Integrated Analysis of Toxicology Data supported by ToxBank

OpenTox Euro 2013 Meeting

Mainz, Germany

October 1, 2013

Barry.Hardy@douglasconnect.com

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18M

Islands

Source: Baily Ed, U.S. Fish and Wildlife Service

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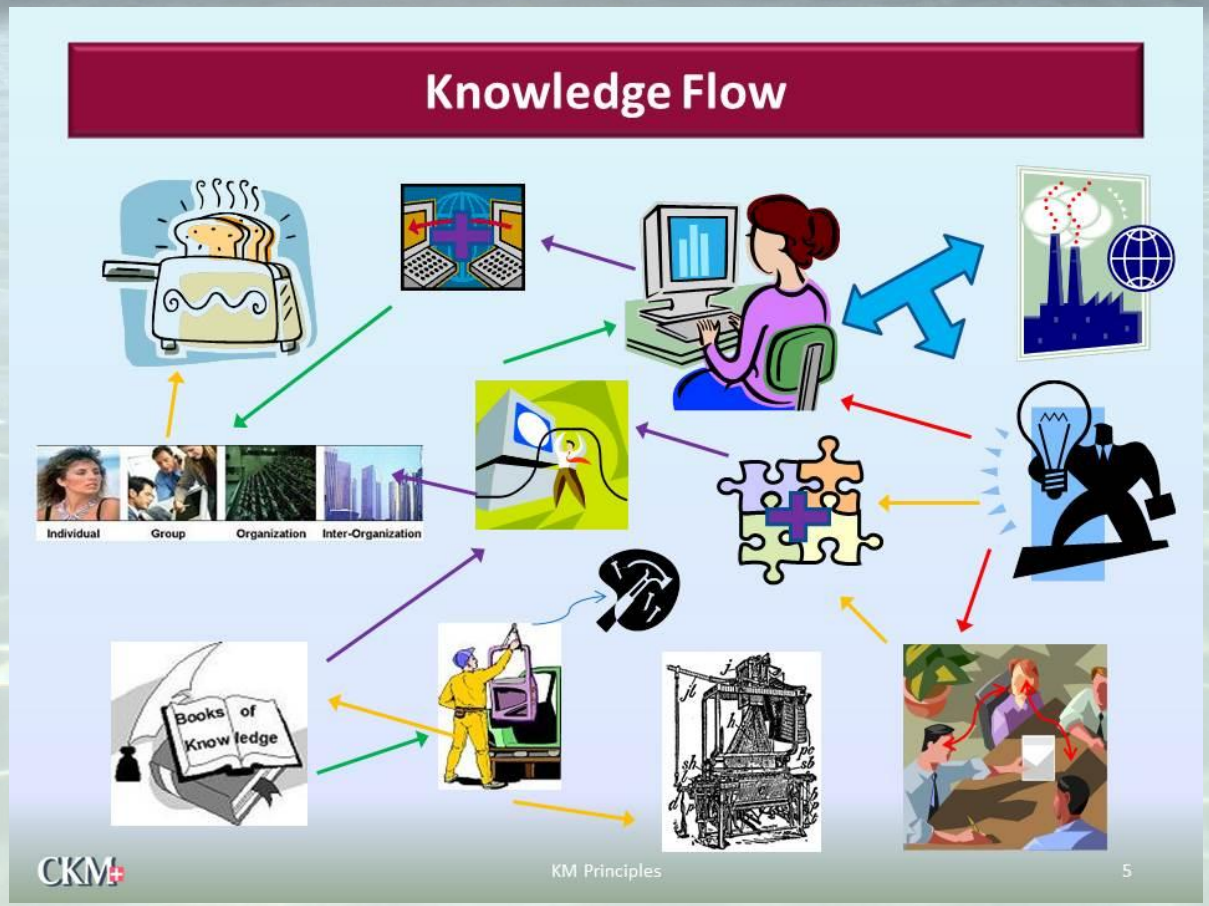
SEVENTH FRAMEWORK PROGRAMME

