Ontology Development in support of Predictive Toxicology Use Cases & Services

OpenTox Presentation

16 November 2010

EBI, Hinxton, UK

Barry Hardy (Douglas Connect)

OpenTox

SEVENTH FRAMEWORK PROGRAMME

A Predictive Toxicology Pathways Question for you to reflect on during my introduction…

How do we best leverage current knowledge and methods with regards to biological pathway analysis to design improved approaches to predictive toxicology that increase our ability to characterise the potential of chemicals to cause adverse human health effects and including an understanding of mode of action, mechanisms involved in the mode of action and the interaction of biological entities, pathways and networks in the perturbations introduced by the chemicals?

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Collaborating Partners

In Silico Toxicology, Switzerland

Douglas Connect, Switzerland

Albert Ludwigs University Freiburg, Germany

Ideaconsult, Bulgaria

National Technical University of Athens, Greece

Istituto Superiore di Sanità, Italy

Fraunhofer Institute for Toxicology & Experimental Medicine, Germany

Technical University of Munich, Germany

David Gallagher, UK

Institute of Biomedical Chemistry of the Russian Academy of Medical Sciences, Russia

Seascape Learning & JNU, India

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OpenTox Advisory Board

- European Centre for the Validation of Alternative Methods
- Pharmatrope
- Bioclipse
- U.S. Environmental Protection Agency
- U.S. Food & Drug Administration
- Nestlé
- Roche
- AstraZeneca
- LHASA
- Leadscope
- University of North Carolina
- EC Environment Directorate General
- Organisation for Economic Cooperation & Development
- CADASTER
- Bayer Healthcare

OpenTox

Our Funding Support...

For more information on OpenTox, please visit

www.opentox.org

To join the community site/groups:

www.opentox.org/join_form

Contact me:

barry.hardy -(at)- douglasconnect.com

OpenTox - An Open Source Predictive Toxicology Framework, www.opentox.org, is funded under the EU Seventh Framework Program: HEALTH-2007-1.3-3 Promotion, development, validation, acceptance and implementation of QSARs (Quantitative Structure-Activity Relationships) for toxicology, Project Reference Number Health-F5-2008-200787 (2008-2011).

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SEVENTH FRAMEWORK PROGRAMME

Journal of Cheminformatics Publication

Collaborative development of predictive toxicology applications
Journal of Cheminformatics 2010, 2:7 doi:10.1186/1758-2946-2-7

Barry Hardy, Nicki Douglas, Christoph Helma, Micha Rautenberg, Nina Jeliazkova, Vedrin Jeliazkov, Ivelina Nikolova, Romualdo Benigni, OlgaTcheremenskaia, Stefan Kramer, Tobias Girschick, Fabian Buchwald, JoergWicker, Andreas Karwath, Martin Gutlein, Andreas Maunz, Haralambos Sarimveis, Georgia Melagraki, Antreas Afantitis, Pantelis Sopasakis, David Gallagher, Vladimir Poroikov, Dmitry Filimonov, Alexey Zakharov, Alexey Lagunin, Tatyana Gloriozova, Sergey Novikov, Natalia Skvortsova, Dmitry Druzhilovsky, Sunil Chawla, Indira Ghosh, Surajit Ray, Hitesh Patel and Sylvia Escher

Open Access publication available at
www.jcheminf.com/content/2/1/7

OpenTox

OpenTox Ontology specific acknowledgements

- Nina Jeliazkova (Ideaconsult)
- OlgaTcheremenskaia and Romualdo Benigni (ISS, Rome)
- Helvi Grimm and Sylvia Escher (Fraunhofer Institute)

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Semantic Reflections

"Now! ... *That* should clear up a few things around here!"

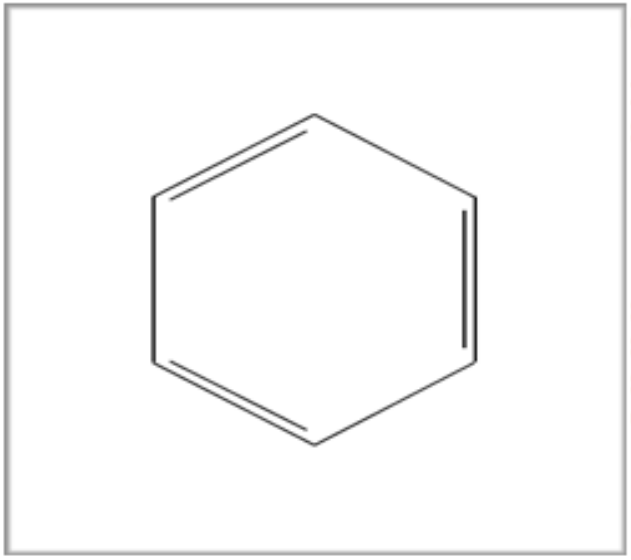
OpenTox

ToxPredict

OpenTox demo application

This page lists your ToxPredict workflow results for the structure(s) you have selected and the model prediction(s) you have chosen to run. You could also retrieve the ToxPredict report in various other formats, e.g. **SDF**, **CML**, **SMI**, **PDF**, **CSV**, **ARFF**, **RDF/XML** or **RDF/N3**.

Download as

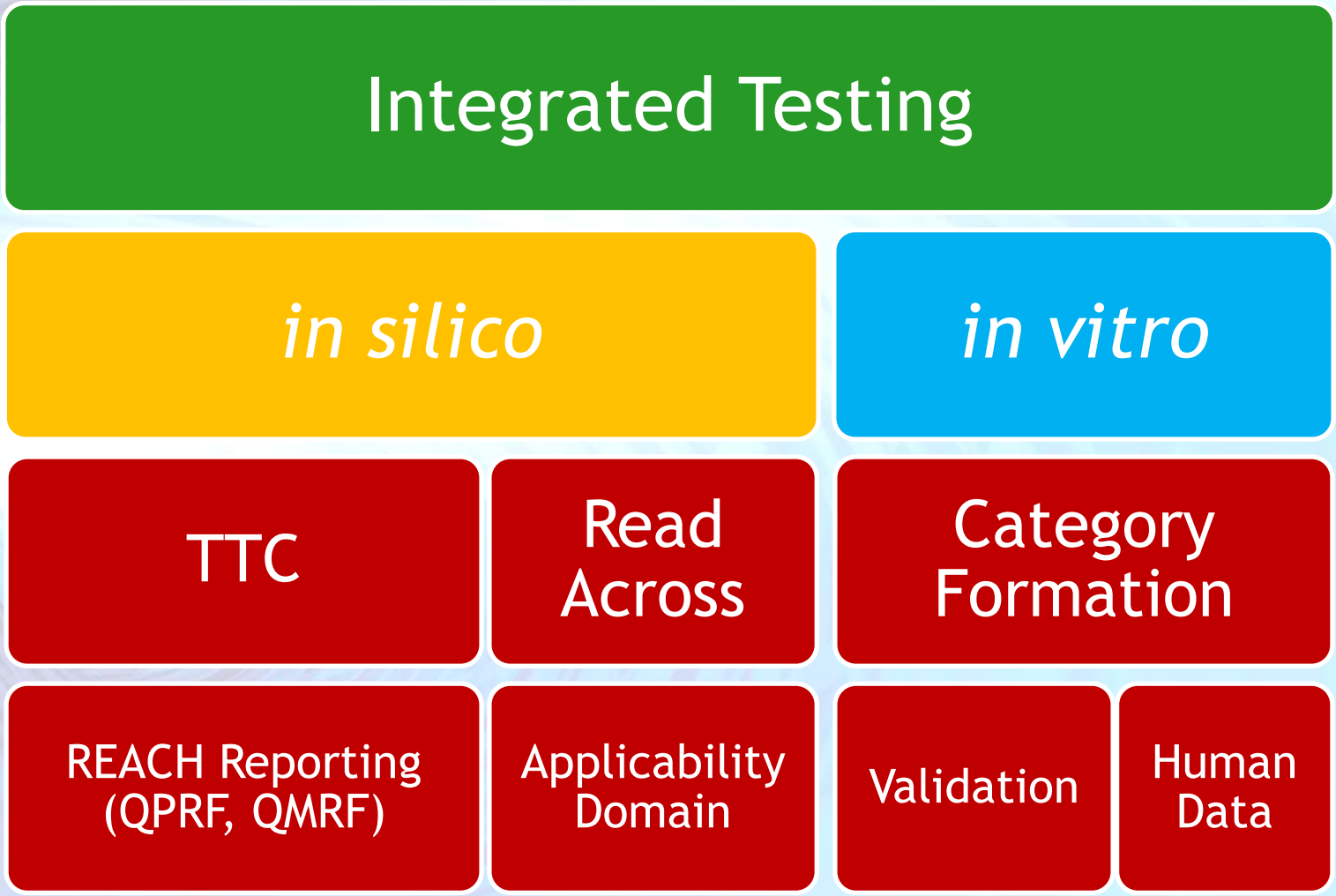


CAS RN	71-43-2
EINECS	200-753-7
IUPAC name	benzene
Synonym	(6)annulene; benzine; Benzol; Benzolene; bicarburet of hydrogen; carbon oil; Coal naphtha; cyclohexatriene; mineral naphtha; motor benzol; nitration benzene; Phene; Phenyl hydride; pyrobenzol.
Synonym	21742.0
Synonym	Benzene
Synonym	benzene
Quality label	OK

MolecularWeight MolecularWeight

MW	78.1112

Compelling Needs of Users



OpenTox

Communicated to OpenTox in 2009 by Grace Patlewicz (Du Pont)

Compelling Needs of Users

Multidisciplinary R&D

Good Support of Flexible Applications

Transparency – Not Black Box!

Mechanistic rationale

QSAR & Expert Systems

Workflows

Automated Integration

Applicability Domain

Categories

Systems Biology

OpenTox

Communciated to OpenTox in 2009 by Stephanie Ringeissen (L'Oréal)

OpenTox - Synergy Predictive Toxicology VO Pilot Strategy Development & Case Study

1. Data Mining of Human Adverse Drug Events
   - Data Mining of Literature Knowledge
2. Creation of Mechanism-based Hypothesis
   - Selection of Biological Pathways & Targets
3. Selection of Compounds
   - Prediction of Metabolites of Compounds
4. Selection of *in vitro* assays relevant to Mechanism
   - Selection and integration of Toxicity Data
5. Creation of Predictive Toxicology Model including Model Validation and Applicability Domain
6. Selection of Low and High Content Assays for Testing in Cell Lines
   - Analysis of Results

OpenTox

Interacting Components create Solutions

Adaptor Solution in Jeddah, 2008

OpenTox

Some Ontological questions for reflection…

- What is knowledge?
- What is a toxicity pathway?
- What is a toxicology ontology?
- Why do we need it?
  - *Knowledge is explict and tacit*
  - *Accelerating knowledge conversion and flow*
  - *Supporting biological, biochemical, and mechanism based modelling*
  - *Knowledge-based Use Case driven*
  - *Business case*

On defining a knowledge-based approach

Dr. Germain's wisdom

SECI Model for Knowledge Management

Tacit

Tacit

Tacit

Knowledge Sharing: Discussions

Socialisation

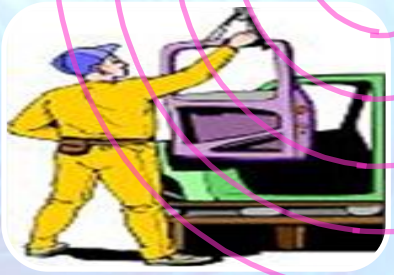
Externalisation

Explicit

Knowledge Creation from R&D: Data, Codes

Acceptance

Learning: Apply Models



Internalisation

Combination

Knowledege Combination: Predictive Models

Tacit

Explicit

Explicit

Explicit

OpenTox

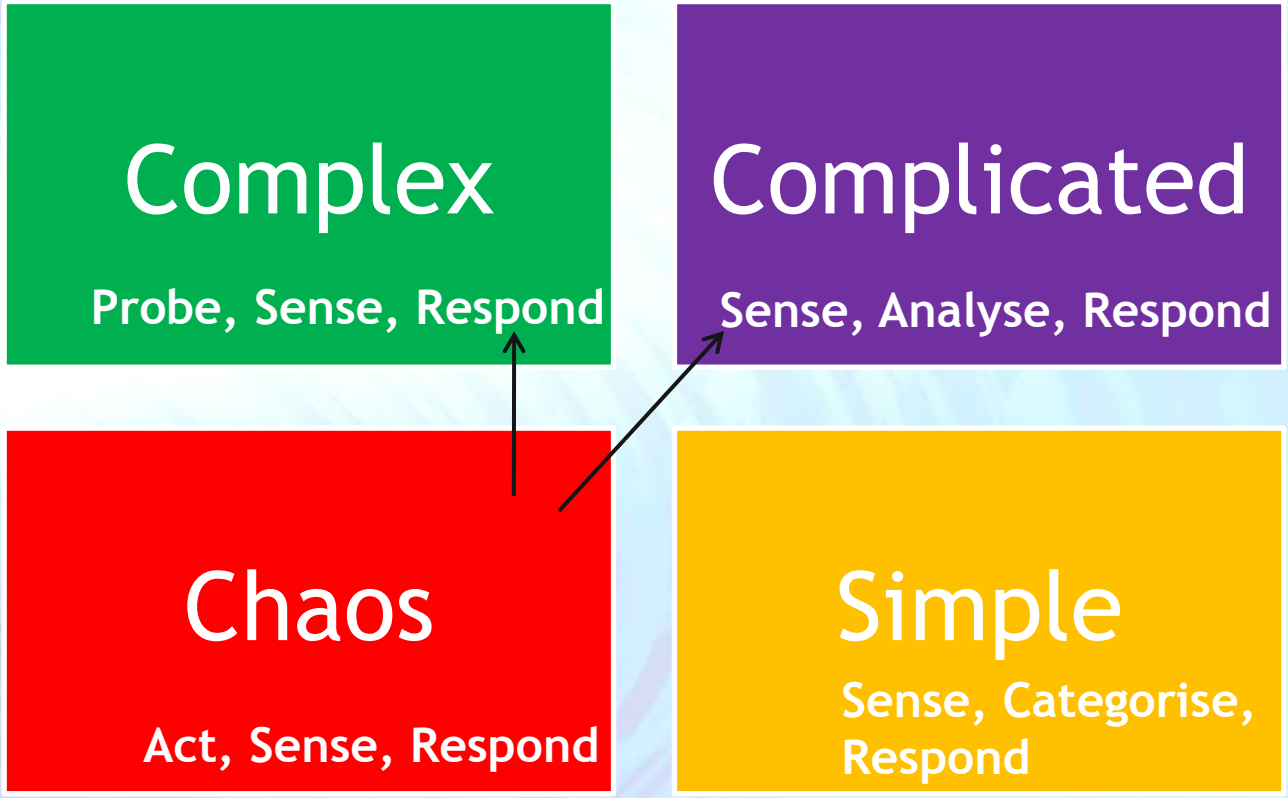
Based on Nonaka & Takeuchi, The Knowledge Creating Company, 1995

Complexity Context

Non Repeatable
Adaptative, Patterns,
Filters

Complex Cause & Effect
Systems Thinking, Analysis

Sense
Making for
Emergent
Practice



Processes
Good
Practice

Leadership
Novel
Practice

Procedures
Best
Practice

Lack of Cause & Effect, Stability-focused
Intervention, Crisis Management

Cause & Effect
Repeatable, SOPs

OpenTox

Based on the Cynefin Framework,
Dave Snowden

OpenTox committed to creating a Semantic Web for Predictive Toxicology (*with its API 1.1 development in 2009*)

Linked Data is a term used to describe the exposing, sharing, and connecting of data on the Semantic Web using:
URIs a generic means to identify entities in the world
HTTP a simple yet universal mechanism for retrieving resources
RDF a generic graph-based data model with which to structure and link data

Linked Data needs:

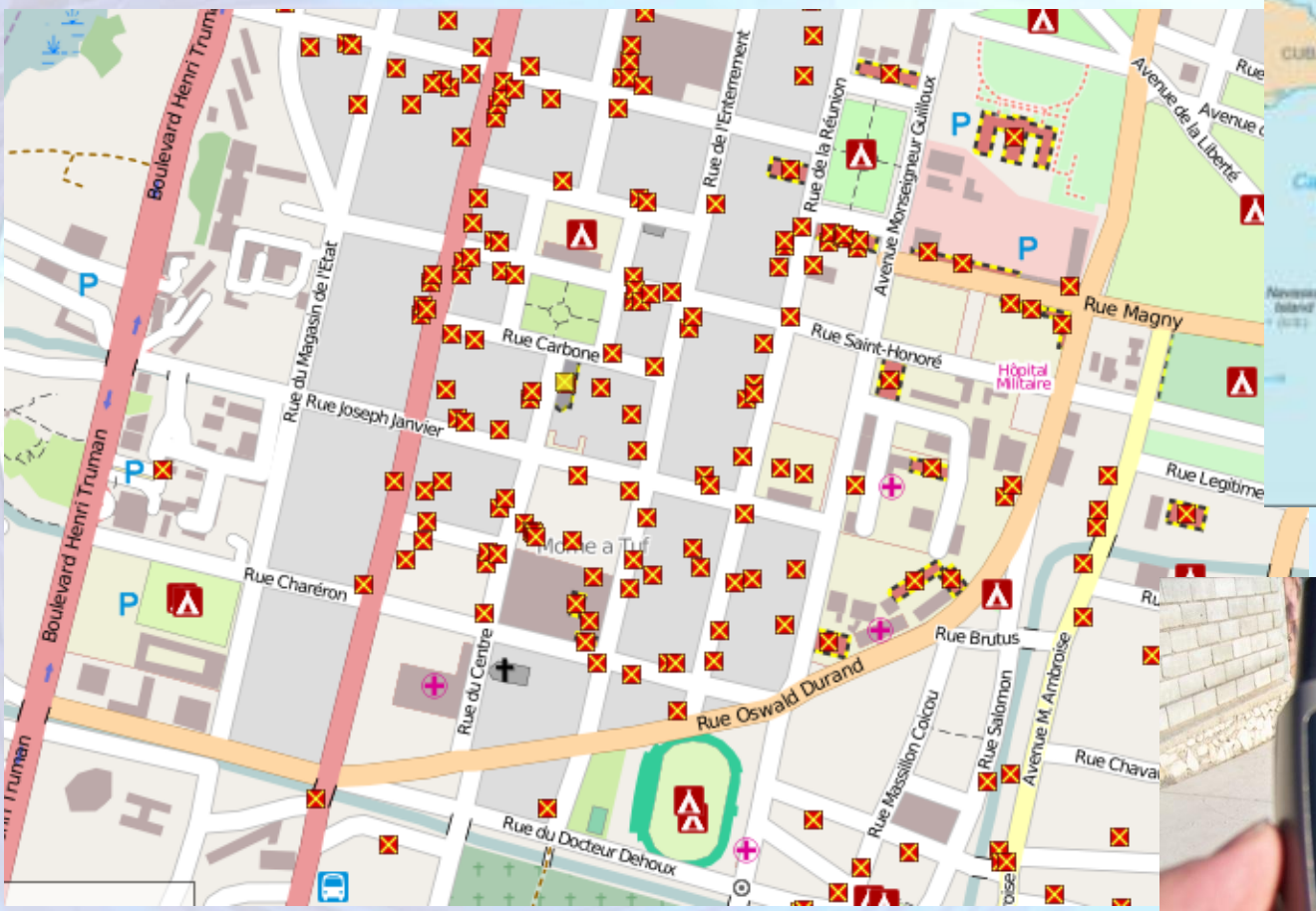
1. Provision of a **URI** that describes a Data Resource
2. Use of **HTTP** to retrieve useful data from the **URI**
3. A Data Format described with standardised semantics (so relationships are enabled) e.g. **RDF**
4. Data should provide links to other Data (through **URIs**)

