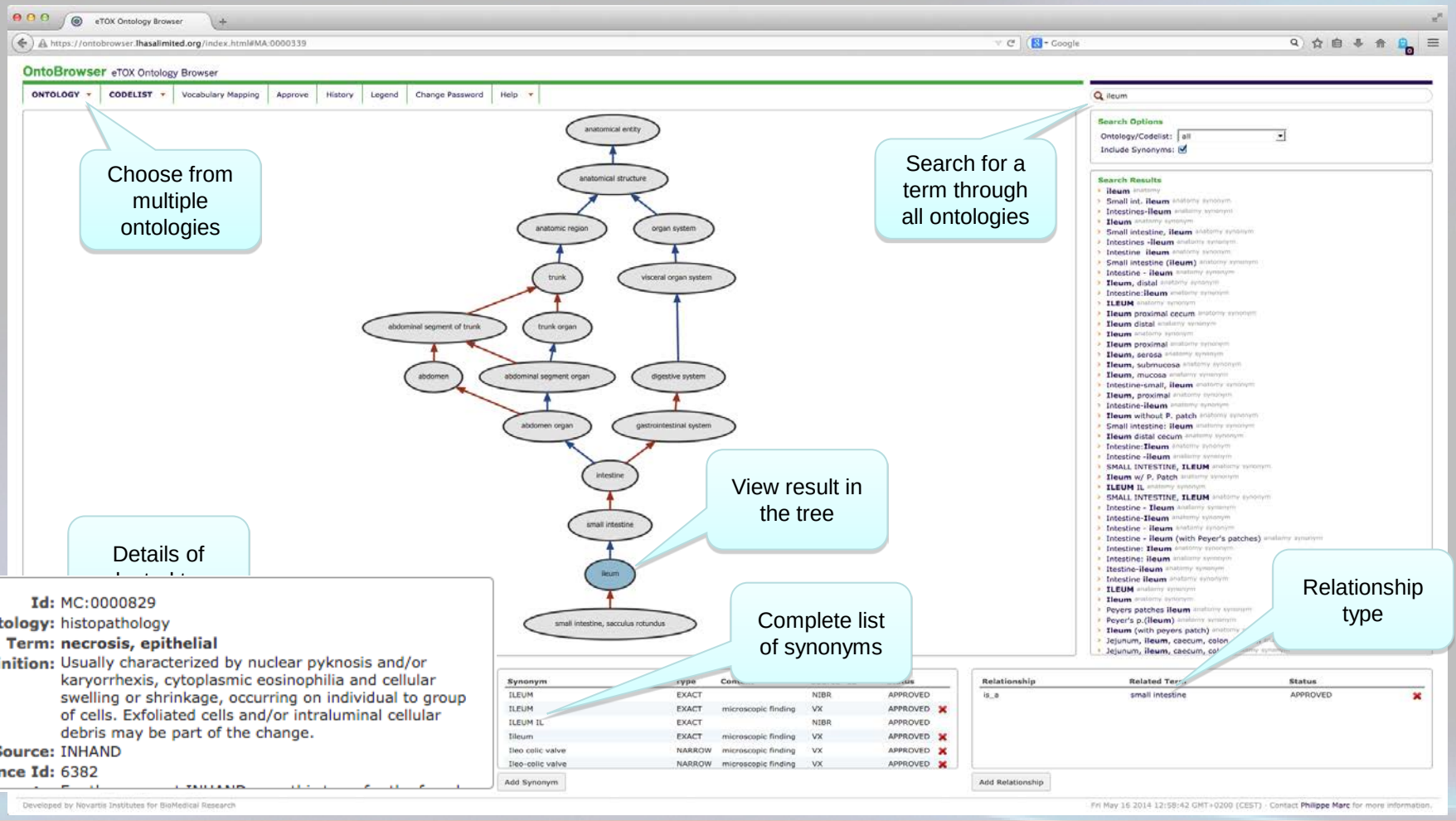


Administration Route

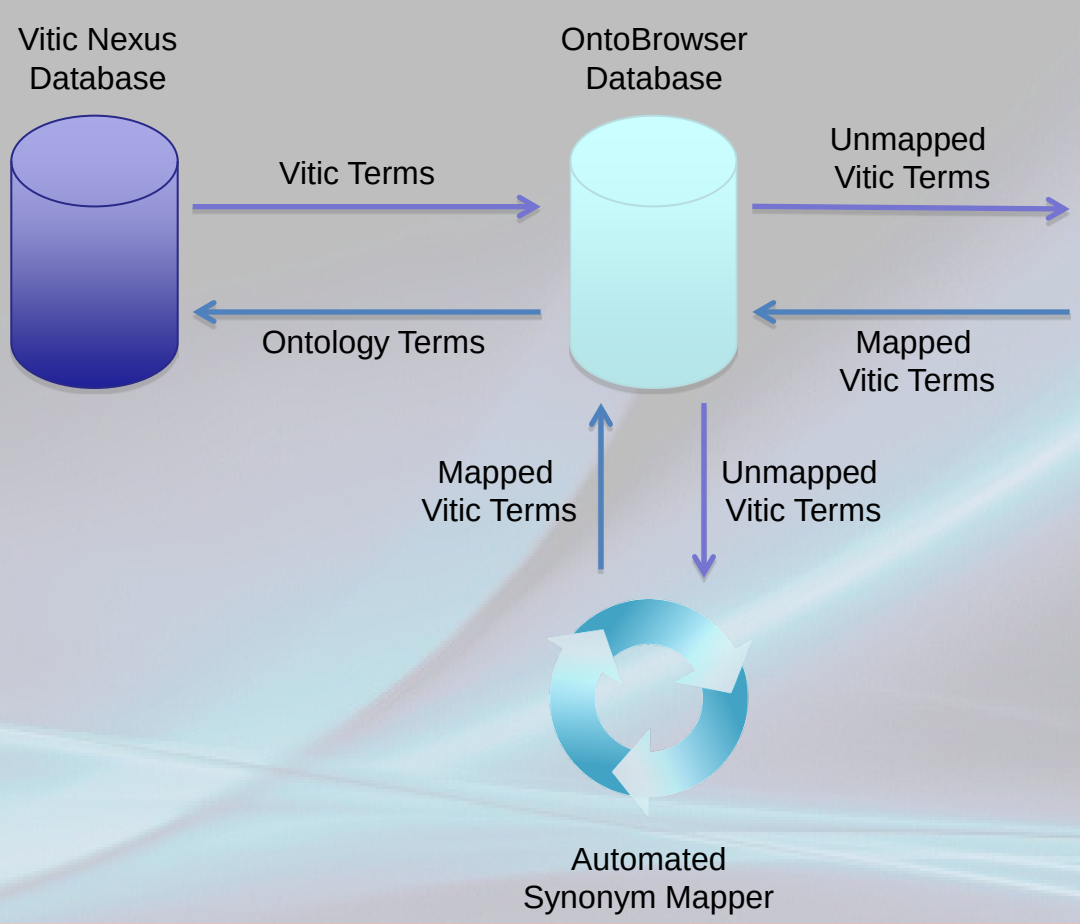
Top 10 organs with treatment related effects shown in histopathology findings