Goal for next year for OpenTox - Accelerating Knowledge Flow of Industry Application and Regulatory Acceptance of New Predictive Toxicology Methods & Testing Strategies based upon an evolving OpenTox framework based on Open Specifications



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SEVENTH FRAMEWORK PROGRAMME

Knowledge-Oriented Framework

Tacit

Tacit

Tacit

Knowledge Sharing: Discussions

Socialisation

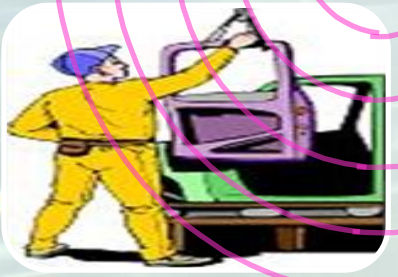
Externalisation

Explicit

Knowledge Creation from R&D: Data, Codes

Acceptance

Learning: Apply Models



Internalisation

Combination

Knowledege Combination: Predictive Models

Tacit

Explicit

Explicit

Explicit

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

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Knowledge Sharing

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OpenTox

We are an Open Knowledge Community!

We collaborate, solve problems and create the best solutions we can together.

We learn from each other.

We accelerate knowledge flow and innovation.

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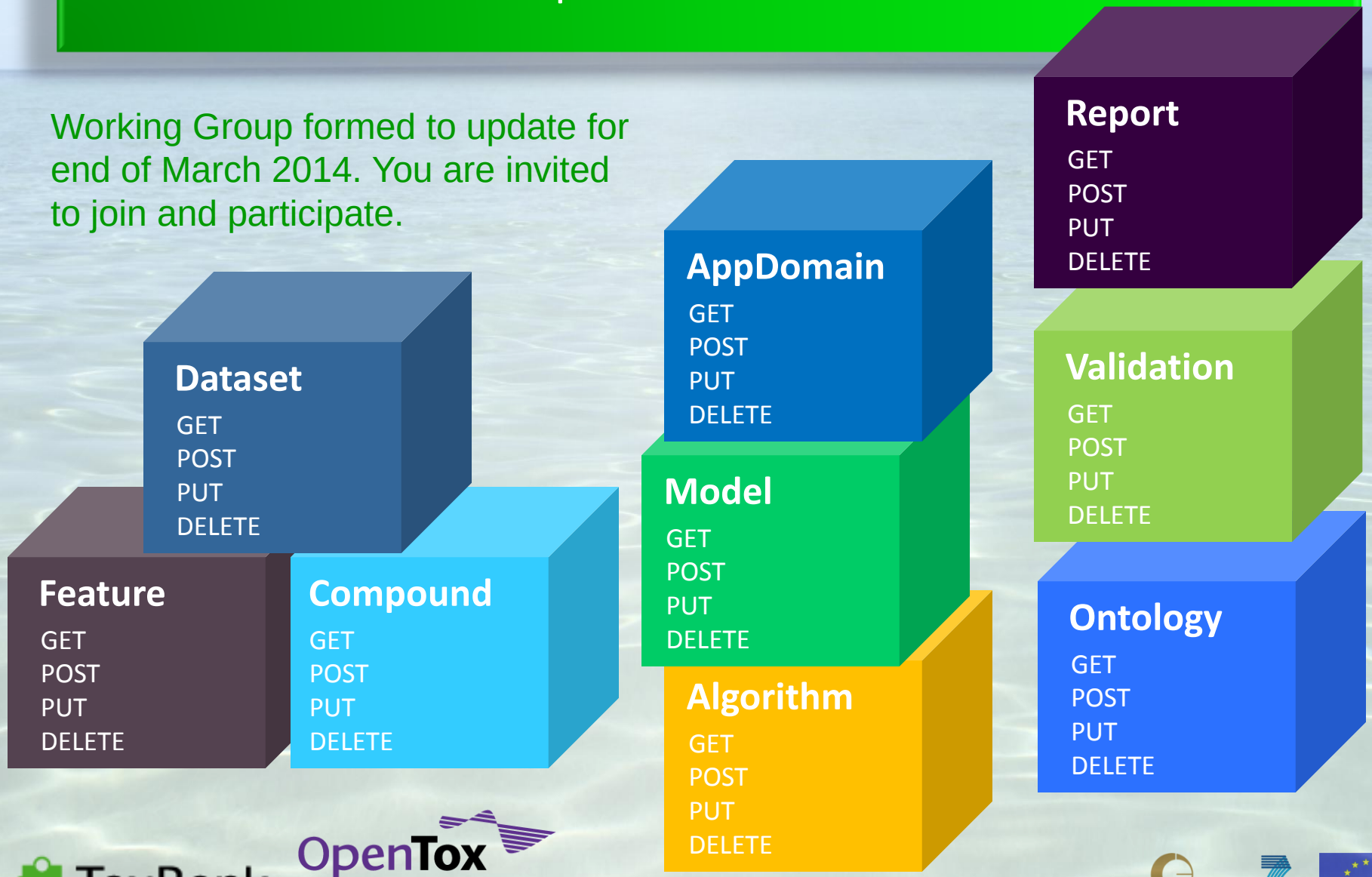
OpenTox standards