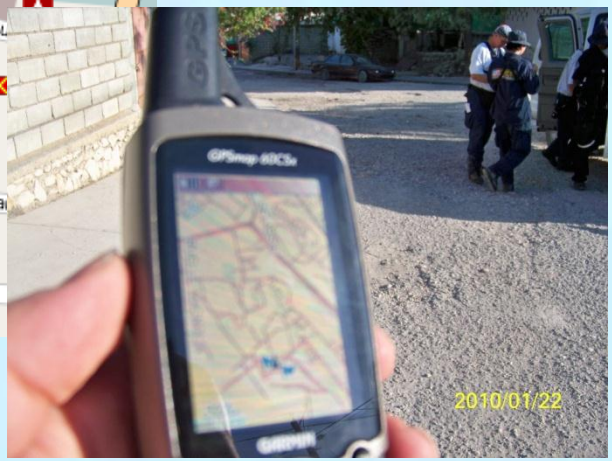
DBpedia = Linked Data approach applied to Wikipedia

Linked Data approach can also be applied to other resource types e.g., for algorithms or models as done in OpenTox… Linked Resource approach enables Knowledge Creation, Combination and Analysis

OpenTox

Solution created by Linked Open Data, Web Applications and Crowdsourcing



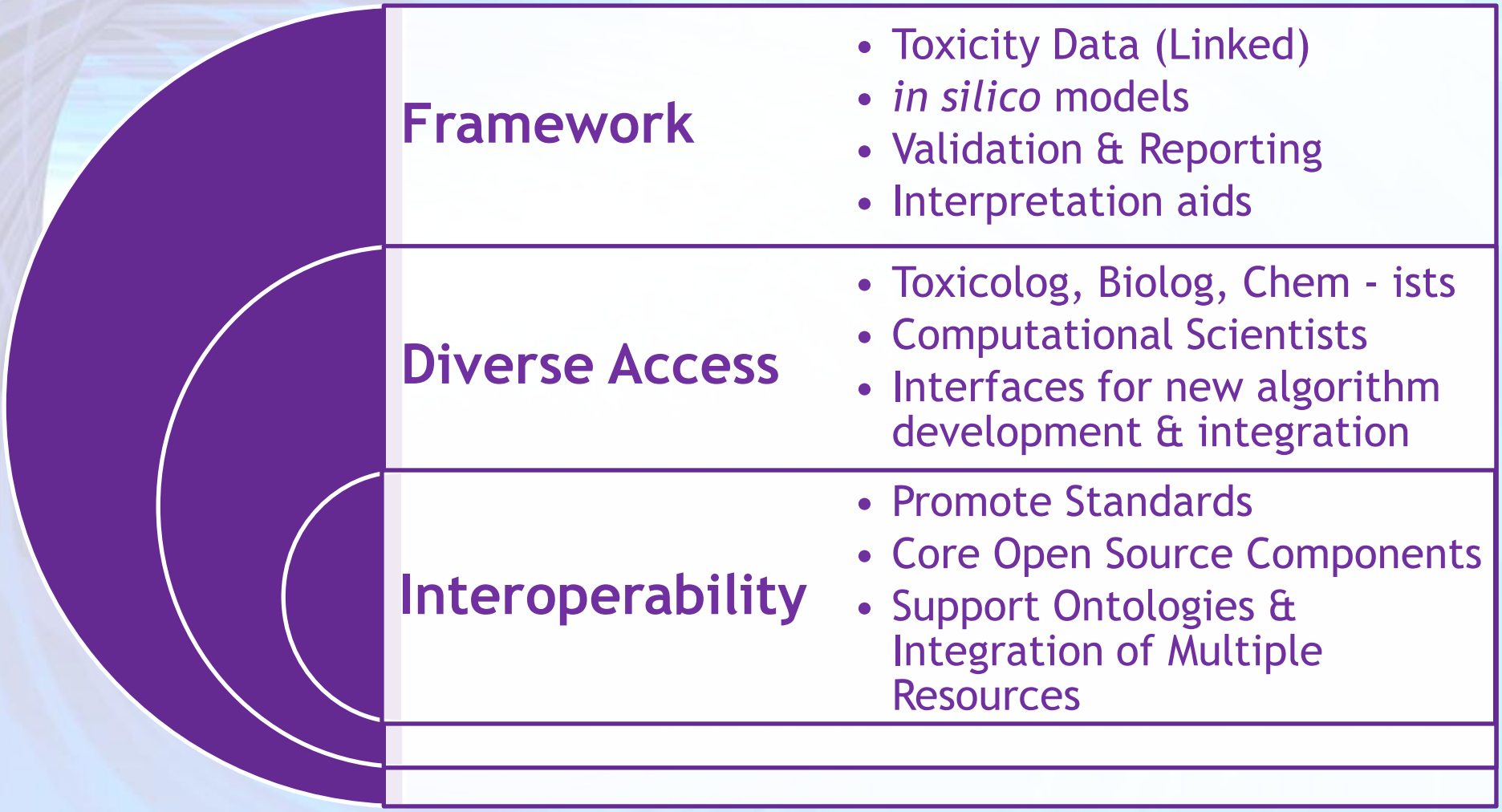


Haiti Earthquake Crisis Response (2010)

wiki.openstreetmap.org

OpenTox

OpenTox is an Integrating Framework



OpenTox

	OECD Principle	OpenTox addresses Validation Principles by...
1	Defined Endpoint	providing a unified source of well defined and documented toxicity data with a common vocabulary
2	Unambiguous Algorithm	providing transparent access to well documented models and algorithms as well as to the source code
3	Defined Applicability Domain	integrating tools for the determination of applicability domains during the validation of prediction models
4	Goodness-of-fit, robustness and predictivity	providing scientifically sound validation routines for the determination of errors and confidences
5	Mechanistic interpretation (if possible)	integrating tools for the inference, correlation or prediction of toxicological mechanisms and the recording of opinions and analysis in reports

OpenTox

OpenTox Components

Compounds: Structures, names, ...

Features: Chemical and biological (toxicological) properties, substructures, ...

Datasets: Relationships between compounds and features

Algorithms: Instructions for solving problems

Models: Algorithms applied to data yield models which can be used for predictions

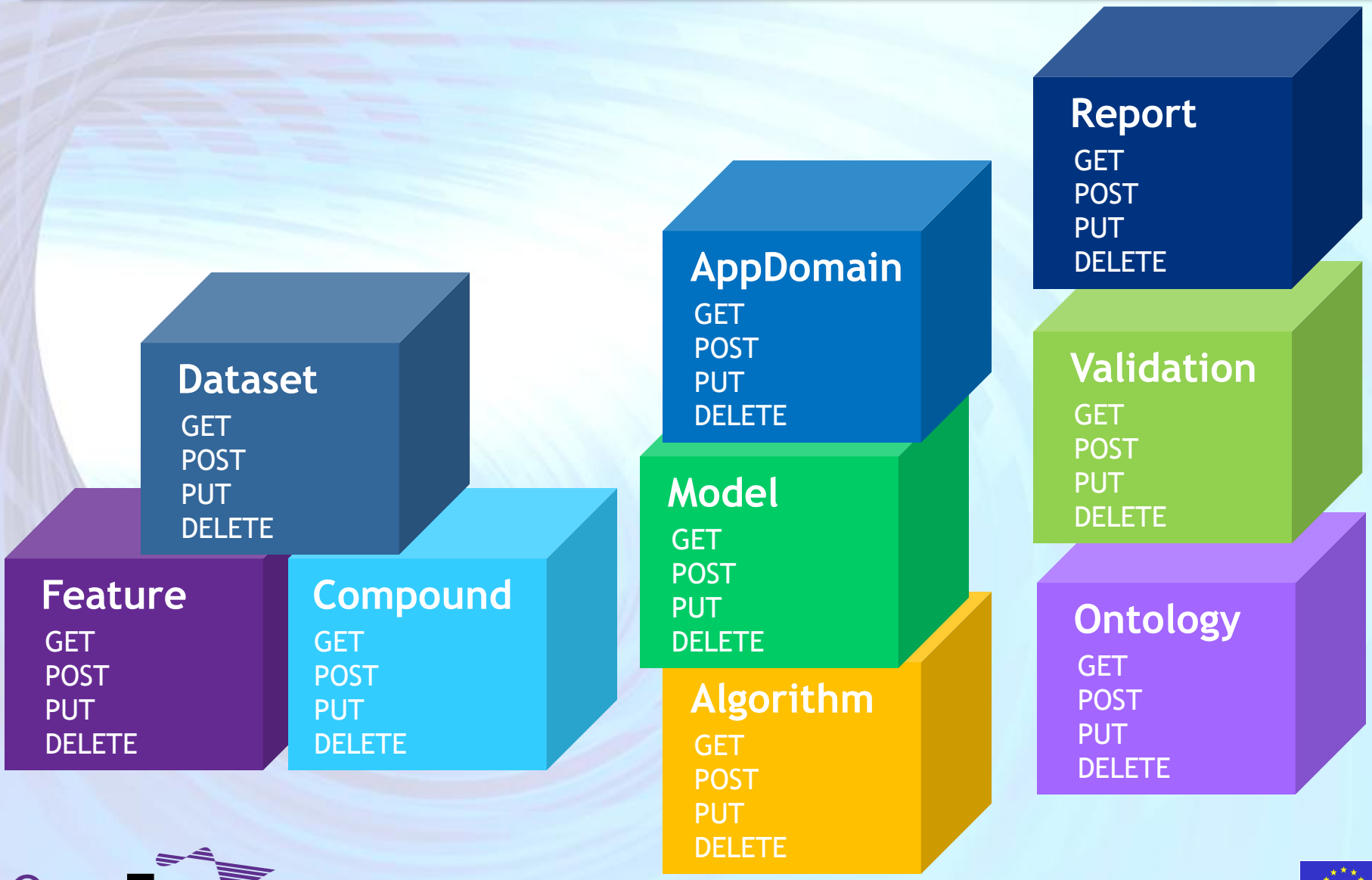
Validation: Methods for estimating the accuracy of model predictions

Reports: Report predictions and models e.g. to regulatory authorities

Tasks: Handle long running calculations

Authentification and Authorisation: Protect confidential data

Overview of Application Programming Interfaces



OpenTox

Representational State Transfer (REST)

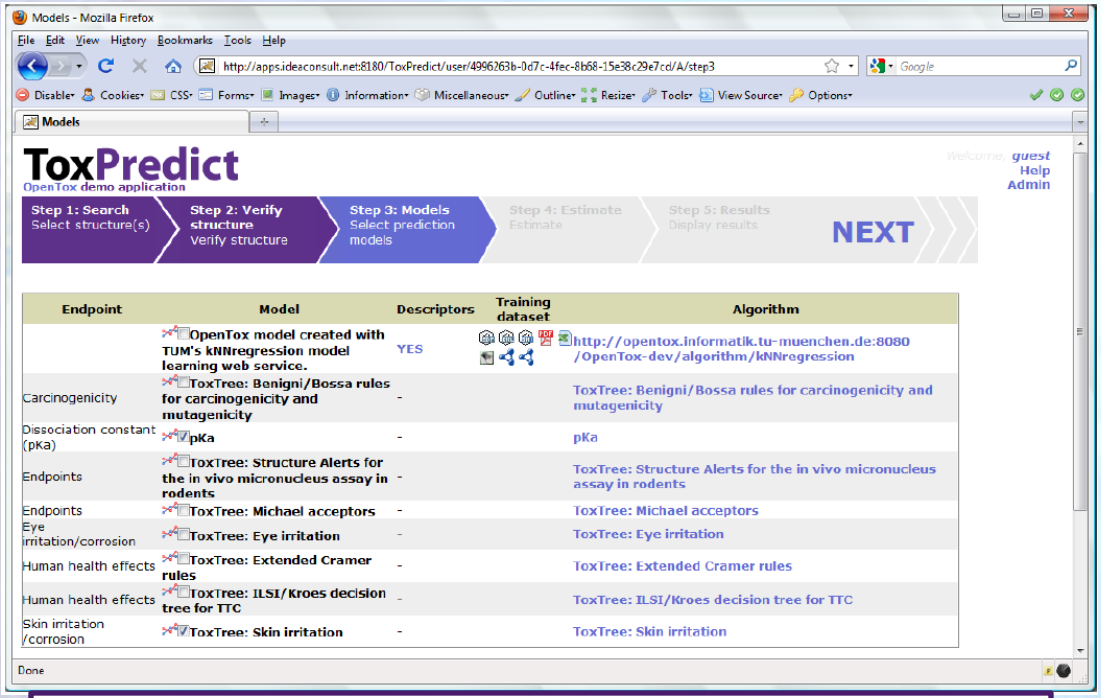
What?

- Architectural style for distributed information systems on the Web
- Simple interfaces, data transfer via **hypertext transfer protocol (HTTP)**, stateless client/server protocol
  - GET, POST, PUT, DELETE
- Each **resource** is **addressed** by its own **web address**

Why?

- **Lightweight** approach to **web services**
- **Simplifies/enables** development of **distributed and local systems**
- Language independent

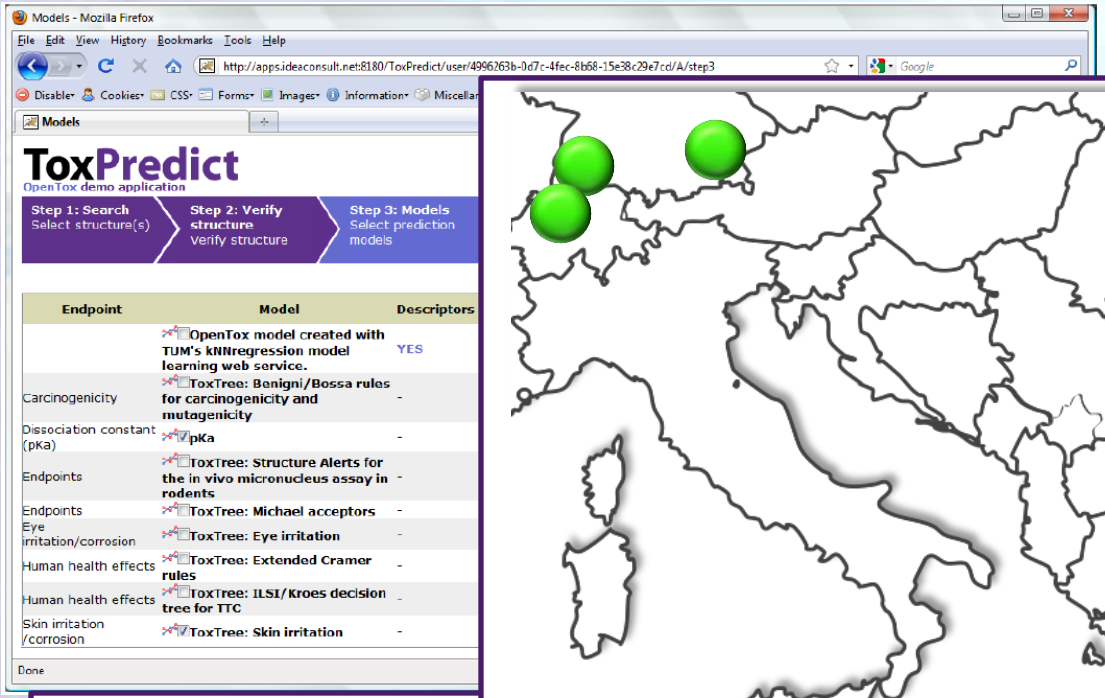
What you can do with it …



Simple building of predictive toxicology applications based on well-established methods and databases

OpenTox

What you can do with it …



Simple building c

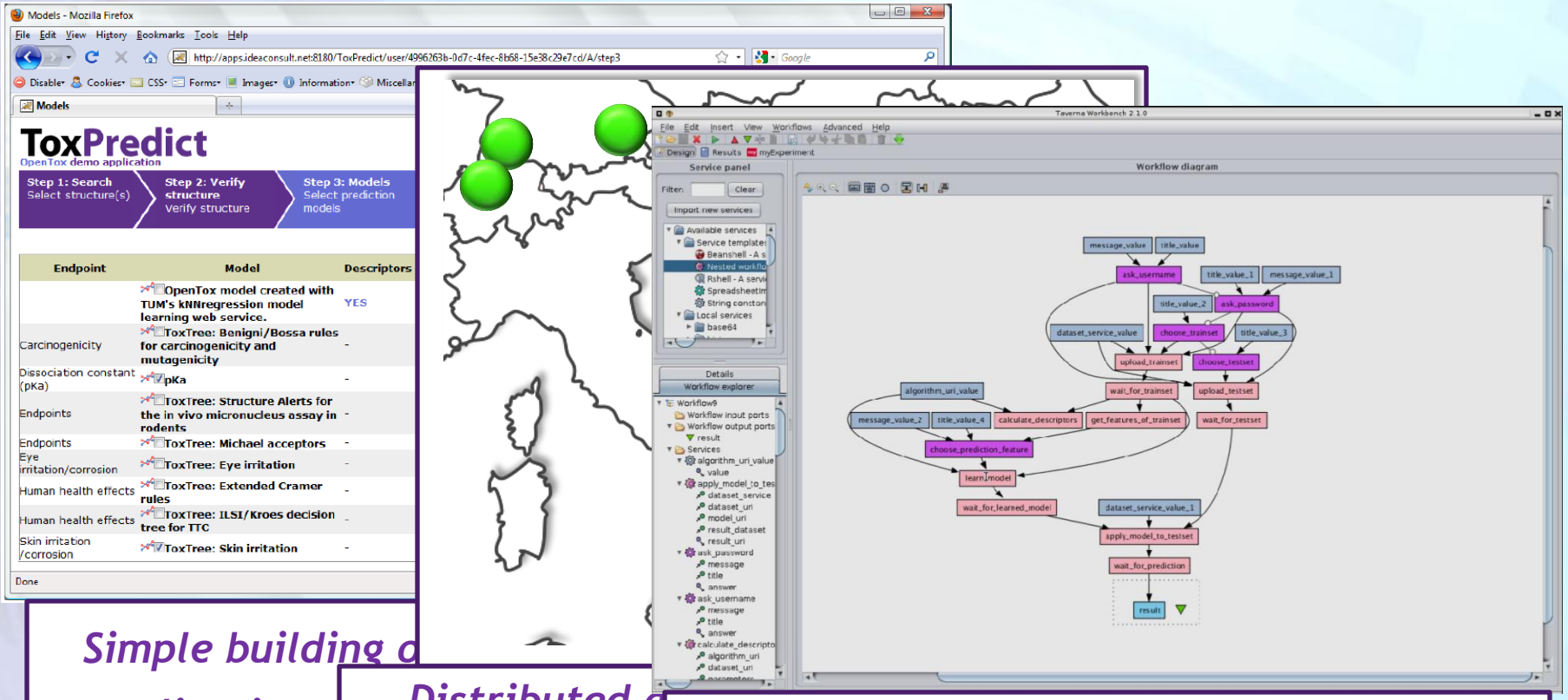
applications

methods and

Distributed applications, integrating wide range of data, models, prediction methods