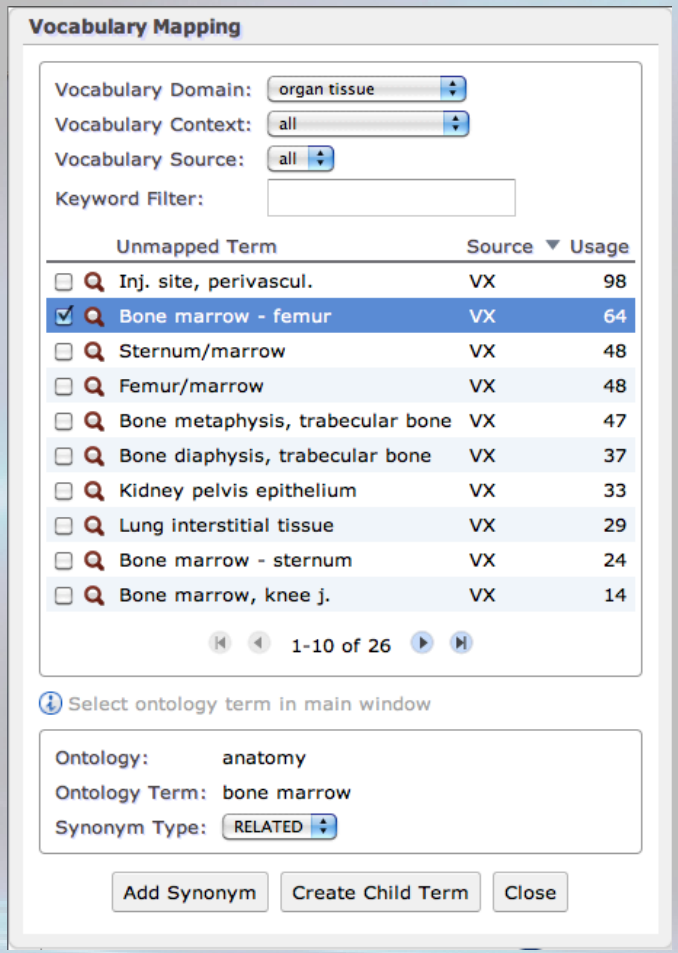


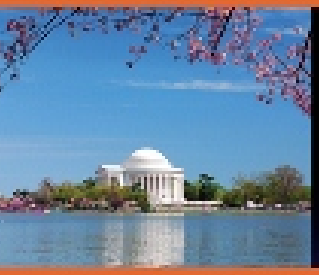
OntoBrowser: Creating Preferred Terms



OntoBrowser: Mapping Synonyms







The need for eTRANSAFE (IMI2)

Efficient and adequate safety assessment remains one of the main challenges in the drug discovery, development and submission process. Recent advances (i.e. eTOX) have shown that sharing public & private pre-clinical data is achievable.

In parallel, the electronic CDISC-SEND format has been chosen for pre-clinical data submission to the FDA. This offers the opportunity to generate and exploit a large amount of organised data to allow the in-depth assessment of the preclinical species predictivity to human.

Ultimately, the challenge is to enhance the drug development process by better prediction of outcomes and, in so doing, reduce the number of failed studies with a consequential reduction in the use of animals.

Relationship between eTOX & eTRANSAFE

(2010-2016)

Integrating bioinformatics and chemoinformatics approaches for the development of expert systems allowing the *in silico* prediction of toxicities

(2017-2022)

Enhancing TRANslational SAFEty Assessment through Integrative Knowledge Management

Aims of eTRANSAFE

- Develop an internationally accepted guideline for data sharing
- Accrue large sets of preclinical and high-level clinical safety data
- Conduct retrospective data analyses to assess the translation of preclinical to clinical safety outcomes (i.e. interconnection with human data)
- Ensure that participating companies have similar or greater access to data than regulators to facilitate discussion
- Achieve regulatory readiness (supporting/implementing SEND)
- Develop innovative tools for data mining, analysis, display, modelling and prediction

Structure of eTRANSAFE

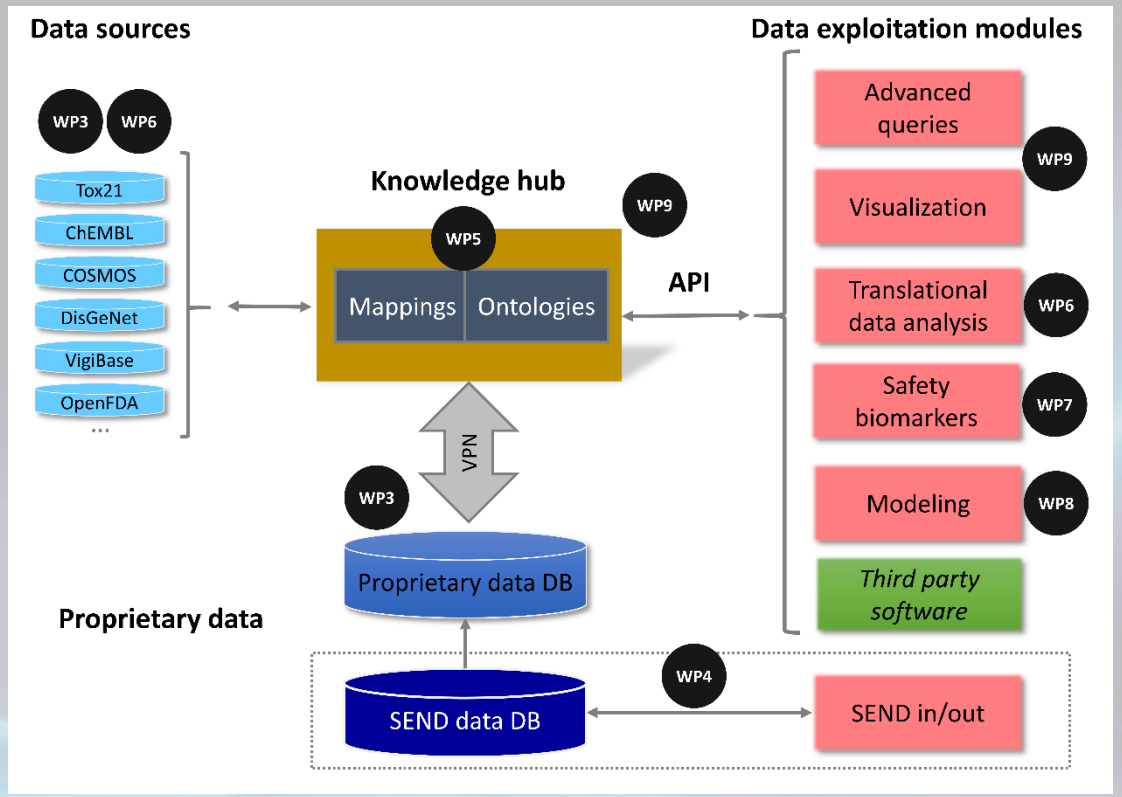
- The eTRANSAFE consortium comprises the majority of the eTOX consortium members (Pharma & non-Pharma)
- The members are from industry (<60%) & Academia (>40%):