Working Group formed to update for end of March 2014. You are invited to join and participate.



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OpenTox

www.opentox.org/dev/apis/api-1.2

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Plug In Components that solve Problems

Adaptor Solution in Jeddah, 2008

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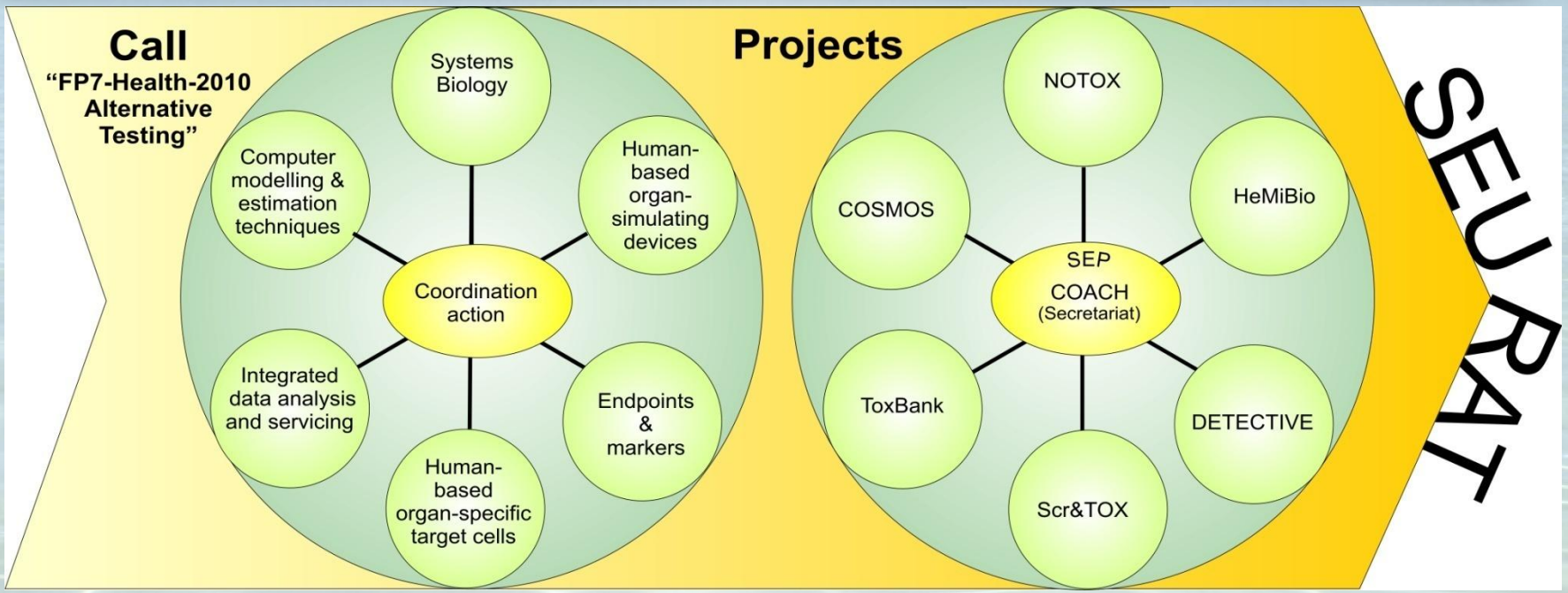
SEVENTH FRAMEWORK PROGRAMME