OpenTox

What you can do with it …



Simple building

applications

methods and

Distributed

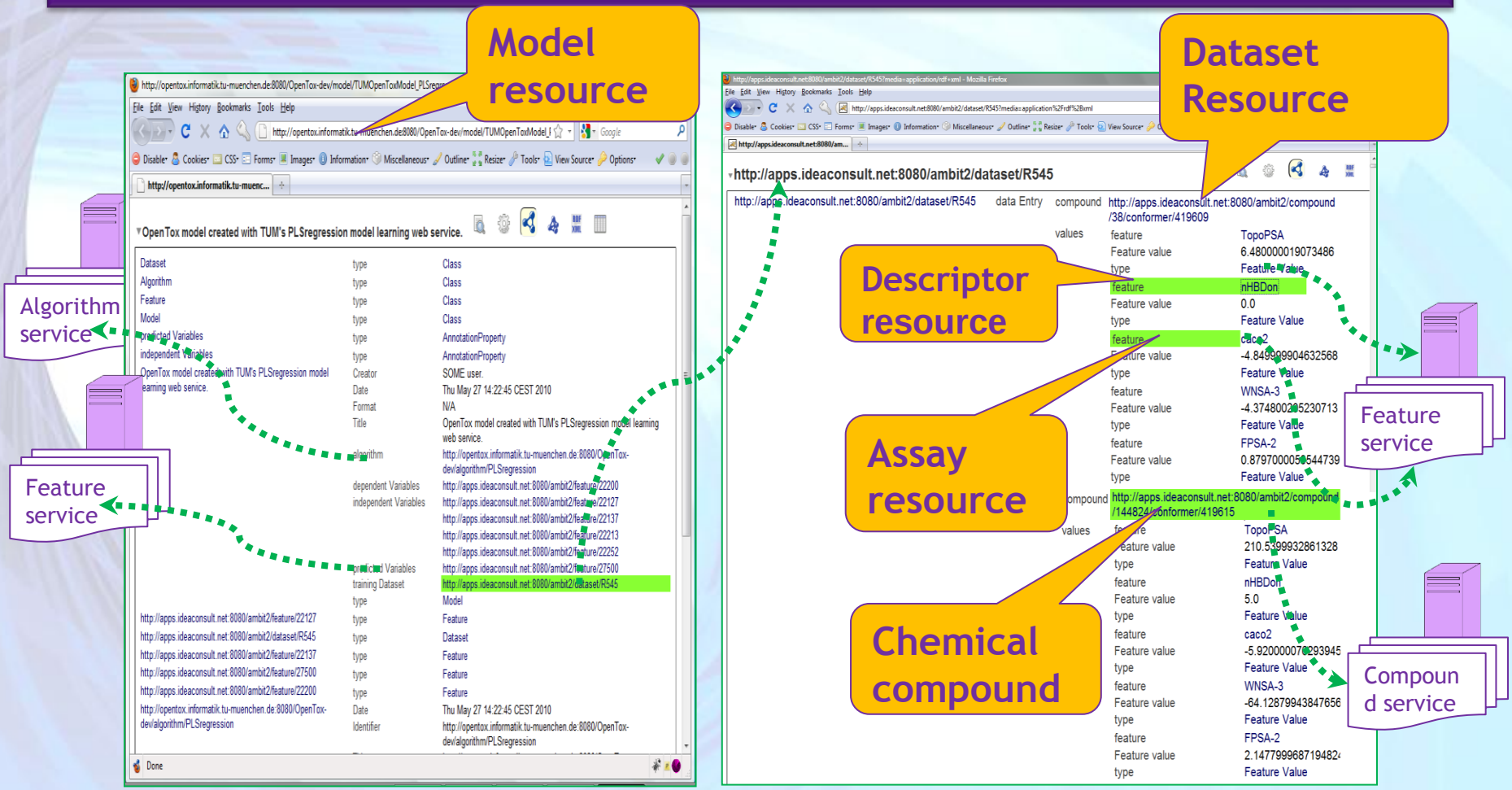
wide range o

methods

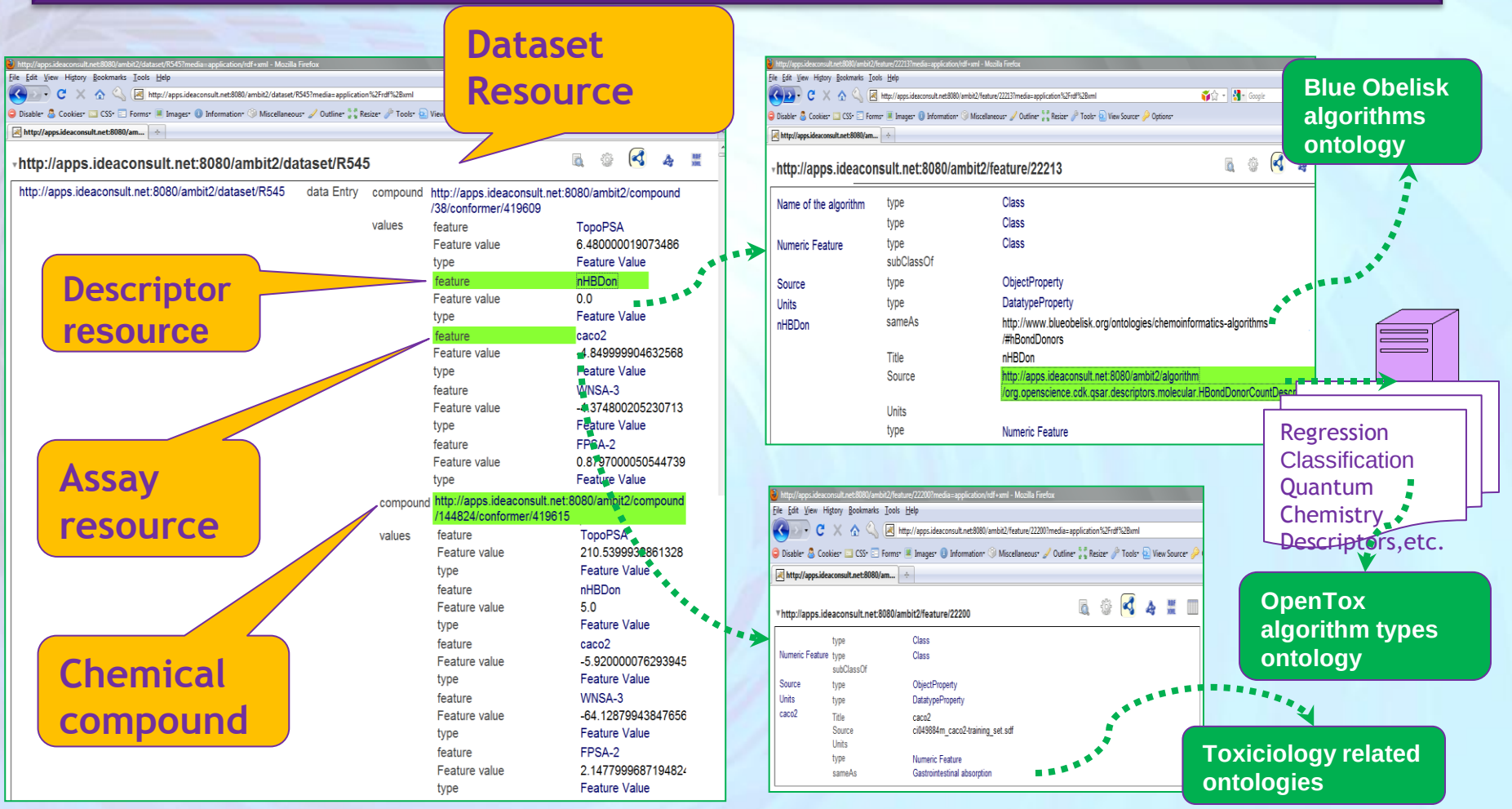
Integration into workflow systems for computational biology

OpenTox

Linked resources: Compound, Algorithm, Model, Dataset, Features

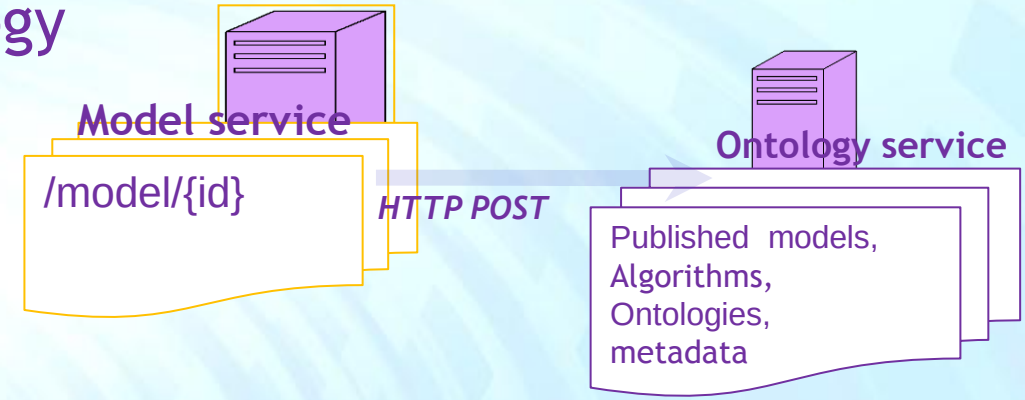


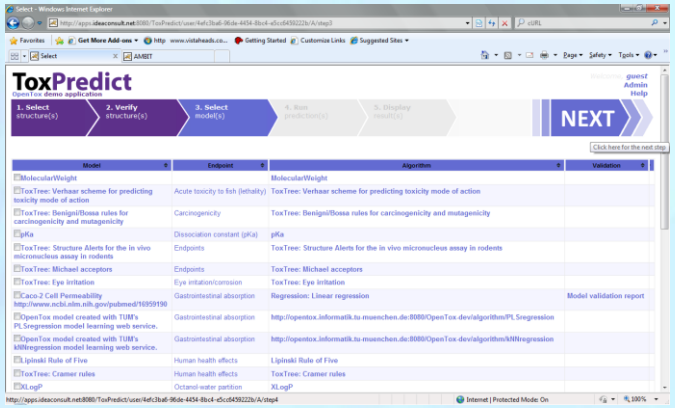
Linked resources:
Compound, Algorithm, Model, Dataset, Features



Make the model available

- Register at OpenTox ontology service
  - RDF triple storage
  - Accepts HTTP POST
  - SPARQL endpoint
- Curl –X POST –d ”uri=http://apps.ideaconsult.net:8080/ambit2/model/57” http://apps.ideaconsult.net:8080/ontology
- Becomes visible for applications





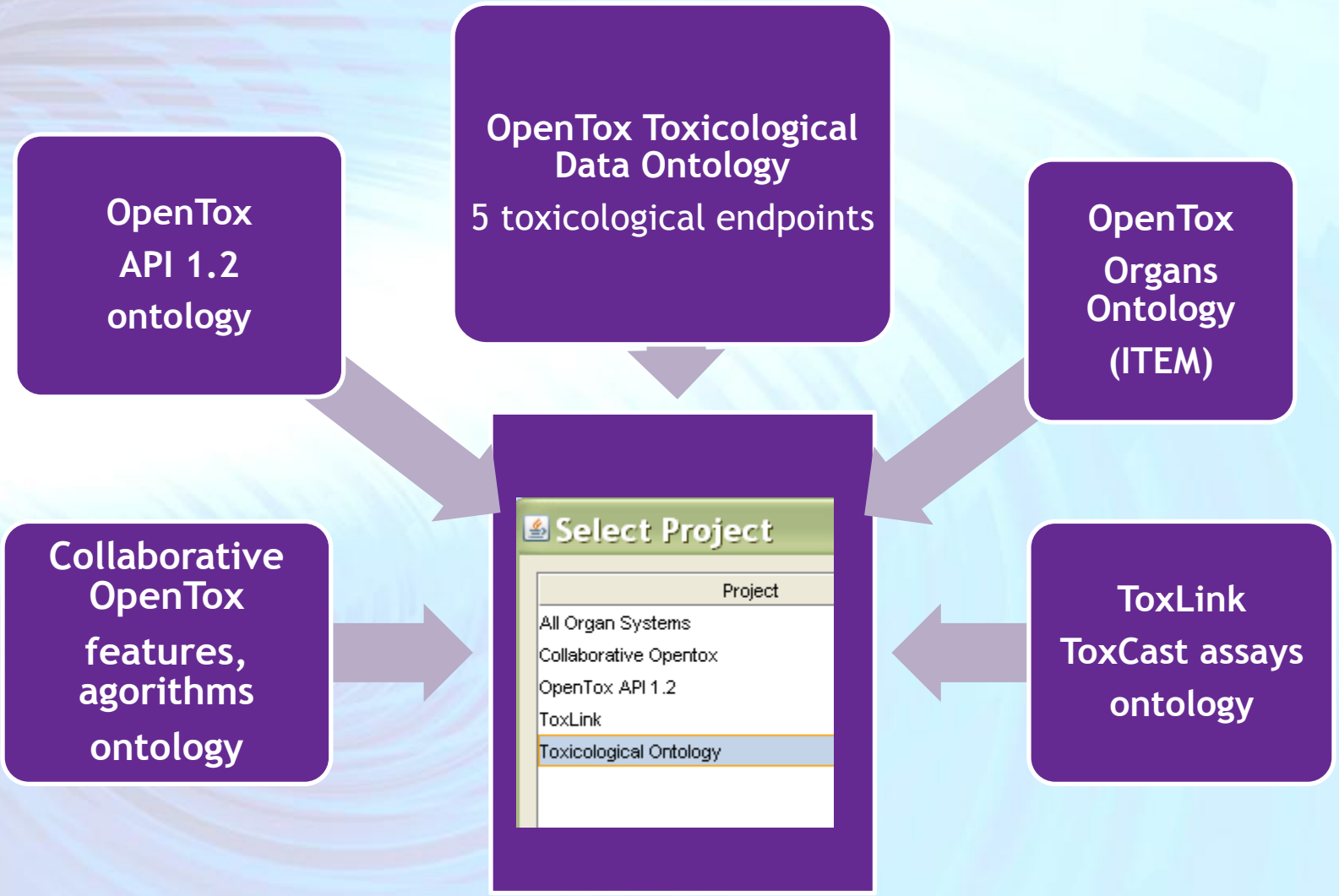
Need for communications in the community overcoming different languages and vocabularies

Explaining the rules of different games on a conservation project trip in the Caprivi, Namibia

From Conservation Project Trip in Caprivi Delta

OpenTox

Collaborative Ontology Development: Collaborative Protege Server

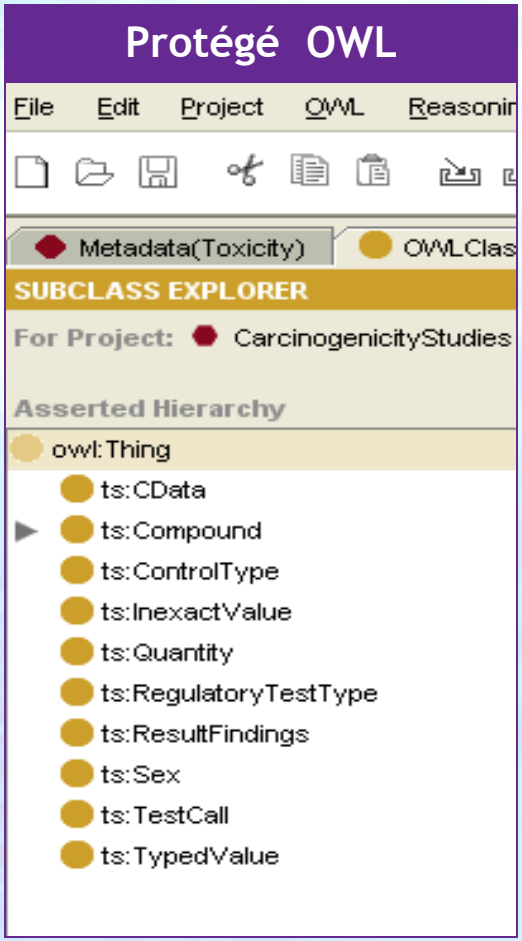


OpenTox

ToxML: conversion in OWL ontology

- Initial work to check out how costly would be to convert ToxML to an OWL ontology
- Why:
- -to integrate the Leadscope databases in the OpenTox service
- -to combine with data coming from different databases (e.g. for complex queries)

ToxML xsd schema



Some parts of the taxonomy may need to be reorganized

Procedures:

- each element which doesn't have a type in the schema is converted to an OWL class

each element which has a type in the summary file is considered as a property

the parent relationships are kept

Needs for extensions: e.g. target sites, target cells, species are free text fields. Solutions: development extension in OWL, e.g. Organs Ontology has been developed importing of parts of the neighboring ontologies

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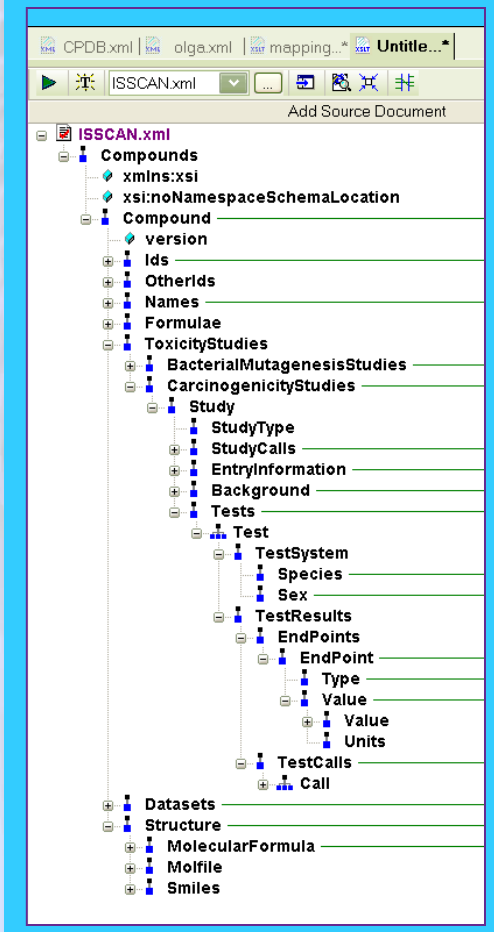
www.opentox.org/dev/ontology/collaborative_protege

Toxicological Endpoint Ontology Development

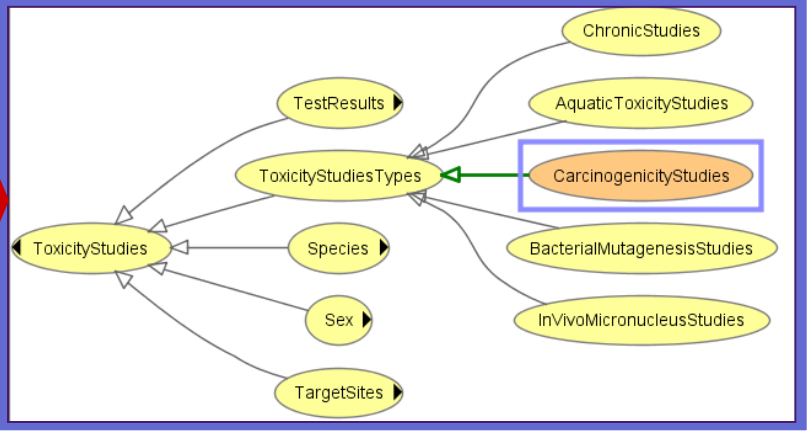
ToxML schema



Other publicly available resources:
DSSTox, GoReni (ITEM), ISSCAN ...