Fundació Institut Mar d'Investigacions Mèdiques (IMIM)	Synapse Research Management Partners S.L.
Lhasa Limited	European Molecular Biology Laboratory (for ELIXIR)
Erasmus Universitair Medisch Centrum Rotterdam	Universiteit Leiden
Universität Wien	Simcyp Limited
Molecular Networks GmbH – Computerchemie	Optibrium Limited
Liverpool John Moores University	Fraunhofer-Gesellschaft zur Foerderung der Angewandten Forschung e.V.
PDS Computer Software Limited	Universitat Pompeu Fabra

- The currently subscribed efpia member companies are:

Novartis Pharma AG	Bayer Aktiengesellschaft
Sanofi-Aventis Research and Development	F. Hoffmann-La Roche Ltd
Merck KGaA	Janssen Pharmaceutica NV
Institute de Recherche Internationales Servier	AbbVie Deutschland GmbH & Co. KG
AstraZeneca AB	Boehringer Ingelheim International GmbH
Clarivate Analytics	

eTRANSAFE Roadmap



eTRANSAFE is a 5-year IMI project that will develop an **integrative data infrastructure** and **innovative computational methods and tools** that aim to drastically improve the predictivity and reliability of **translational safety assessment** during the drug development process.

See Poster PP32

Visualization of Group Related Differences in Histopathology Data

❑ Goal

To develop ideas regarding the potential for graphical displays to communicate histopathology results and to aid in data analysis

❑ Project Status

- Completed (with possible ongoing collaboration with eTRANSAFE*)

❑ Accomplishments

- Publication (2016):

  Graphical display of histopathology data from toxicology studies for drug discovery and development: An industry perspective. Regulatory Toxicology and Pharmacology, 2016; 82:167-172

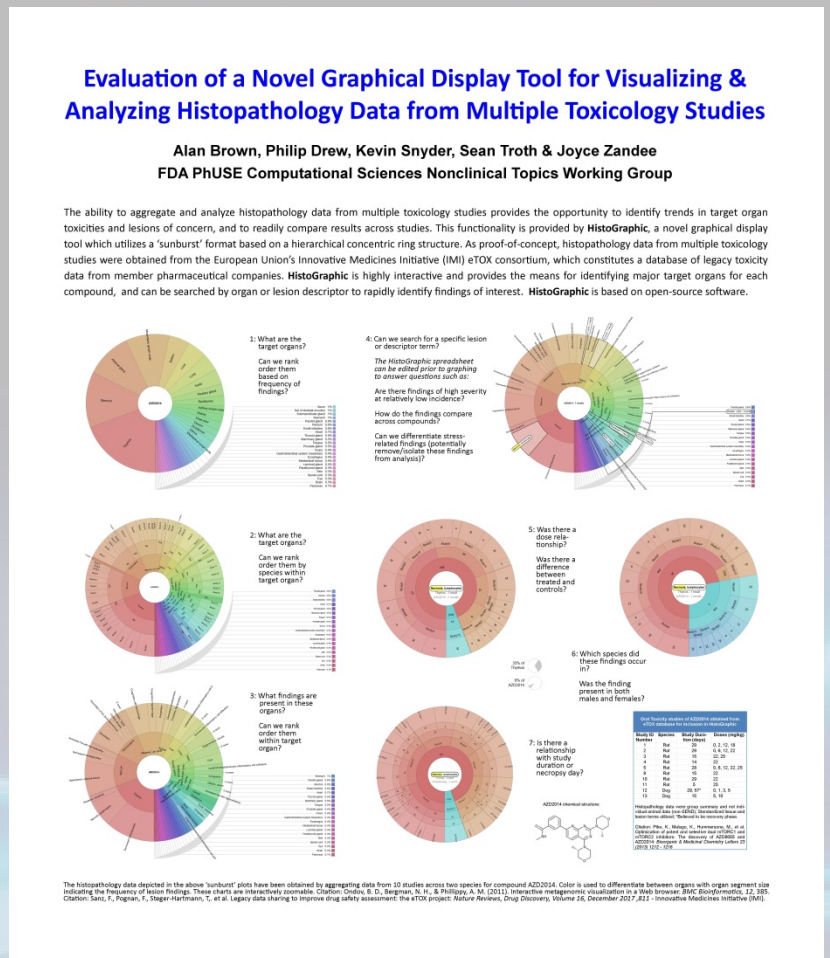
- Posters at 2016, 2017 & 2018 FDA PhUSE CSS Conferences:

  2016: Graphical Display of Histopathology Data from Toxicological Studies - An Industry Survey

  2017: Graphical Display of Histopathology Data from Multiple Toxicology Studies

  2018: **Evaluation of a Novel Graphical Display Tool for Visualizing & Analyzing Histopathology Data from Multiple Toxicology Studies**

Accessing eTOX study data: HistoGraphic Demonstration



Evaluation of a Novel Graphical Display Tool for Visualizing & Analyzing Histopathology Data from Multiple Toxicology Studies

Alan Brown, Philip Drew, Kevin Snyder, Sean Troth & Joyce Zandee
FDA PhUSE Computational Sciences Nonclinical Topics Working Group

The ability to aggregate and analyze histopathology data from multiple toxicology studies provides the opportunity to identify trends in target organ toxicities and lesions of concern, and to readily compare results across studies. This functionality is provided by **HistoGraphic**, a novel graphical display tool which utilizes a 'sunburst' format based on a hierarchical concentric ring structure. As proof-of-concept, histopathology data from multiple toxicology studies were obtained from the European Union's Innovative Medicines Initiative (IMI) eTOX consortium, which constitutes a database of legacy toxicity data from member pharmaceutical companies. **HistoGraphic** is highly interactive and provides the means for identifying major target organs for each compound, and can be searched by organ or lesion descriptor to rapidly identify findings of interest. **HistoGraphic** is based on open-source software.

1: What are the target organs?

Can we rank order them based on frequency of findings?

4: Can we search for a specific lesion or descriptor term?

The HistoGraphic spreadsheet can be edited prior to graphing to answer questions such as:

Are there findings of high severity at relatively low incidence?

How do the findings compare across compounds?

Can we differentiate stress-related findings (potentially remove/isolate these findings from analysis)?

2: What are the target organs?

Can we rank order them by species within target organ?

5: Was there a dose relationship?

Was there a difference between treated and controls?

6: Which species did these findings occur in?

Was the finding present in both males and females?

3: What findings are present in these organs?

Can we rank order them within target organ?

7: Is there a relationship with study duration or necropsy day?

The histopathology data depicted in the above 'sunburst' plots have been obtained by aggregating data from 10 studies across two species for compound AZD2014. Color is used to differentiate between organs with organ segment size indicating the frequency of lesion findings. These charts are interactively zoomable. Citation: Omdov, B. D., Bergman, N. H., & Phillippy, A. M. (2011). Interactive metagenomic visualization in a Web browser. *BMC Bioinformatics, 12*, 385. Citation: Sanz, F., Pognan, F., Steger-Hartmann, T., et al. Legacy data sharing to improve drug safety assessment: the eTOX project: *Nature Reviews, Drug Discovery, Volume 16, December 2017 ,811* - Innovative Medicines Initiative (IMI).

Kevin will now demonstrate how Histo-Graphic can answer questions such as:

1. Can we rank order target organs based on frequency of findings?
2. Can we rank order target organs by species?
3. Can we rank order findings within target organs?
4. Can we search for a specific lesion or descriptor term?
5. Can we detect dose relationships (i.e. difference between treated & controls)?
6. Can we detect species/gender effects?
7. Can we detect a relationship with study duration?

See Poster PP18