The Building Blocks of SEURAT-1



~ 70 research groups from European Universities, Public Research Institutes and Companies (more than 30% SMEs)

www.seurat-1.eu

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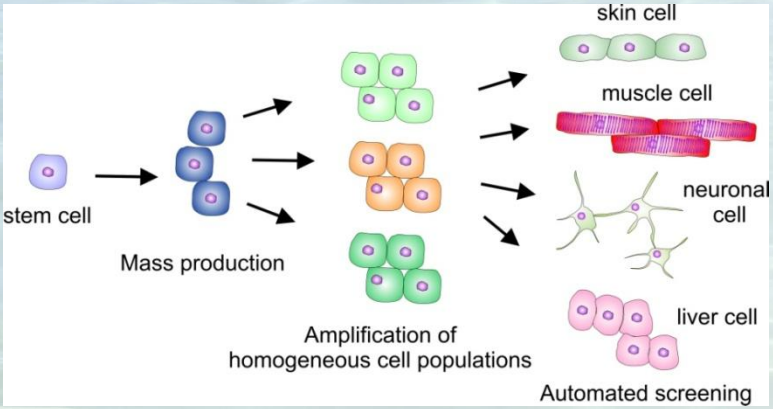
Building block 1: Scr&Tox

- Stem cell differentiation for providing human-based organ specific target cells



Coordinator:
Marc Peschanski
INSERM/i-STEM
France

website:
www.scrtox.eu

The cell factory

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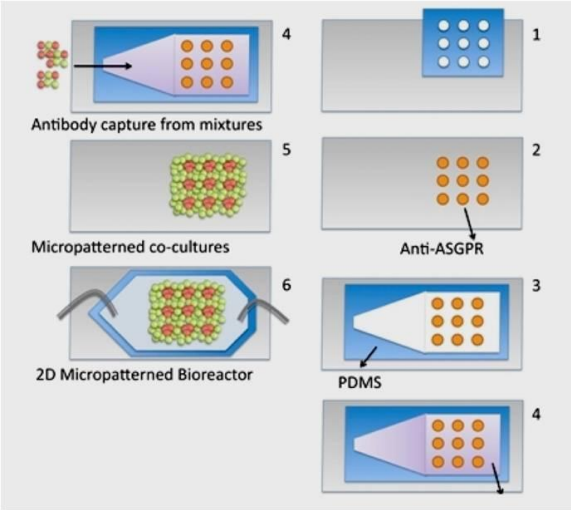
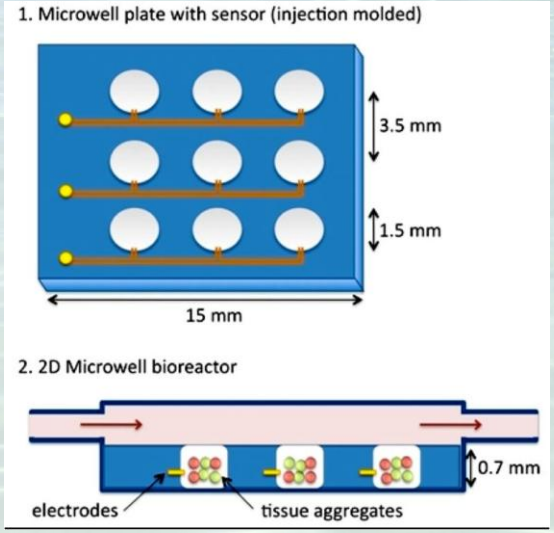
SEVENTH FRAMEWORK PROGRAMME