OpenTox Toxicological Endpoint Ontology

Ontology Development



Collaborative Protégé Environment

Re-use of terms defined in neighbouring ontologies (e.g. OBO)

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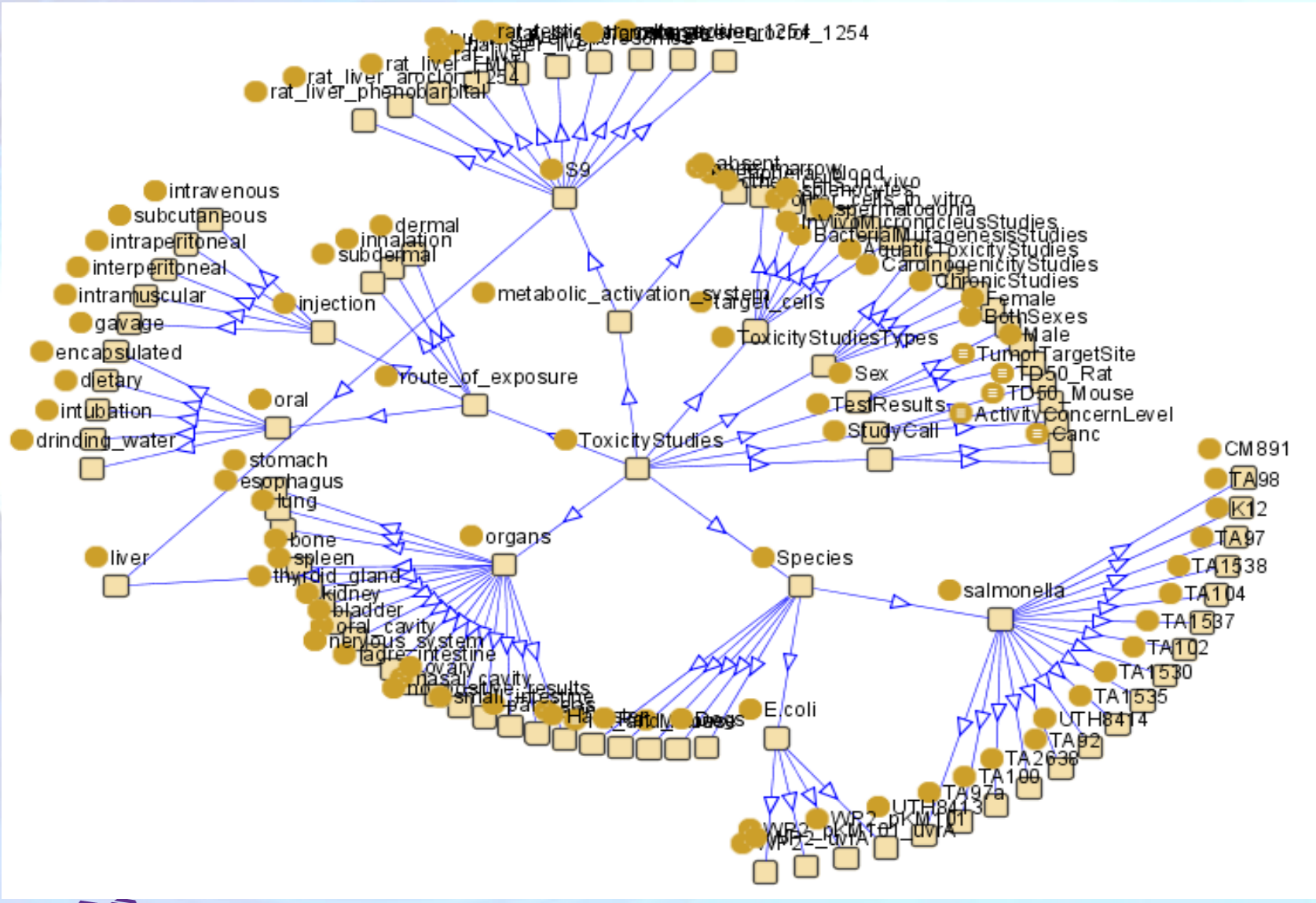
www.opentox.org/dev/ontology/collaborative_protege

Toxicological Ontology: graphical representation



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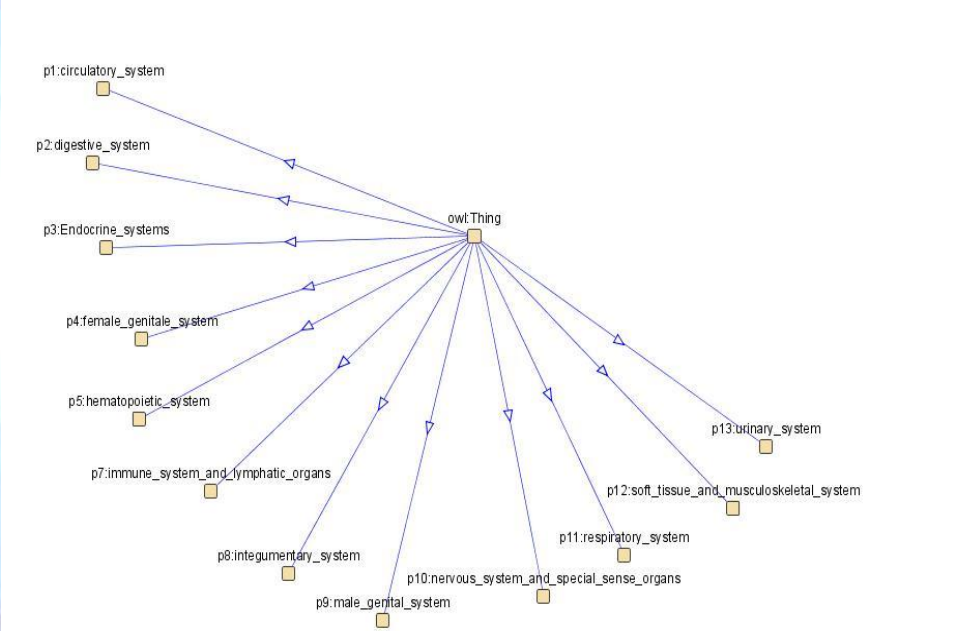
OpenTox Organ Ontology Development

- **organ ontology** consisting of 12 very detailed organsystems

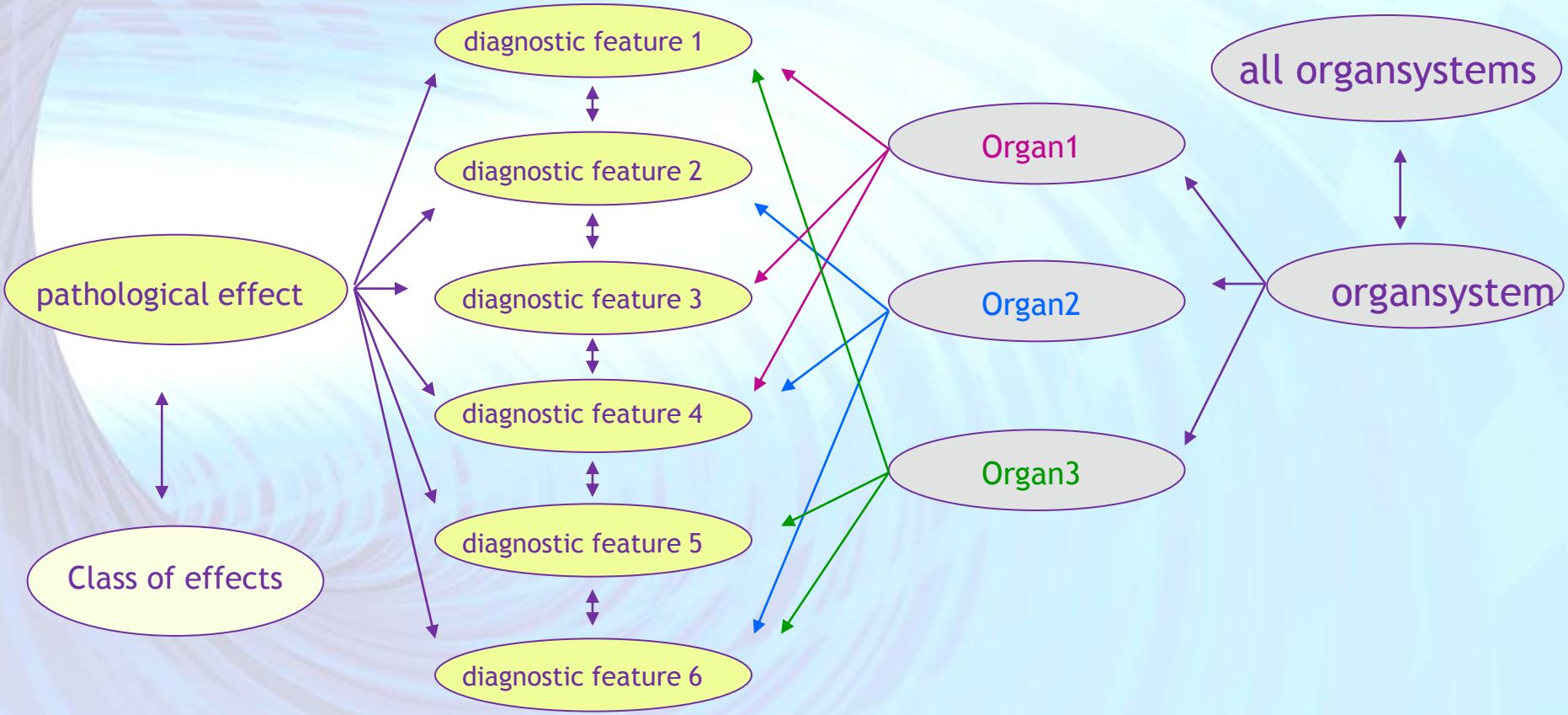


- **effect ontology**, which is linked to the organ ontology
- comprehensive review by FhG pathologists, who have been involved in the INHAND process

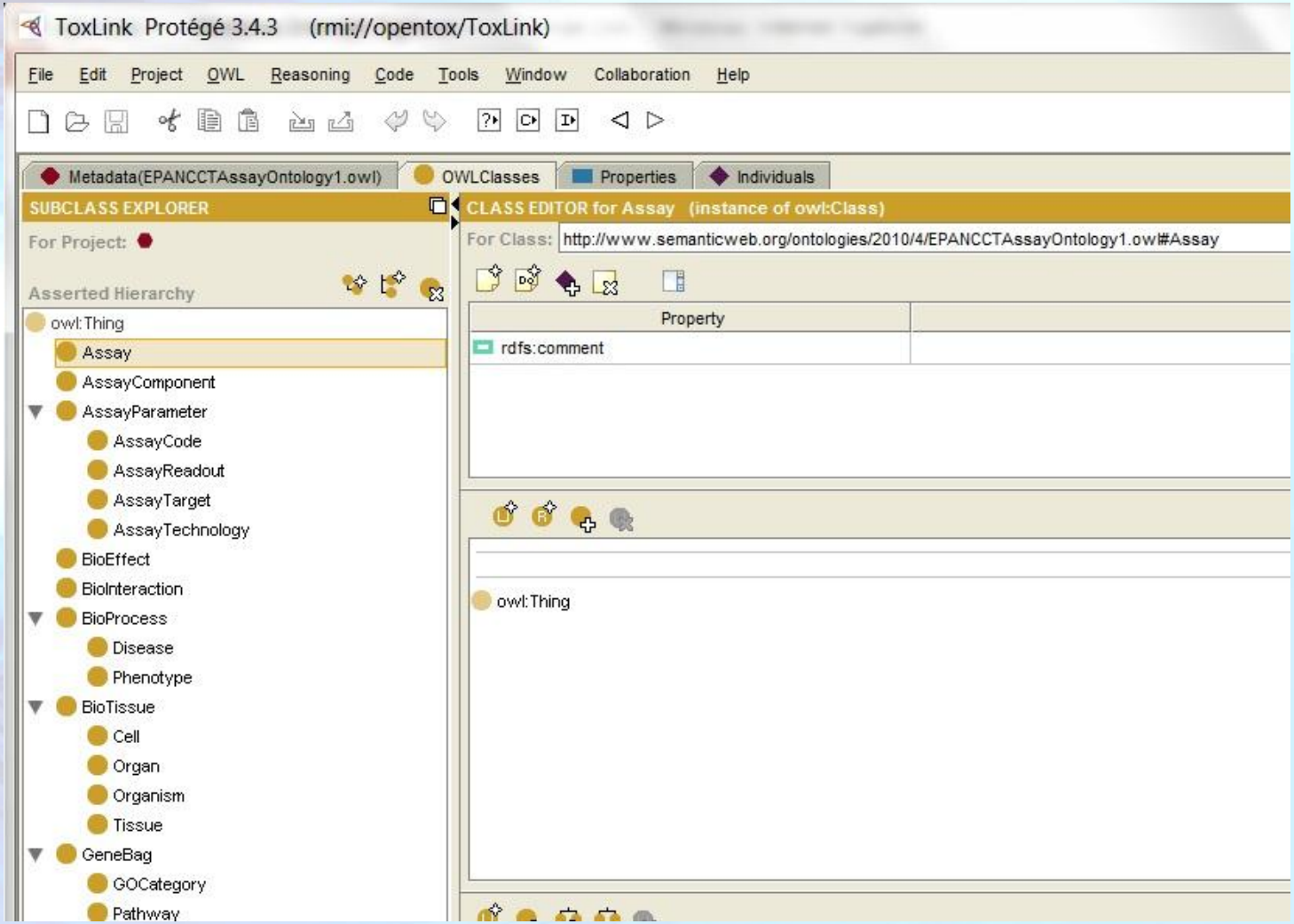
OpenTox

Fraunhofer

OpenTox Organ Ontology



ToxLink: ToxCast Ontology



www.opentox.org/dev/ontology/collaborative_protege

OpenToxipedia

OpenTox

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OpenToxipedia

by **Barry Hardy** — last modified Sep 03, 2009 01:09 PM

OpenTox Community Resource for Toxicology Vocabulary and Ontology

OpenTox is supporting the creation and curation of OpenToxipedia, a community-based predictive toxicology knowledge resource. All members of the community are welcome to provide entries, suggested definiton edits or additional information to entries in the resource.

OpenTox is supporting the application and development of the **ToxML** standard for representation of toxicology data, the **OECD principles for (Q)SAR model validation**, and the use of the **OECD HT** standard for regulatory reporting purposes.

OpenToxipedia provides here a Vocabulary Resource of toxicology terminology. We hope you find the resource useful and consider contributing to terms and their content.

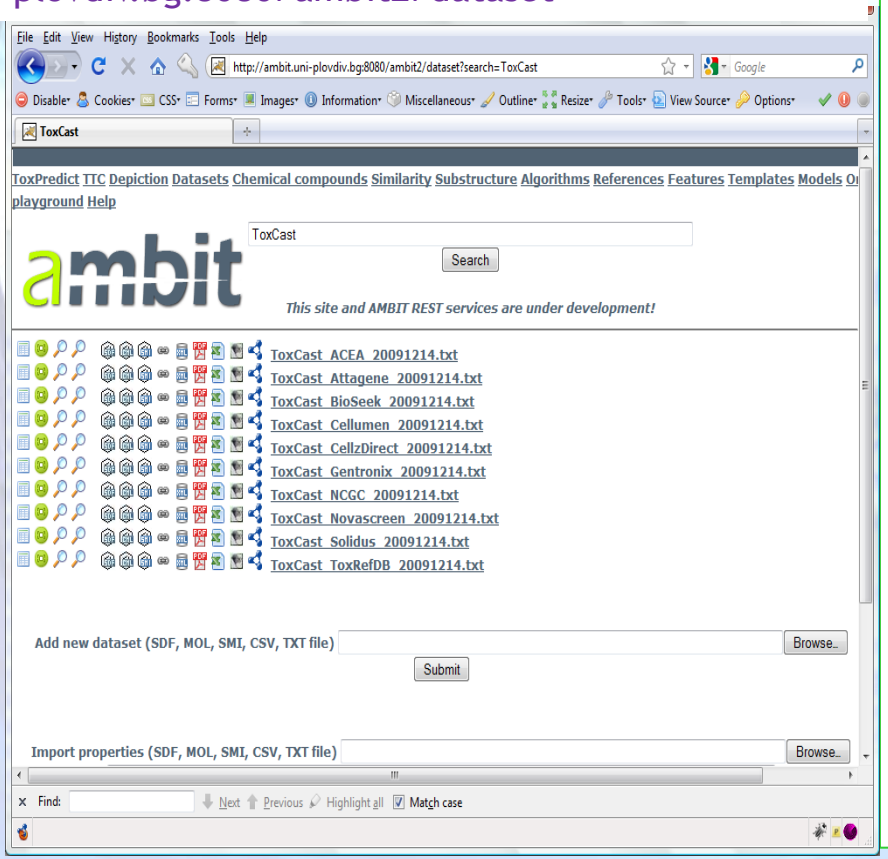
Guidance for Vocabulary Resource entries

www.opentox.org/opentoxipedia

OpenTox

Example: ToxCast

Dataset service at http://ambit.uni-plovdiv.bg:8080/ambit2/dataset



Query an OpenTox ontology service at http://ambit.uni-plovdiv.bg:8082/ontology

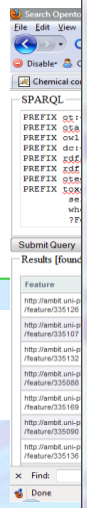
```
PREFIX ot:<http://www.opentox.org/api/1.1#>
PREFIX ota:<http://www.opentox.org/algorithms.owl#>
PREFIX owl:<http://www.w3.org/2002/07/owl#>
PREFIX dc:<http://purl.org/dc/elements/1.1/>
PREFIX rdfs: <http://www.w3.org/2000/01/rdf-schema#>
PREFIX rdf:<http://www.w3.org/1999/02/22-rdf-syntax-ns#>
PREFIX otee:<http://www.opentox.org/echaEndpoints.owl#>
PREFIX toxcast:<http://www.opentox.org/toxcast#>
                select *
                where {
                ?Feature rdf:type ot:Feature.
  {?Feature dc:title ?title}.
  {?Feature owl:sameAs ?assay}.
  {?assay toxcast:gene ?geneid}.
  {?assay toxcast:hasProperty ?species}.
  {?species rdf:type toxcast:SPECIES}.
  {?assay toxcast:hasProperty ?target_source}.
  {?target_source rdf:type toxcast:ASSAY_TARGET_SOURCE}
  {?assay toxcast:hasProperty ?target_family}.
  {?target_family rdf:type toxcast:ASSAY_TARGET_FAMILY}.
  {?assay toxcast:hasProperty ?target}.
  {?target rdf:type toxcast:ASSAY_TARGET}.
   {?assay toxcast:hasProperty toxcast:Cytochrome_P450}.
                }
order by ?feature ?assay ?target
```

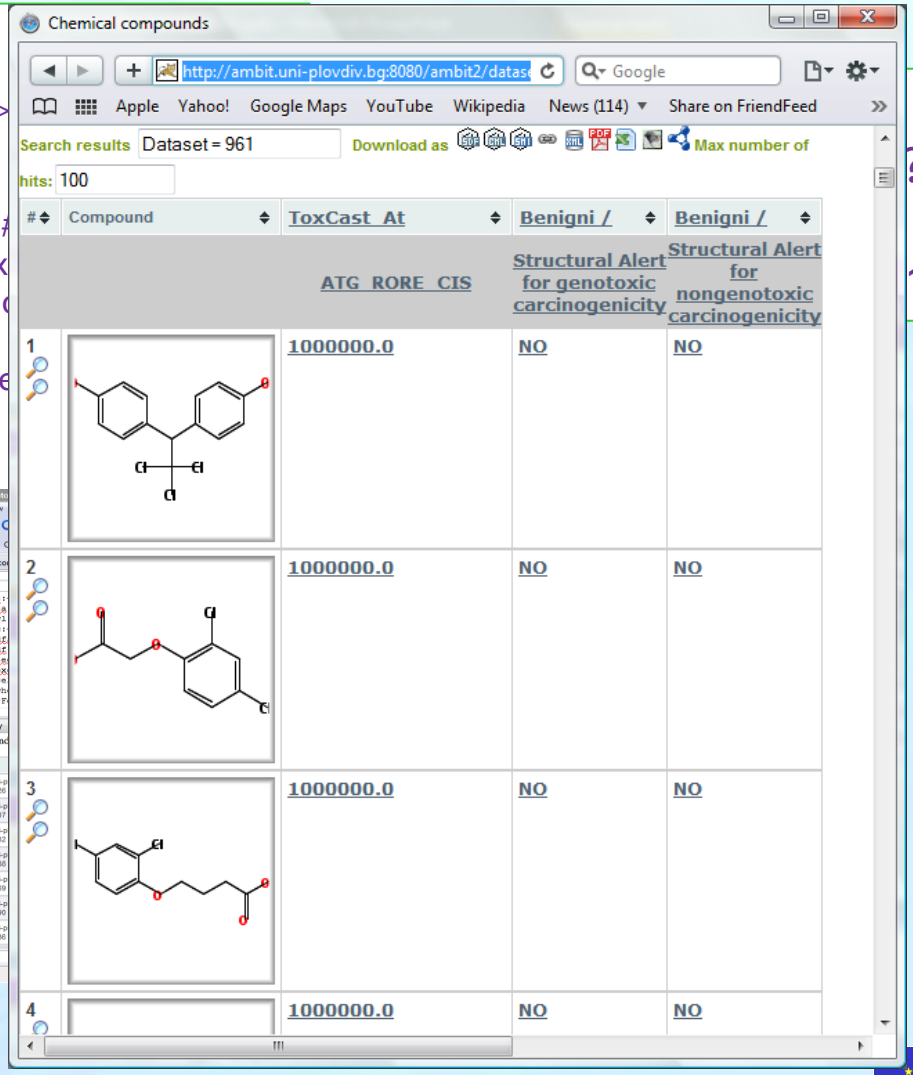
OpenTox

Example: ToxCast

```
PREFIX ot:<http://www.opentox.org/api/1.1#>
PREFIX ota:<http://www.opentox.org/algorithms.owl#>
PREFIX owl:<http://www.w3.org/2002/07/owl#>
PREFIX dc:<http://purl.org/dc/elements/1.1/>
PREFIX rdfs: <http://www.w3.org/2000/01/rdf-schema#
PREFIX rdf:<http://www.w3.org/1999/02/22-rdf-syntax
PREFIX otee:<http://www.opentox.org/echaEndpoints.
PREFIX toxcast:<http://www.opentox.org/toxcast#>
                select ?Feature ?title ?id ?assay ?geneid ?ge
                where {
                ?Feature rdf:type ot:Feature.
  {?Feature dc:title ?title}.
  {?Feature owl:sameAs ?assay}.
  {?assay toxcast:gene ?geneid}.
  {?assay toxcast:hasProperty ?genename}.
  {?genename rdf:type toxcast:GENE_NAME}.

                }
```





?feat

126

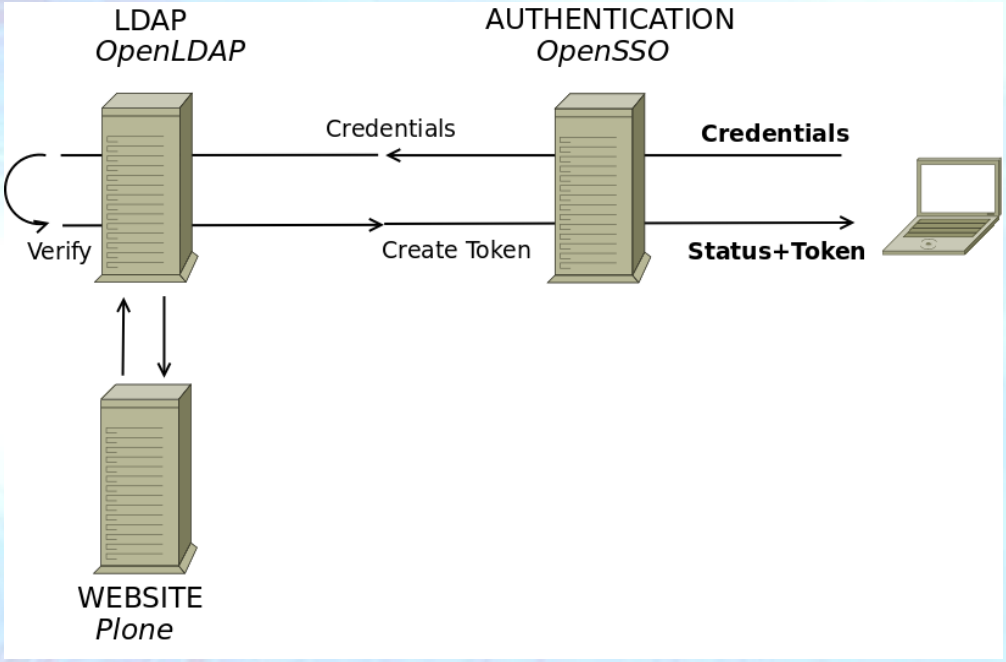
Query an OpenTox ontology service at
http://ambit.uni-plovdiv.bg:8082/ontology

OpenTox

Controlling Access to Confidential Information

- OpenTox makes resources available through URIs
- OpenTox provides facilities to protect confidential information located at URIs. Two tasks are involved here:
  - Authentication: Confirming the identity of the user requesting access
  - Authorisation: Granting the confirmed identity access according to a set of restrictions described in policies

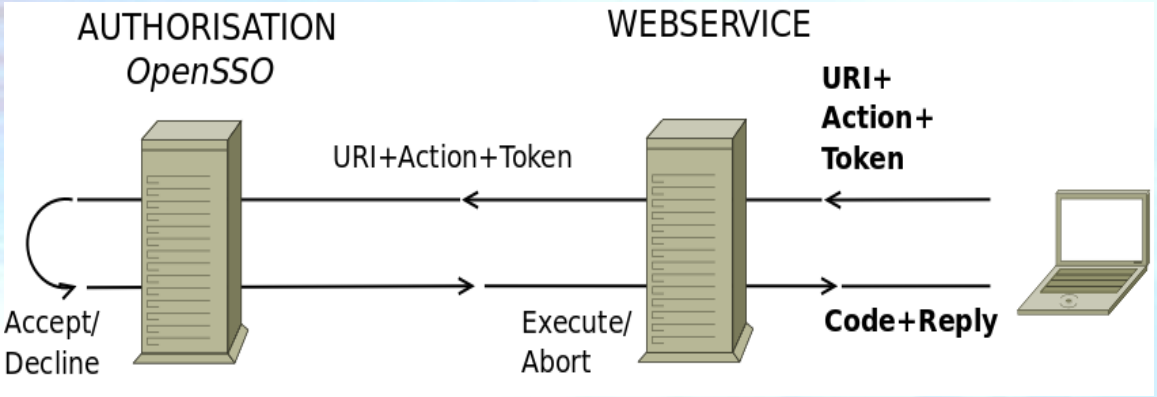
Authentication



- Registered users are instantly available as potential users of OpenTox web services
- Users receive a token upon service request

OpenTox

Authorisation



- Tokens encode user identity
- Tokens are valid for a certain time period only (customizable)
- The triplet URI+Action+Token makes up the call to be authorised
- All messages are encrypted (SSL)
- Resource Owners create and modify policies defining access rules

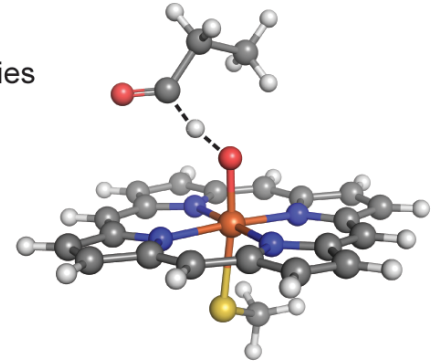
OpenTox

SMARTCyp Service for Predicting Metabolites

Atom Reactivity Library

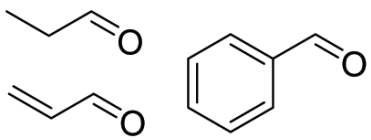
A. Calculate Quantum Chemical Reference Energies

Calculate transition state energies using density functional theory



B. Define SMARTS Rules

Group calculations by fragments and calculate average energies

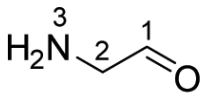


[CX3H1](=O)[#6]

40.2 kJ/mol

SMARTCyp

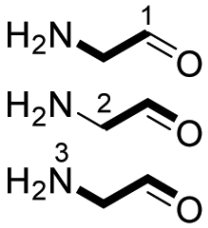
1. Assign Energies By SMARTS matching



Atom	SMARTS	Energy
1	[CX3H1](=O)[#6]	40.2
2	[CX4][N]	39.8
3	[N^3][H1,H2]	54.1

2. Compute Accessibility Descriptor

$A_i = Maxbonds_i / Maxbonds_{all}$



$A_1 = 2 / 3 = 0.67$

$A_2 = 2 / 3 = 0.67$

$A_3 = 3 / 3 = 1.00$

3. Compute Score and Rank Atoms

Score, S = E - 8A
Lowest score gets rank 1

$S_1 = 40.2 - 8*0.67 = 34.84$

$S_2 = 39.8 - 8*0.67 = 34.44$

$S_3 = 54.1 - 8*1.00 = 46.10$

Atom 1 - Rank 2

Atom 2 - Rank 1

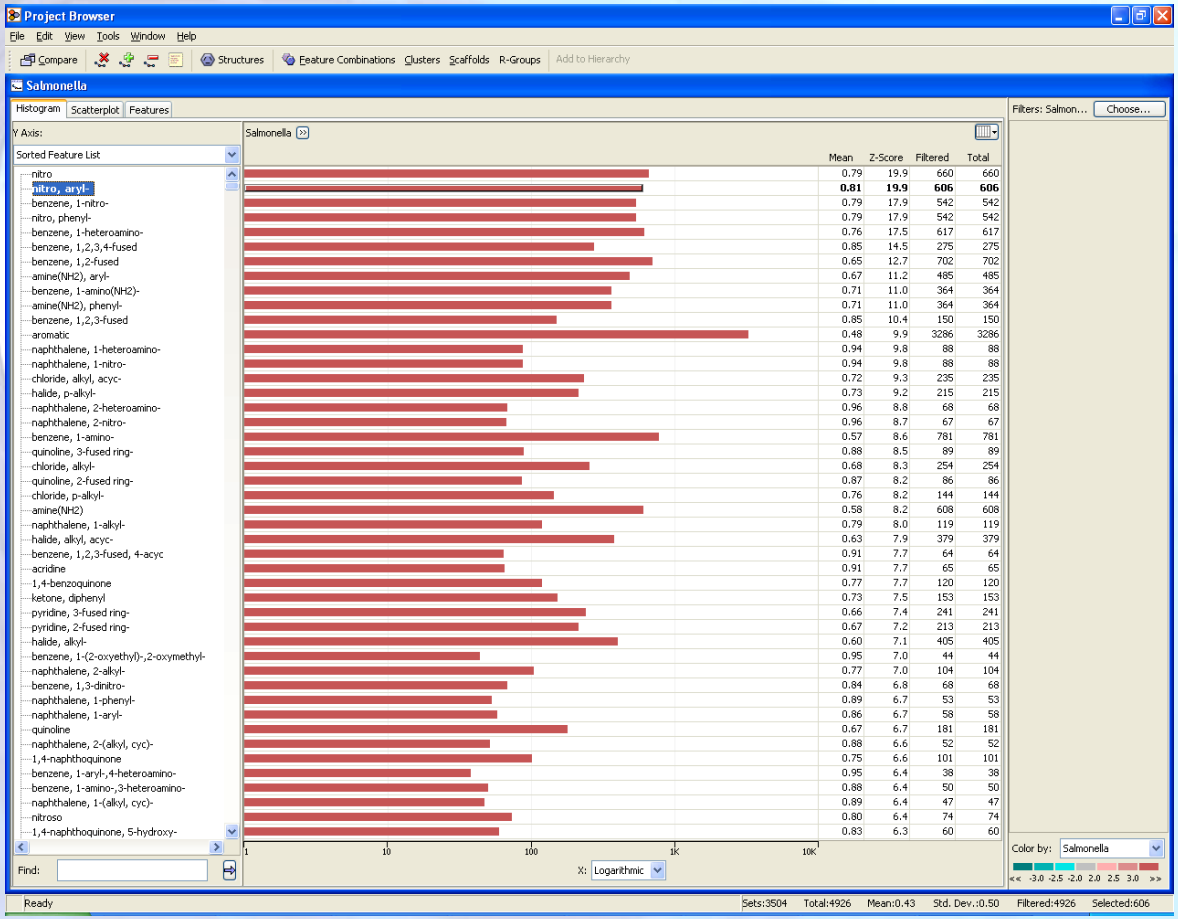
Atom 3 - Rank 3

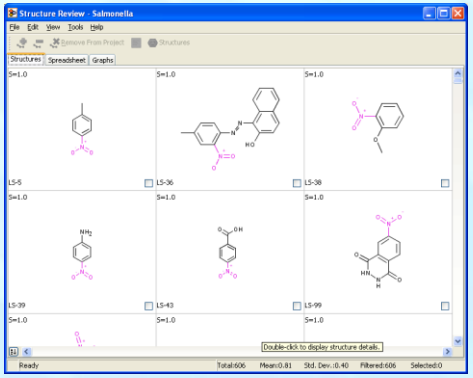
SMARTCyp - developed by Patrik Rydberg, University of Copenhagen

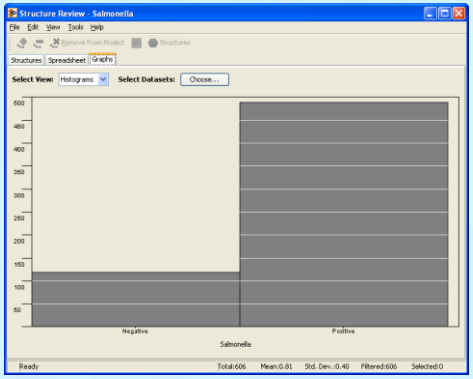
www.farma.ku.dk/index.php/SMARTCyp/7990/0/

OpenTox

OpenTox - Leadscope







OpenTox

OpenTox - Bioclipse

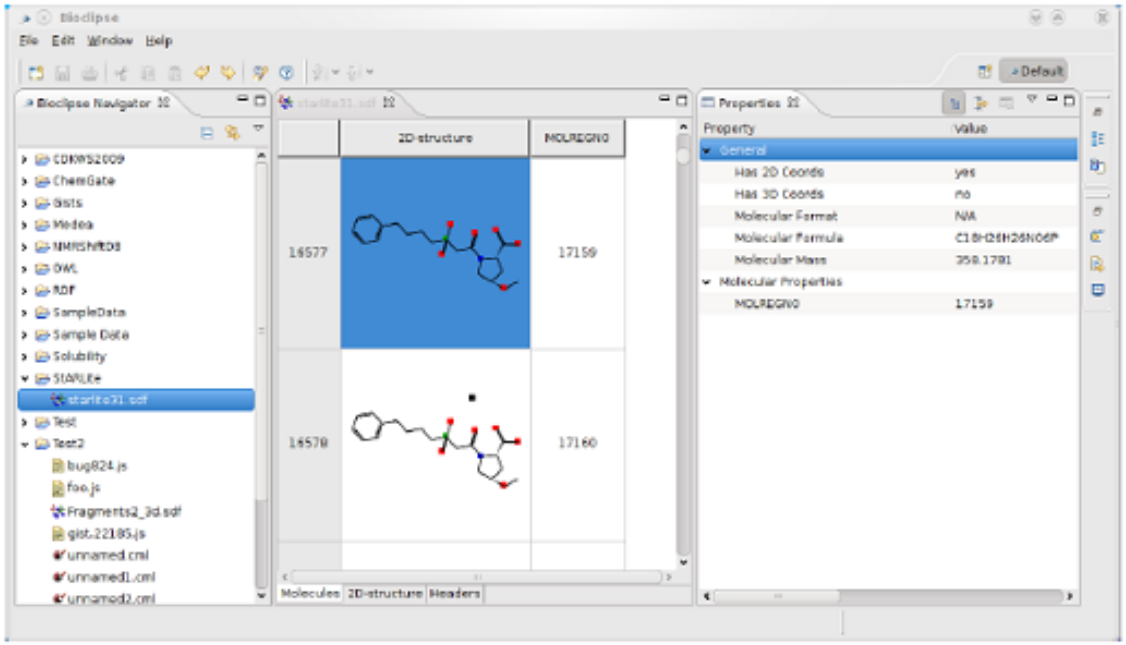
UPPSALA UNIVERSITET

Problem

Building Blocks

Conclusion

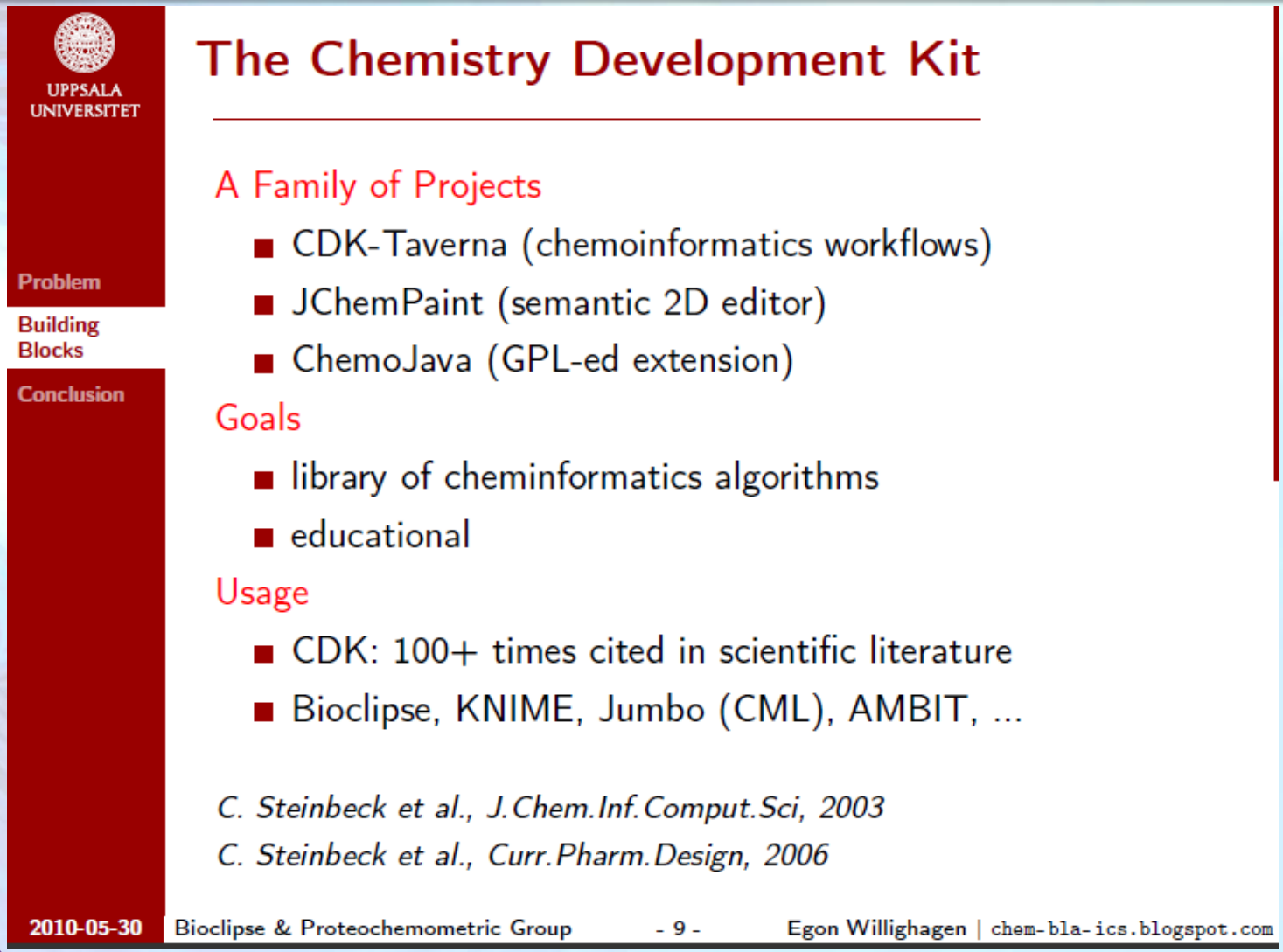
Bioclipse



O. Spjuth et al., BMC Bioinformatics 2007, 8:59

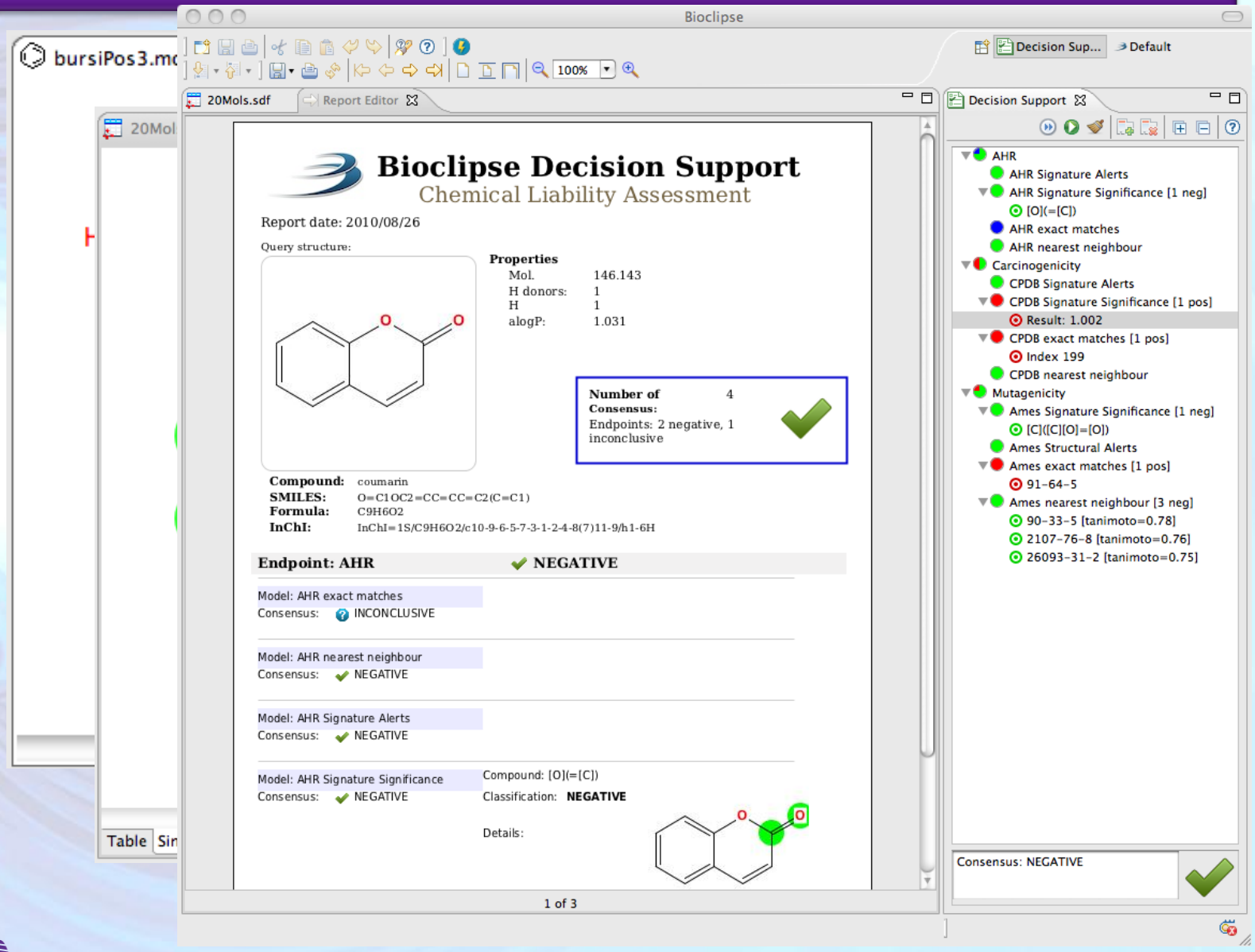
OpenTox

OpenTox - CDK



OpenTox

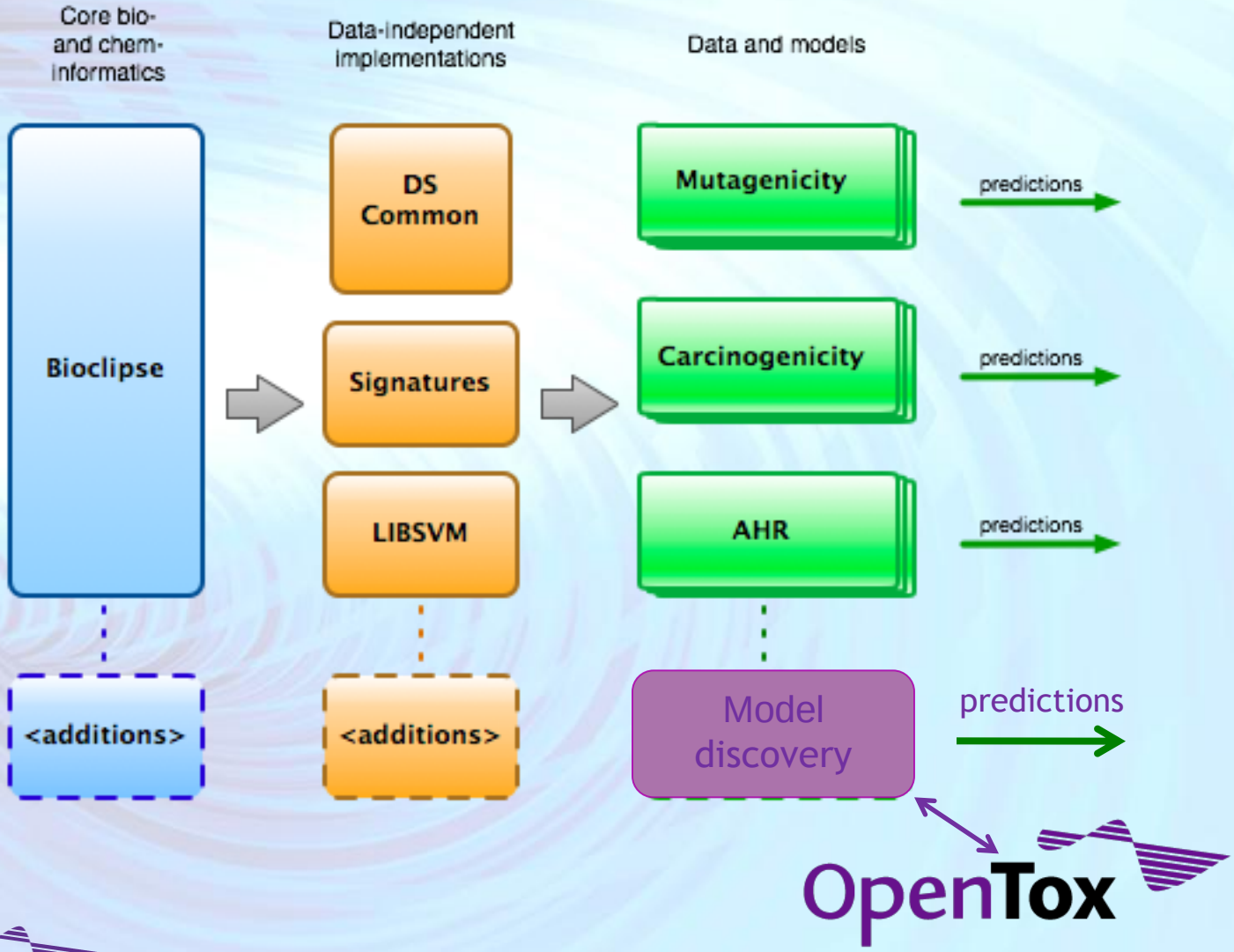
Bioclipse Visualisation Workbench



OpenTox

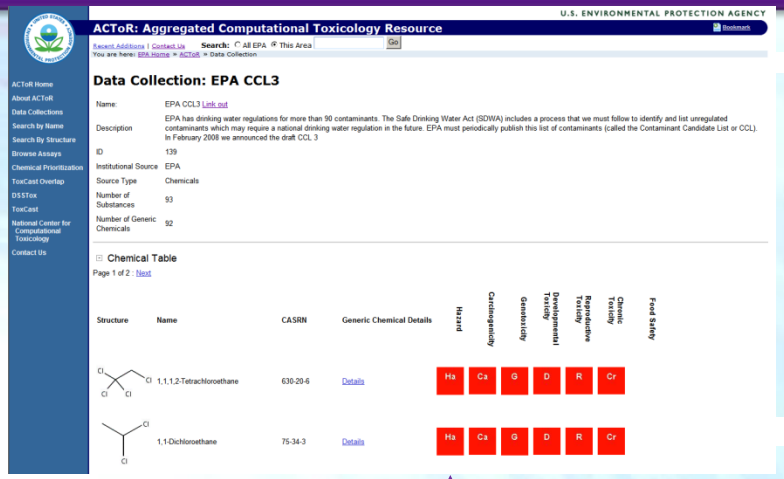
O. Spjuth, L. Carlsson, M. Eklund, E. Ahlberg Helgee, and Scott Boyer. *Integrated decision support for assessing chemical liabilities*. In preparation

Bioclipse - OpenTox Interoperation



OpenTox

OpenTox - ToxCast



ACToR Web Browser

ACToR API

Chemical

Chemical ID, Structure

Targeted Testing

Assay

Tabular Data, Links to Web Resources

ToxRefDB

...

DevToxDB

Specialized Toxicology Databases

Genomics

MicroArray Data

BioRefDB

Biological Reference Data

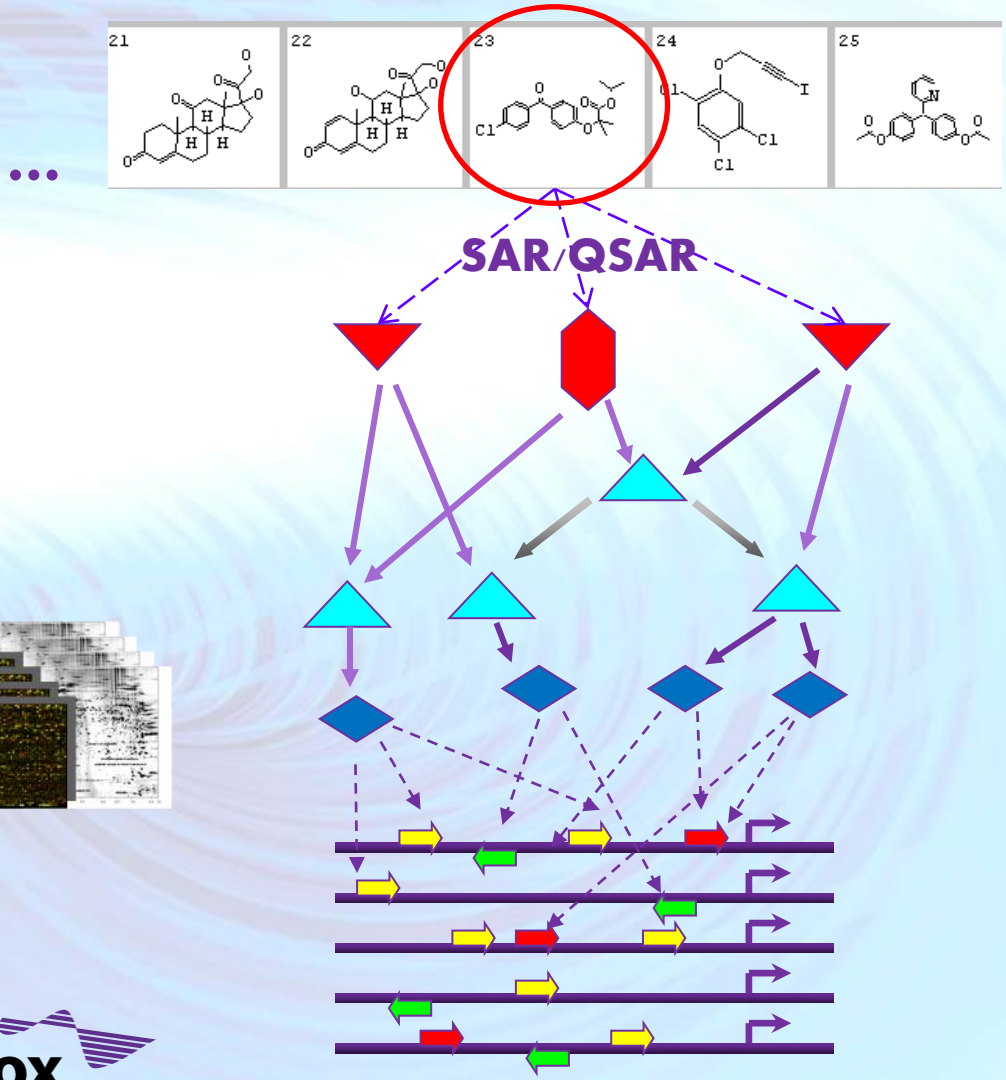
ToxMiner

Data Mining

Internet Searches

actor.epa.gov

Integrated Workflow of Bioinformatics, Systems Biological and Cheminformatics Tools



Cheminformatics
Biological activities of the compounds

Systems Biology
Network analysis and simulation, potential drug targets

Bioinformatics
Regulatory modules, transcription factors

OpenTox

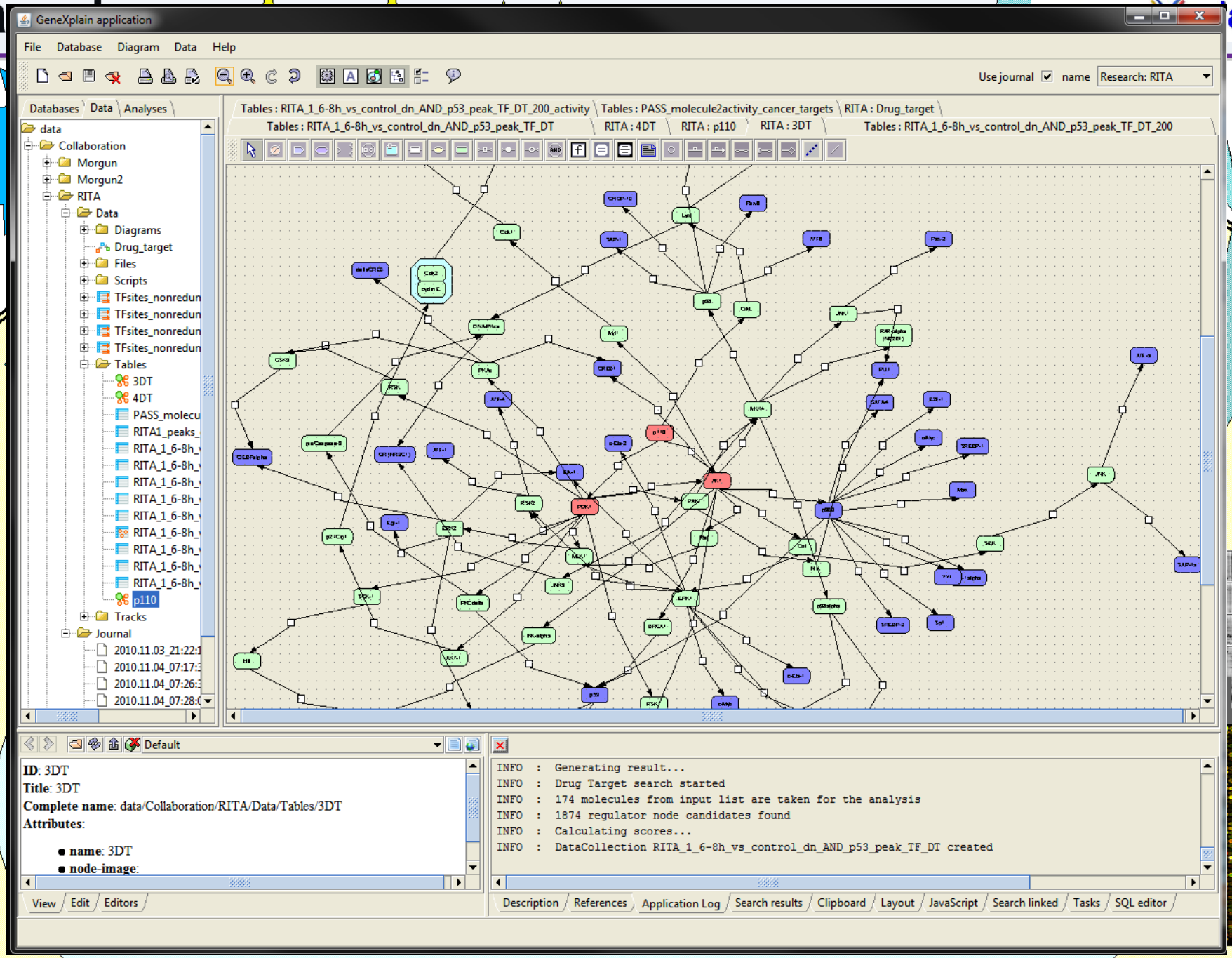
Lets talk in:

BioUML

Unified Modeling Language (UML) is a standardized general-purpose modeling language

OpenTox

0100100010011101
Institute of Systems Biology


GeneXplain application
File Database Diagram Data Help
Use journal name Research: RITA
Databases Data Analyses
data
Collaboration
Morgun
Morgun2
RITA
Data
Diagrams
Drug_target
Files
Scripts
TFsites_nonredun
TFsites_nonredun
TFsites_nonredun
TFsites_nonredun
Tables
3DT
4DT
PASS_molecu
RITA1_peaks_
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2010.11.04_07:17:3
2010.11.04_07:26:3
2010.11.04_07:28:0
Tables : RITA_1_6-8h_vs_control_dn_AND_p53_peak_TF_DT_200_activity
Tables : PASS_molecule2activity_cancer_targets
RITA : Drug_target
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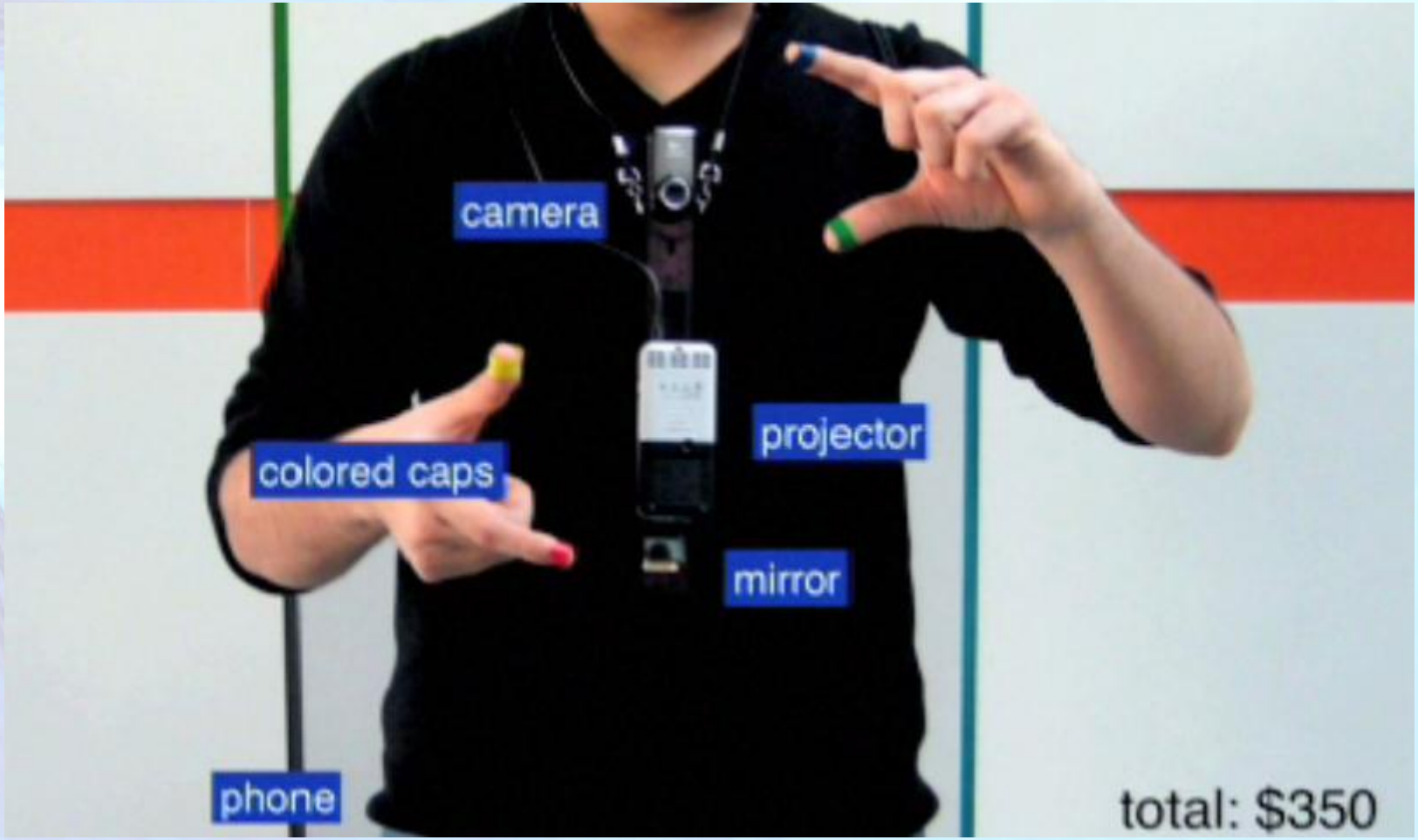
RITA : 4DT
RITA : p110
RITA : 3DT
Tables : RITA_1_6-8h_vs_control_dn_AND_p53_peak_TF_DT_200
Default
ID: 3DT
Title: 3DT
Complete name: data/Collaboration/RITA/Data/Tables/3DT
Attributes:
name: 3DT
node-image:
INFO : Generating result...
INFO : Drug Target search started
INFO : 174 molecules from input list are taken for the analysis
INFO : 1874 regulator node candidates found
INFO : Calculating scores...
INFO : DataCollection RITA_1_6-8h_vs_control_dn_AND_p53_peak_TF_DT created
View Edit Editors
Description References Application Log Search results Clipboard Layout JavaScript Search linked Tasks SQL editor

Augmented Reality



MIT Media Lab

Processing Packaging Information

MIT Media Lab

OpenTox

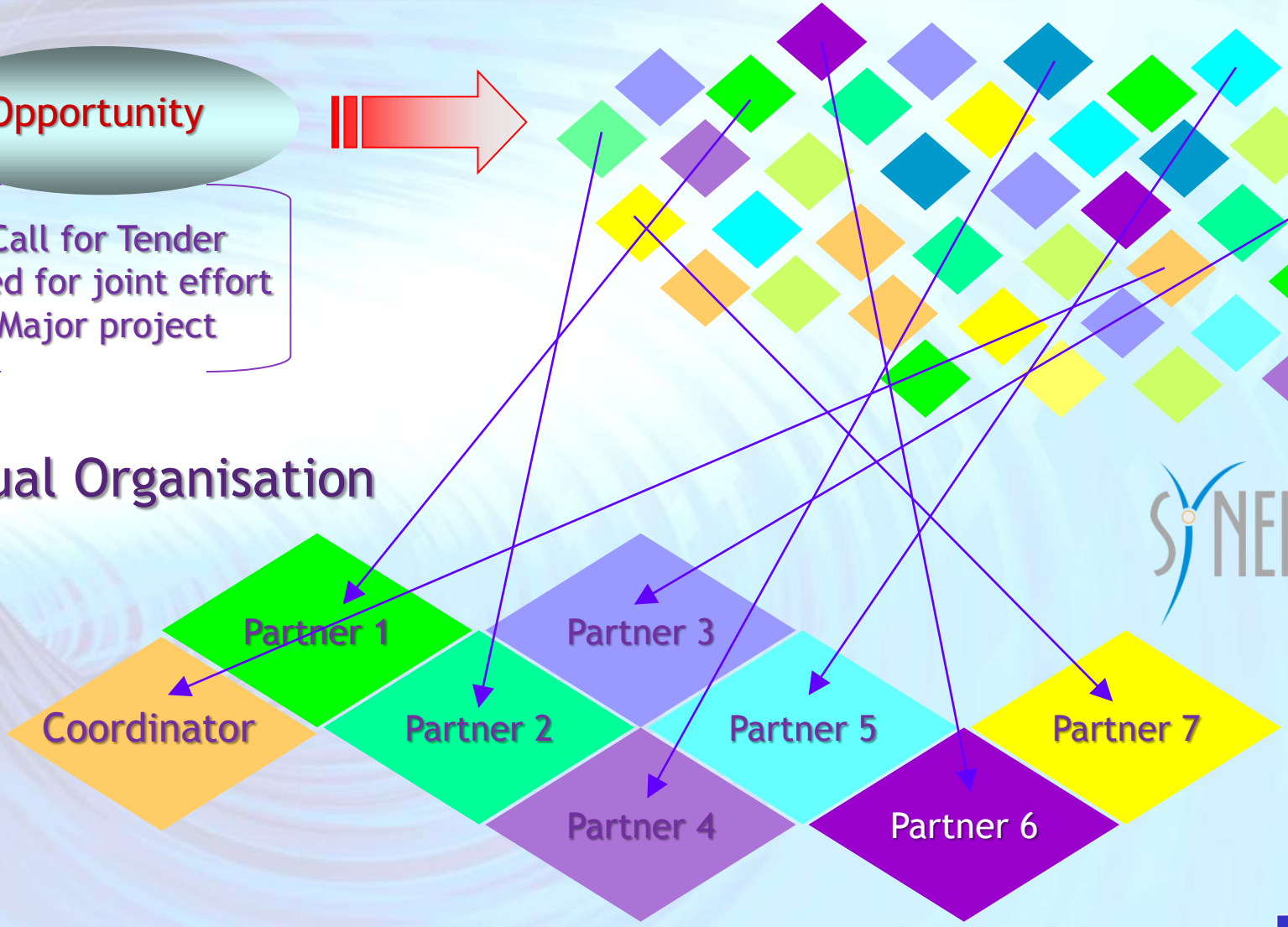
Creation of VO from Collaboration Pool

Network

Opportunity

Call for Tender
Need for joint effort
Major project

Virtual Organisation

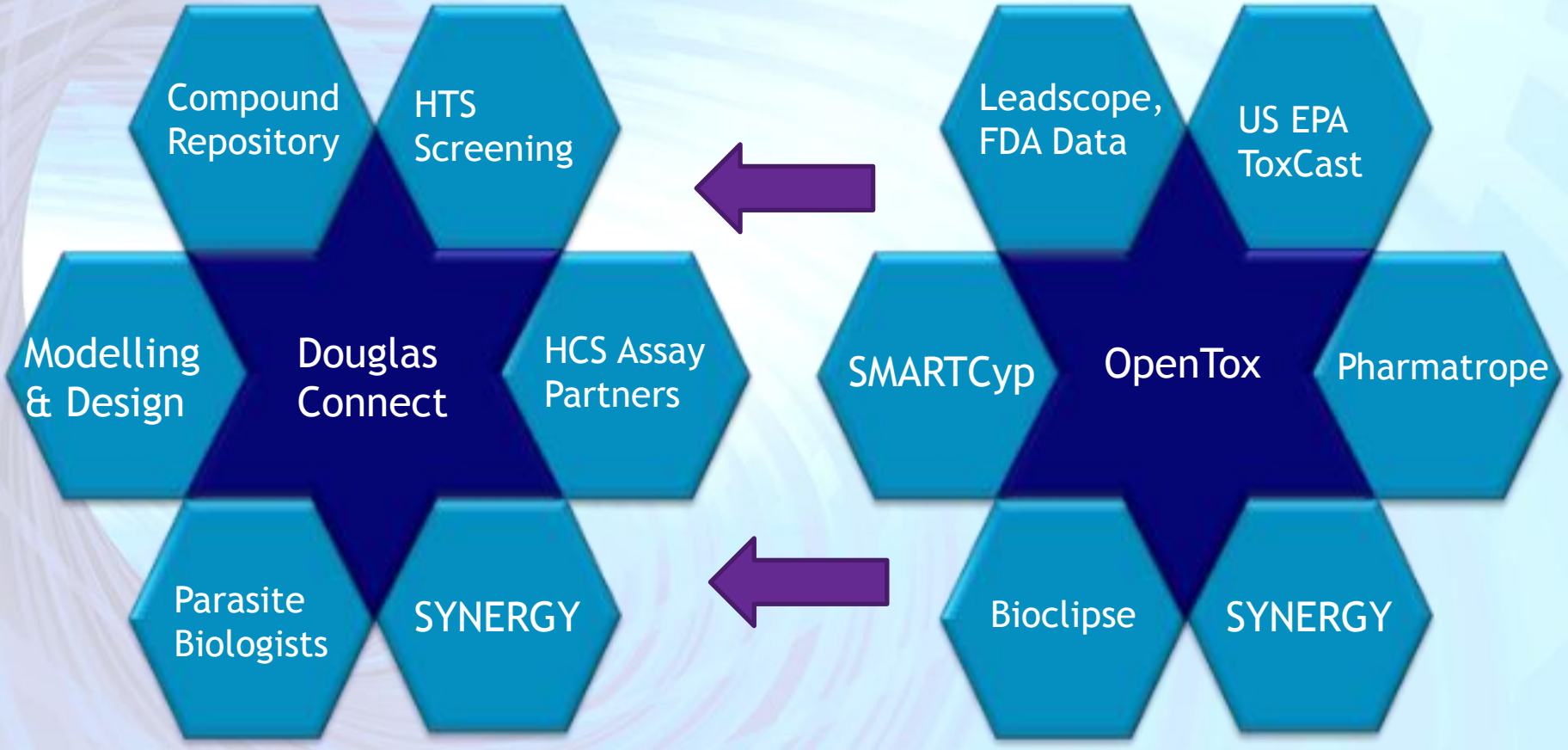


SYNERGY

OpenTox

www.synergy-ist.eu

Virtual Organisation Pilots



Neglected Disease Drug Design VO

Predictive Toxicology VO

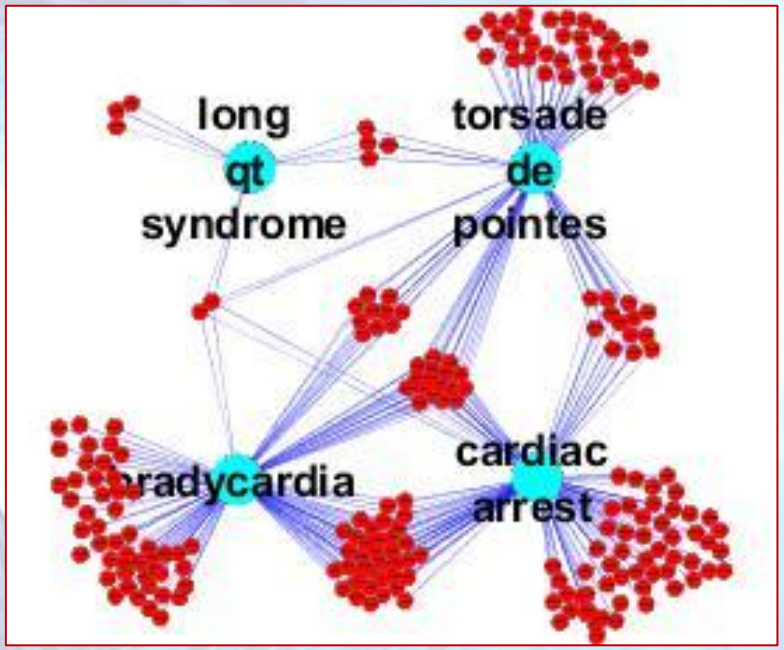
OpenTox

OpenTox - Synergy Predictive Toxicology VO Pilot Strategy Development & Case Study

1. Data Mining of Human Adverse Drug Events
   - Data Mining of Literature Knowledge
2. Creation of Mechanism-based Hypothesis
   - Selection of Biological Pathways & Targets
3. Selection of Compounds
   - Prediction of Metabolites of Compounds
4. Selection of *in vitro* assays relevant to Mechanism
   - Selection and integration of Toxicity Data
5. Creation of Predictive Toxicology Model including Model Validation and Applicability Domain
6. Selection of Low and High Content Assays for Testing in Cell Lines
   - Analysis of Results

OpenTox

Analysis of Adverse Events Based on Pharmacological Activity



- Cardiac adverse events
- Related to hERG ion channel?

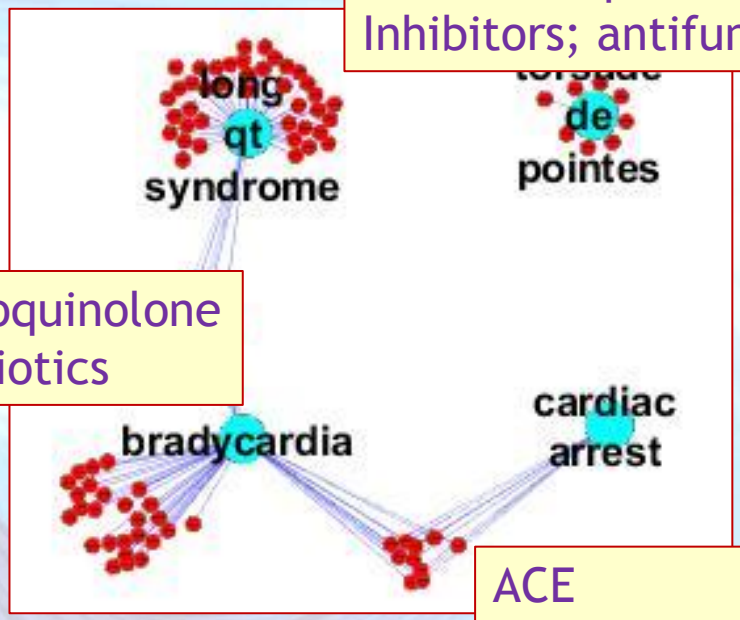
cyan = adverse event, red = drug
lines define links

- Question addressed:
  - Are the adverse events a function of inhibiting the pharmacological target
  - Or is the adverse event due to an off-target activity

OpenTox

PHARMATROPE

Example: Cardiac Adverse Events



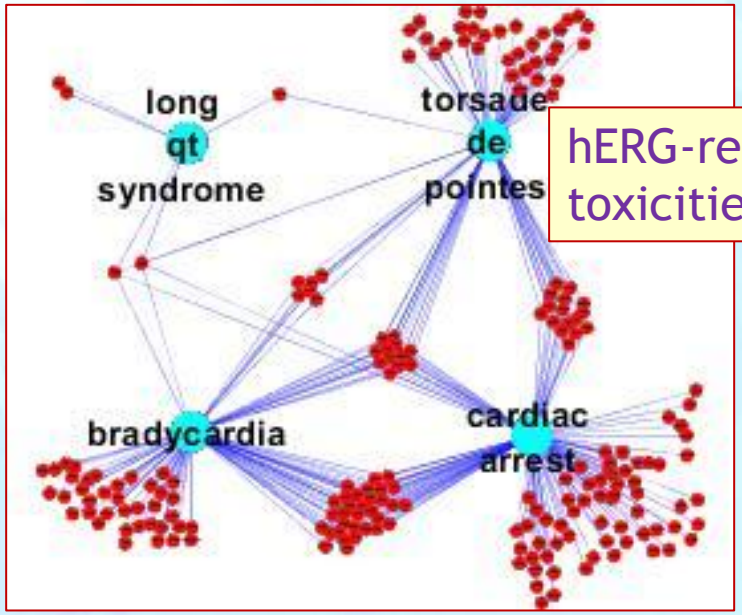
serotonin uptake Inhibitors; antifungals

fluoroquinolone antibiotics

ACE Inhibitors

- On-target events

cyan = adverse event, red = drug lines define links



hERG-related toxicities?

- Off-target events

OpenTox

PHARMATROPE

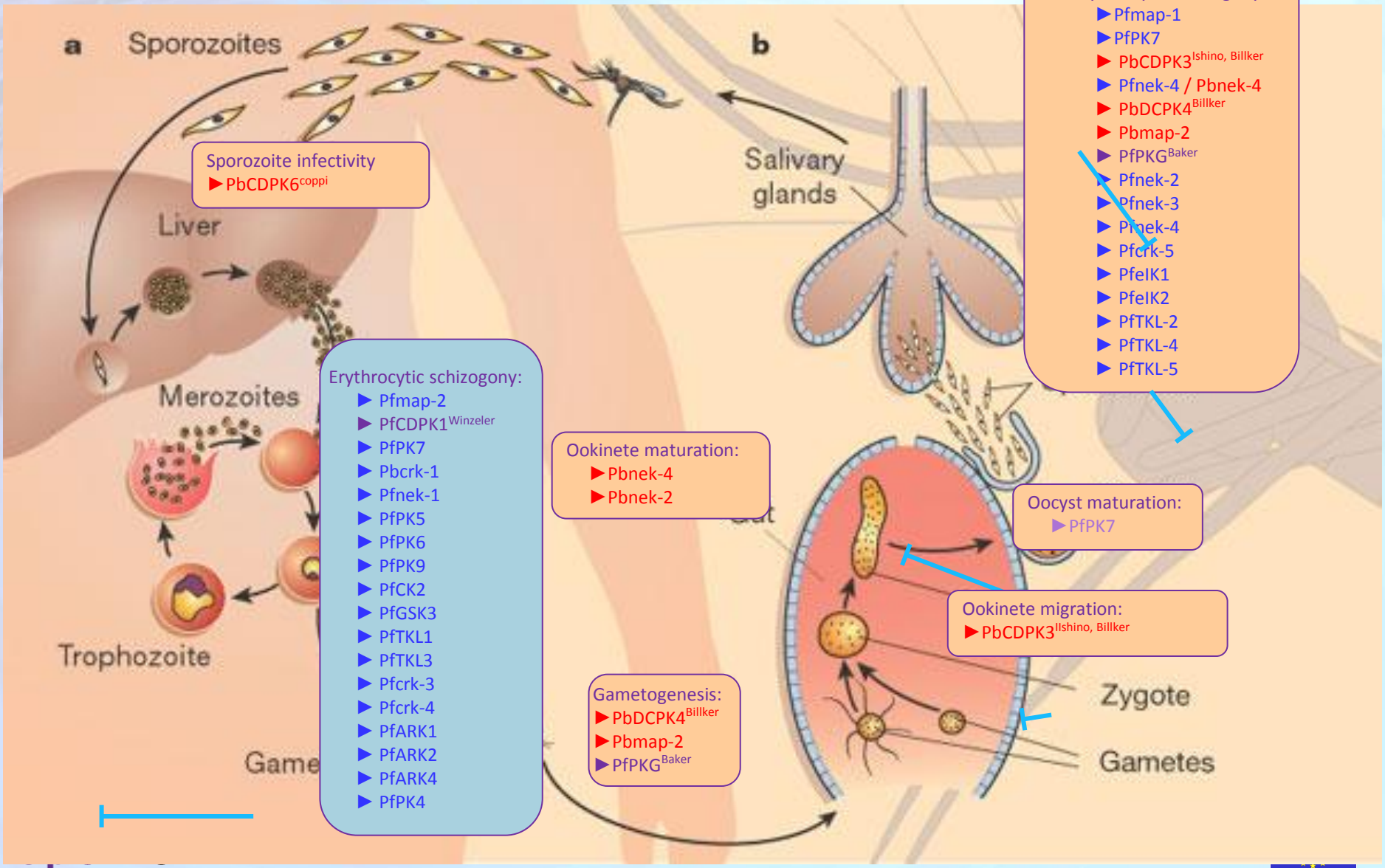
Ontology Issues

- MeSH tems inadequate to describe drug activity
  - Higher granularity definitions required
    - e.g. “ACE inhibitor” instead of “antihypertensive agent”
  - Are alternative definitions available?
- MedDRA terms are used to define adverse events
  - Drug pharmacological action needs to be defined in the same terms

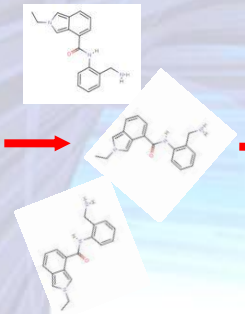
OpenTox

PHARMATROPE

SAM VO targeting Plasmodium Kinases

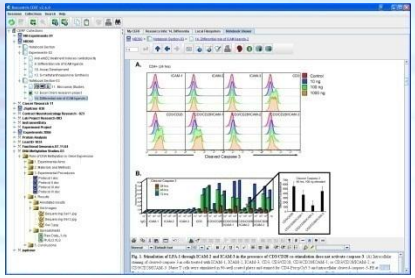


Synergy Drug Design Collaboration Pilot

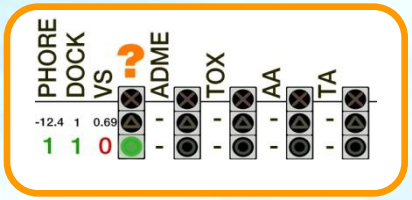


Screened Library

Data

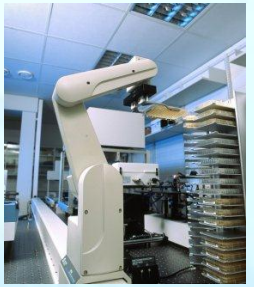


CERF

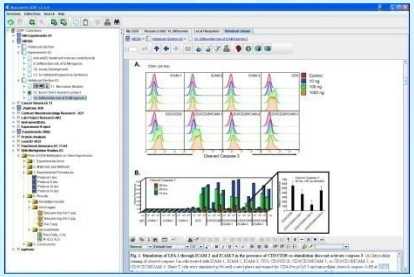


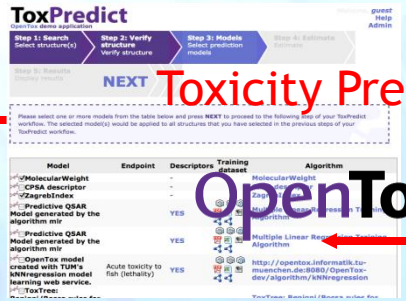
Refine Predictions

SYNERGY



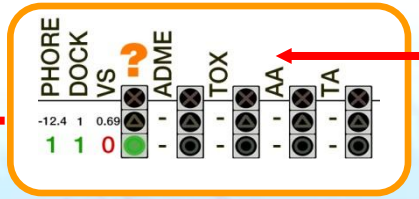
Data



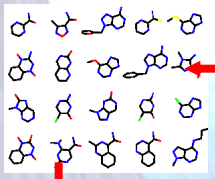


Toxicity Predictions

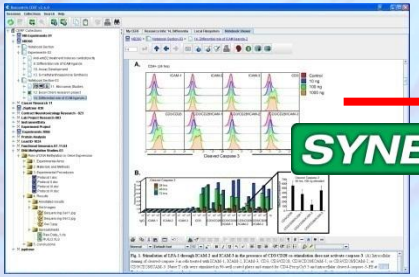
OpenTox



SYNERGY



Toxicity Assays



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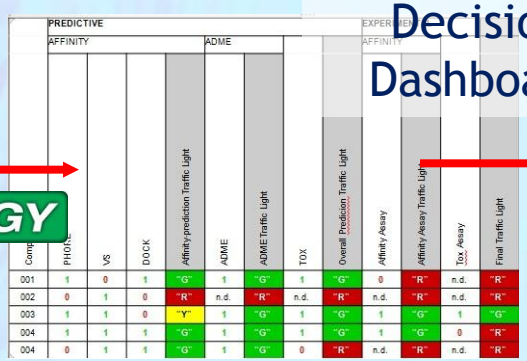
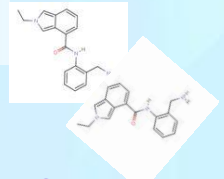


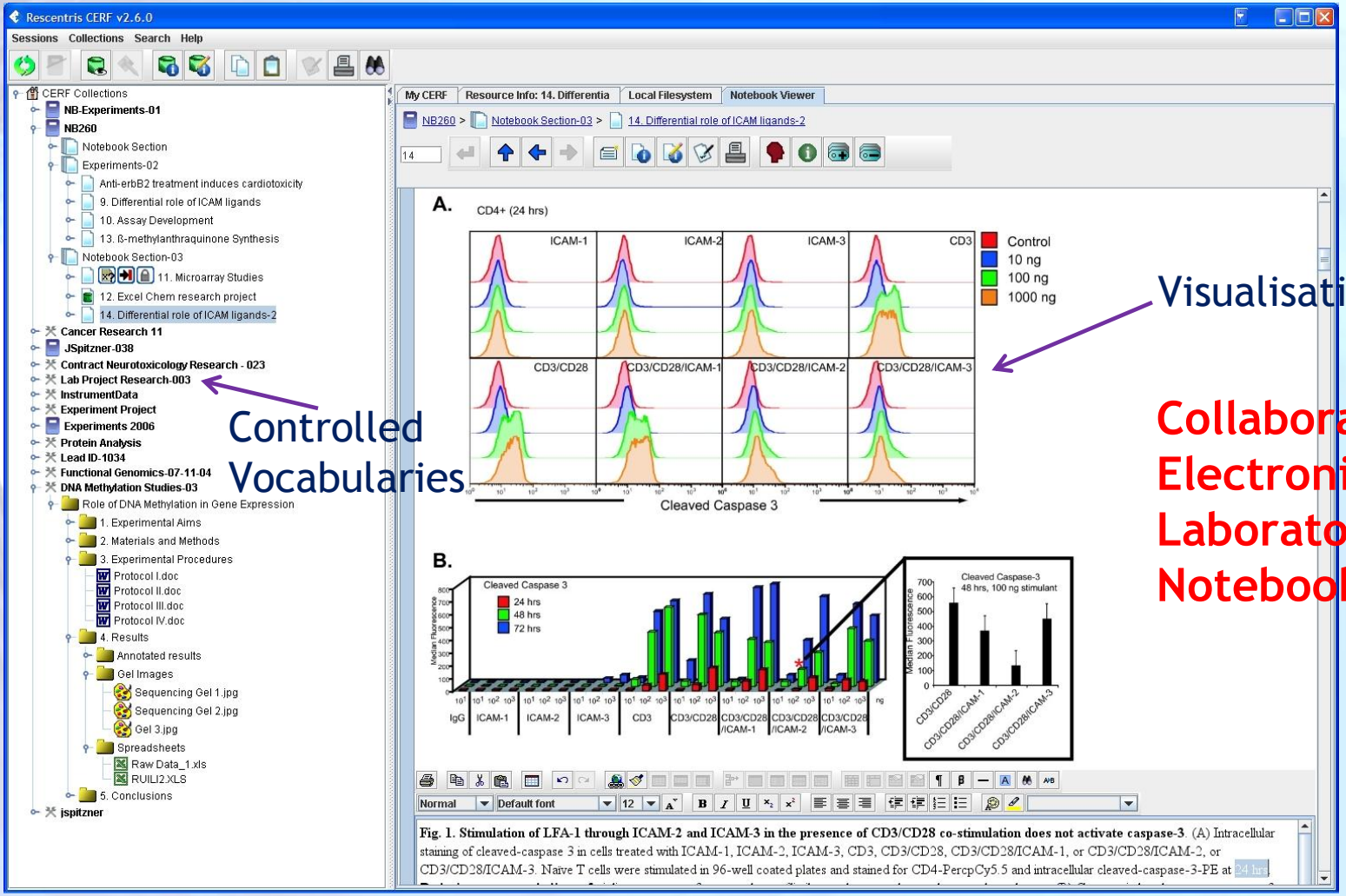
Decision Dashboard



(Safer) Drug Leads

OpenTox

Recording of Collaborative R&D



Controlled Vocabularies

Visualisation

Collaborative Electronic Laboratory Notebook (ELN)

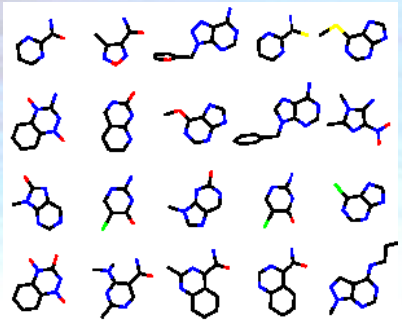
OpenTox

OpenTox - Synergy Predictive Toxicology VO Pilot Strategy Development & Case Study

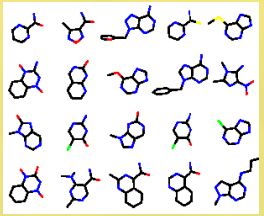
1. Data Mining of Human Adverse Drug Events
   - Data Mining of Literature Knowledge
2. Creation of Mechanism-based Hypothesis
   - Selection of Biological Pathways & Targets
3. Selection of Compounds
   - Prediction of Metabolites of Compounds
4. Selection of *in vitro* assays relevant to Mechanism
   - Selection and integration of Toxicity Data
5. Creation of Predictive Toxicology Model including Model Validation and Applicability Domain
6. Selection of Low and High Content Assays for Testing in Cell Lines
   - Analysis of Results

OpenTox

1. A library of compounds is entered to the ELN



ELN

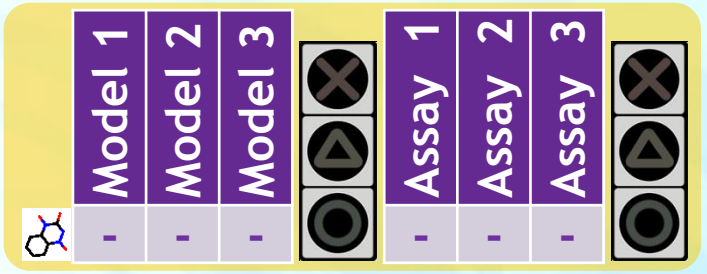


Synergy

OpenTox

2. Each compound is assigned a data structure in ELN

ELN

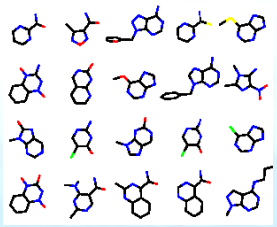


Synergy

OpenTox

OpenTox

3. ELN passes compounds to OpenTox and SYNERGY



ELN

	Model 1	Model 2	Model 3	Assay 1	Assay 2	Assay 3
	-	-	-	-	-	-

Synergy

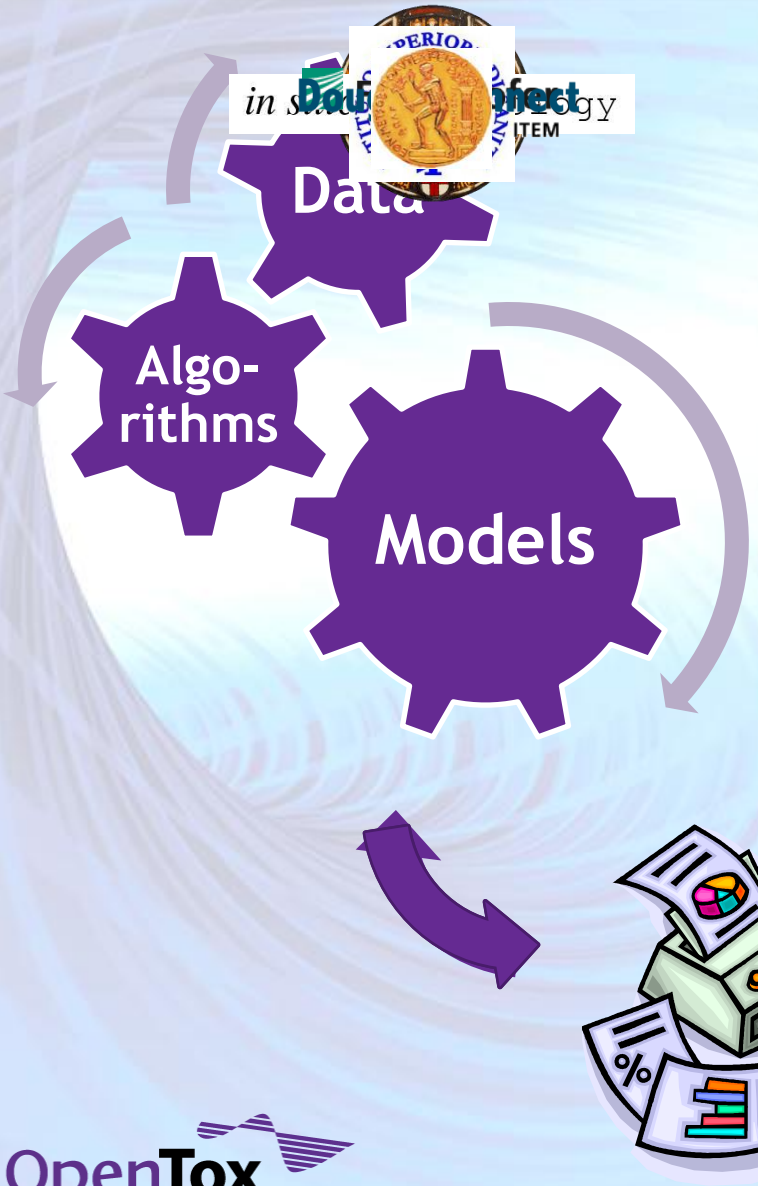
	Model 1	Model 2	Model 3	Assay 1	Assay 2	Assay 3
	-	-	-	-	-	-

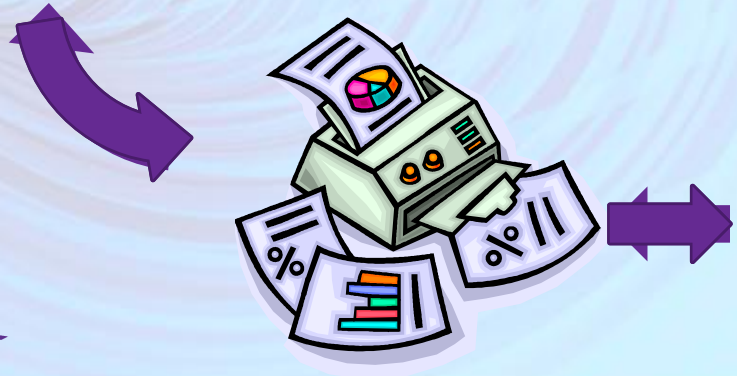
OpenTox

	Model 1	Model 2	Model 3	Assay 1	Assay 2	Assay 3
	-	-	-	-	-	-

OpenTox

4. OpenTox computes toxicity predictions





ELN

	Model 1	Model 2	Model 3	Assay 1	Assay 2	Assay 3
	-	-	-	-	-	-

Synergy

	Model 1	Model 2	Model 3	Assay 1	Assay 2	Assay 3
	-	-	-	-	-	-

OpenTox

	Model 1	Model 2	Model 3	Assay 1	Assay 2	Assay 3
	1	0	1	-	-	-

OpenTox

5. OpenTox sends back a report to ELN

ELN

Model 1	Model 2	Model 3	Assay 1	Assay 2	Assay 3
1	0	1	-	-	-

Synergy

Model 1	Model 2	Model 3	Assay 1	Assay 2	Assay 3
-	-	-	-	-	-

OpenTox

Model 1	Model 2	Model 3	Assay 1	Assay 2	Assay 3
1	0	1	-	-	-

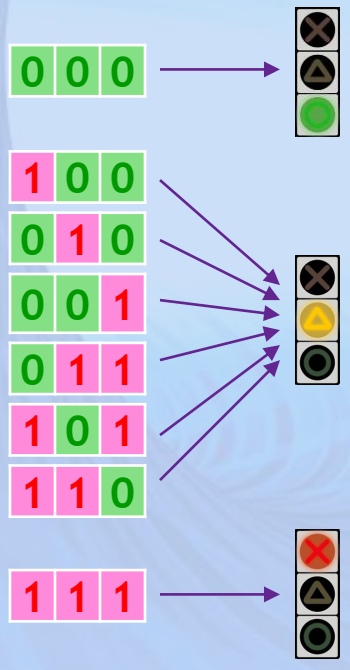
OpenTox

6. ELN sends the results to SYNERGY

OpenTox

7. SYNERGY applies the Recommendation Rules

Recommendation Rules:



Non-toxic, high confidence

Inconclusive results, further study needed

Toxic, high confidence

ELN

Model 1	Model 2	Model 3	Assay 1	Assay 2	Assay 3
1	0	1	-	-	-

Synergy

Model 1	Model 2	Model 3	Assay 1	Assay 2	Assay 3
1	0	1	-	-	-

OpenTox

OpenTox

8. Inconclusive data → SYNERGY calls a meeting

?

ELN

	Model 1	Model 2	Model 3	Assay 1	Assay 2	Assay 3
	1	0	1	-	-	-

Synergy

	Model 1	Model 2	Model 3	Assay 1	Assay 2	Assay 3
	1	0	1	-	-	-

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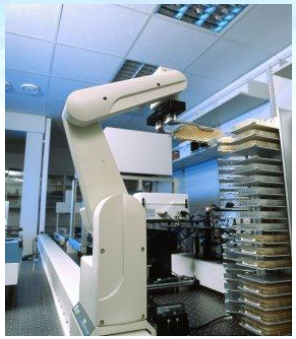
9. Experimental assays confirm toxicity



ELN

Model 1	Model 2	Model 3	Assay 1	Assay 2	Assay 3
1	0	1	-	1	1

Synergy

Model 1	Model 2	Model 3	Assay 1	Assay 2	Assay 3
1	0	1	-	-	-

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Sustainability Model

New Opportunity

K Base

K

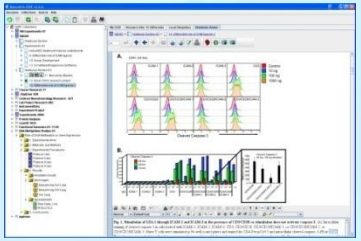
K

Apps

Risk Assessments

Contract

Outcomes



Predictive Toxicology Collaboration Pool

Predictive Toxicology Virtual Organization

R&D Program Services & Support

Contract Payments

PRE-CREATION

CREATION

OPERATION

TERMINATION

Service Support of Virtual Organisation Lifecycle

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Our Drivers – Taking on Technical, Cultural and "Other" Challenges of the Unexpected

Visit with Lions at Mukuni Reintroduction Project, Livingstone, Zambia

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Our Drivers – Taking on Technical, Cultural and "Other" Challenges of the Unexpected

Wildlife ACT, Zululand

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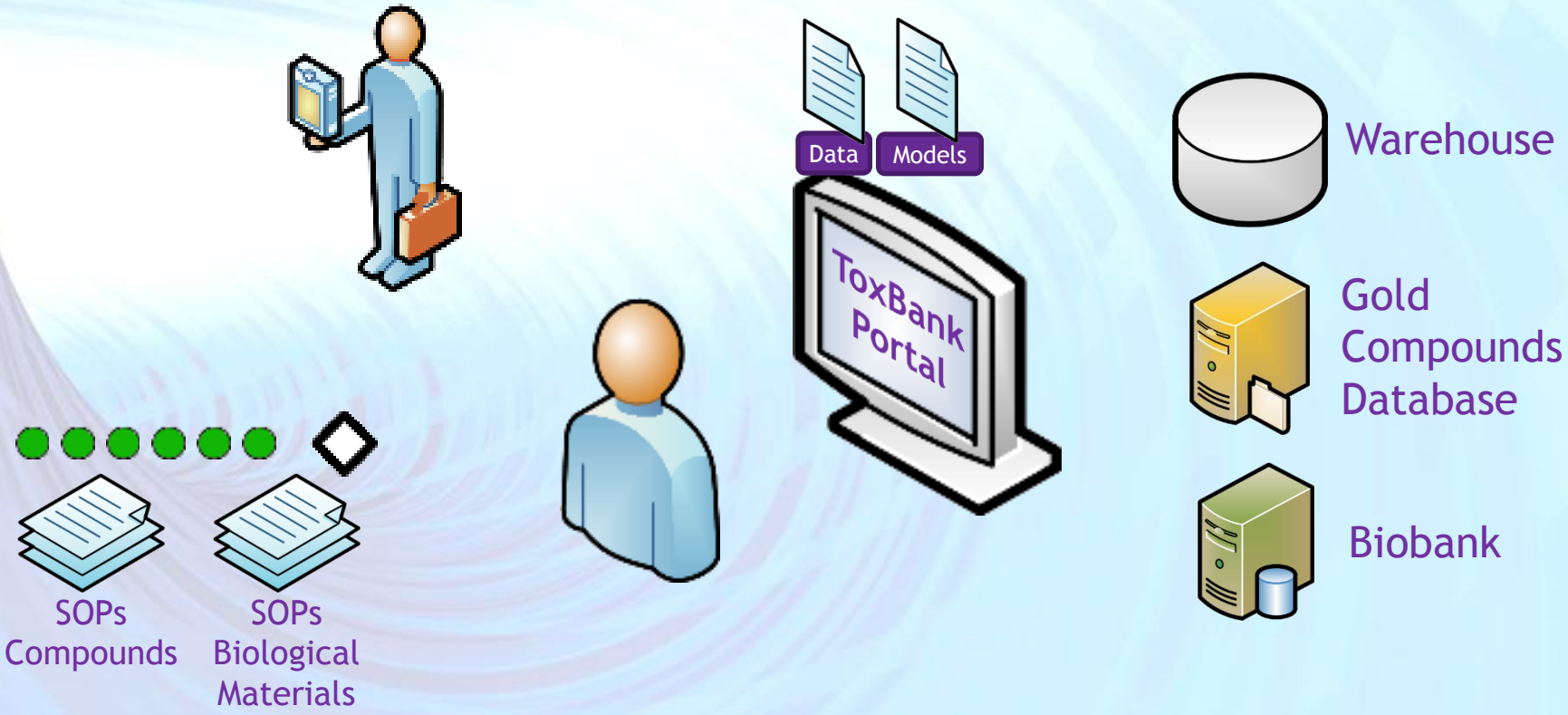
Our Infrastructure Vision for ToxBank supporting all steps of Predictive Toxicology Research based on Alternative Testing methods

User orders compounds and biological materials



This project will be jointly funded by COLIPA and the EC. Any opinions expressed in this slide are those of the author. COLIPA is not liable for any use that may be made of the information contained therein.

ToxBank Infrastructure Project (scheduled for a Jan 2011 start)

Establishment of a …

… cell and tissue banking information resource

… repository for the selected test compounds

… database of reference test compounds

… dedicated web-based data warehouse

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Our Funding Support...

For more information, visit

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OpenTox - An Open Source Predictive Toxicology Framework, www.opentox.org, is funded under the EU Seventh Framework Program: HEALTH-2007-1.3-3 Promotion, development, validation, acceptance and implementation of QSARs (Quantitative Structure-Activity Relationships) for toxicology, Project Reference Number Health-F5-2008-200787 (2008-2011).

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SEVENTH FRAMEWORK PROGRAMME