Building block 2: HeMiBio

- Development of a hepatic microfluidic bioreactor





Coordinator:
Catherine Verfaillie
KU LEUVEN, Belgium

website:
www.hemibio.eu

The *in vitro* liver

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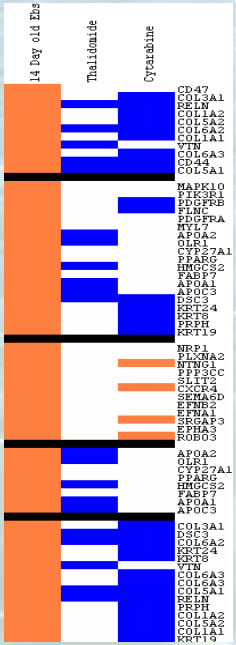
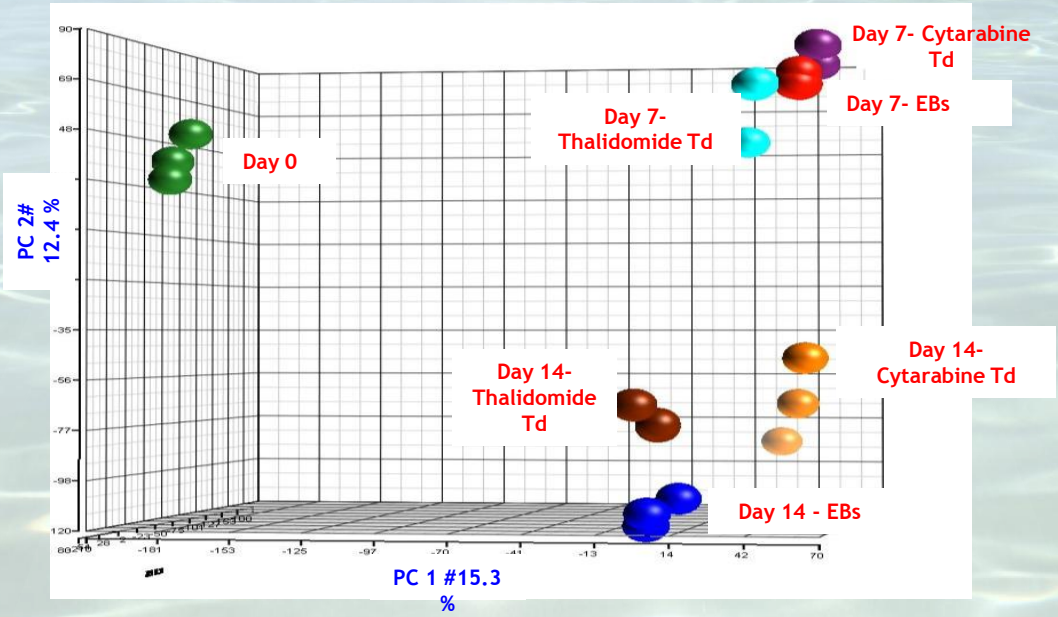
Building block 3: DETECTIVE

- Identification of biomarkers for prediction of toxicity in humans

DETECTIVE
Detection of Endpoints and Biomarkers for Repeated Dose Toxicity Using In Vitro Systems





Coordinator:
Jürgen Hescheler
Klinikum der Universität Köln, Germany

website:

Biomarkers and functional assays

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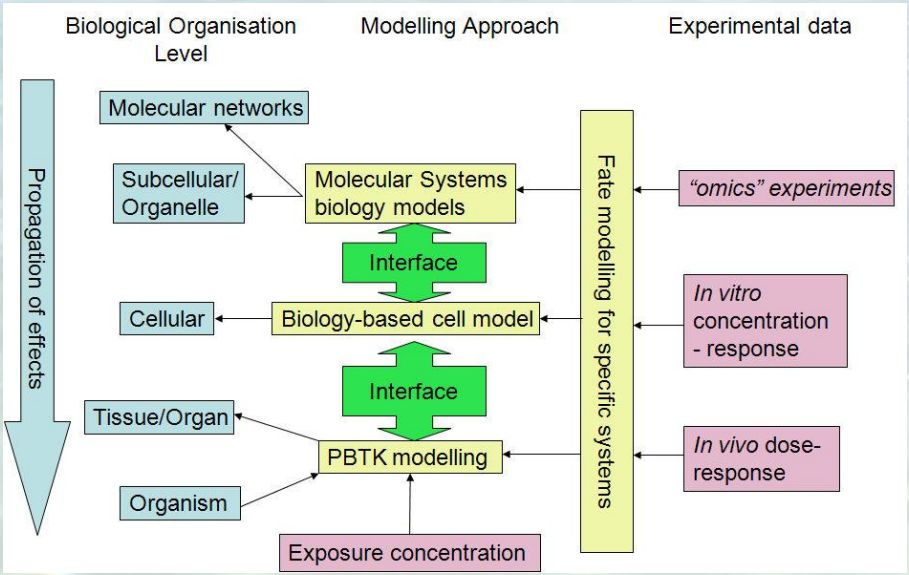
Building block 4: COSMOS

- Delivery of computational tools to predict the effects of chemicals based on *in silico* calculations and estimation techniques



Coordinator:
Mark Cronin
Liverpool John Moores University, UK

website:
www.cosmos-tox.eu

In silico toxicology

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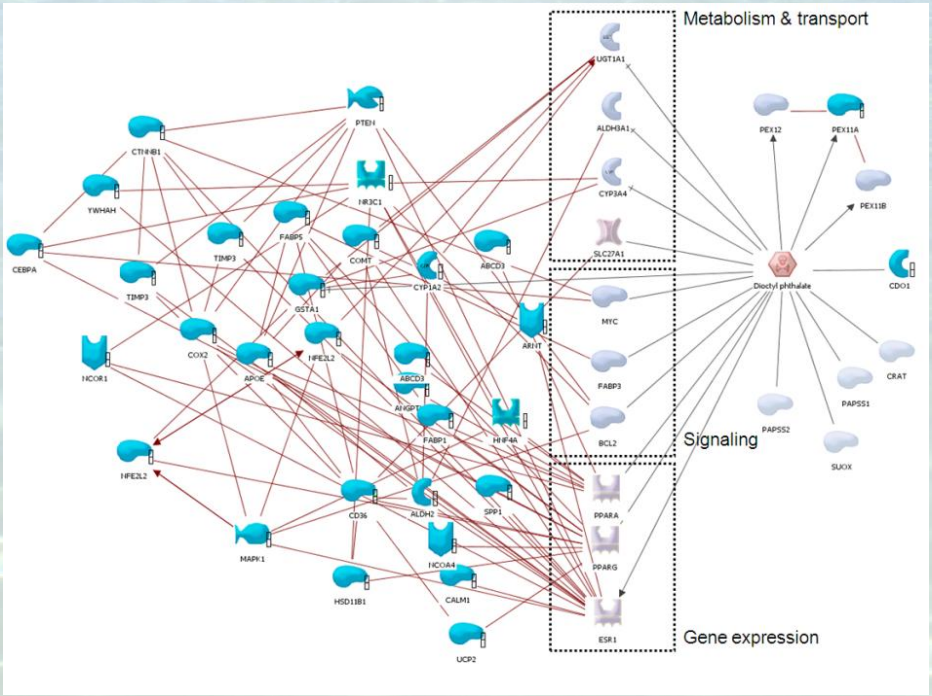
Building block 5: NOTOX

- Development of systems biological tools for organotypic human cell cultures



Coordinator:
Elmar Heinzle
Universität des Saarlandes, Germany

website:
www. notox-sb.eu

Thinking in systems

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ToxBank Infrastructure Project
(started Jan 2011)

www.toxbank.net

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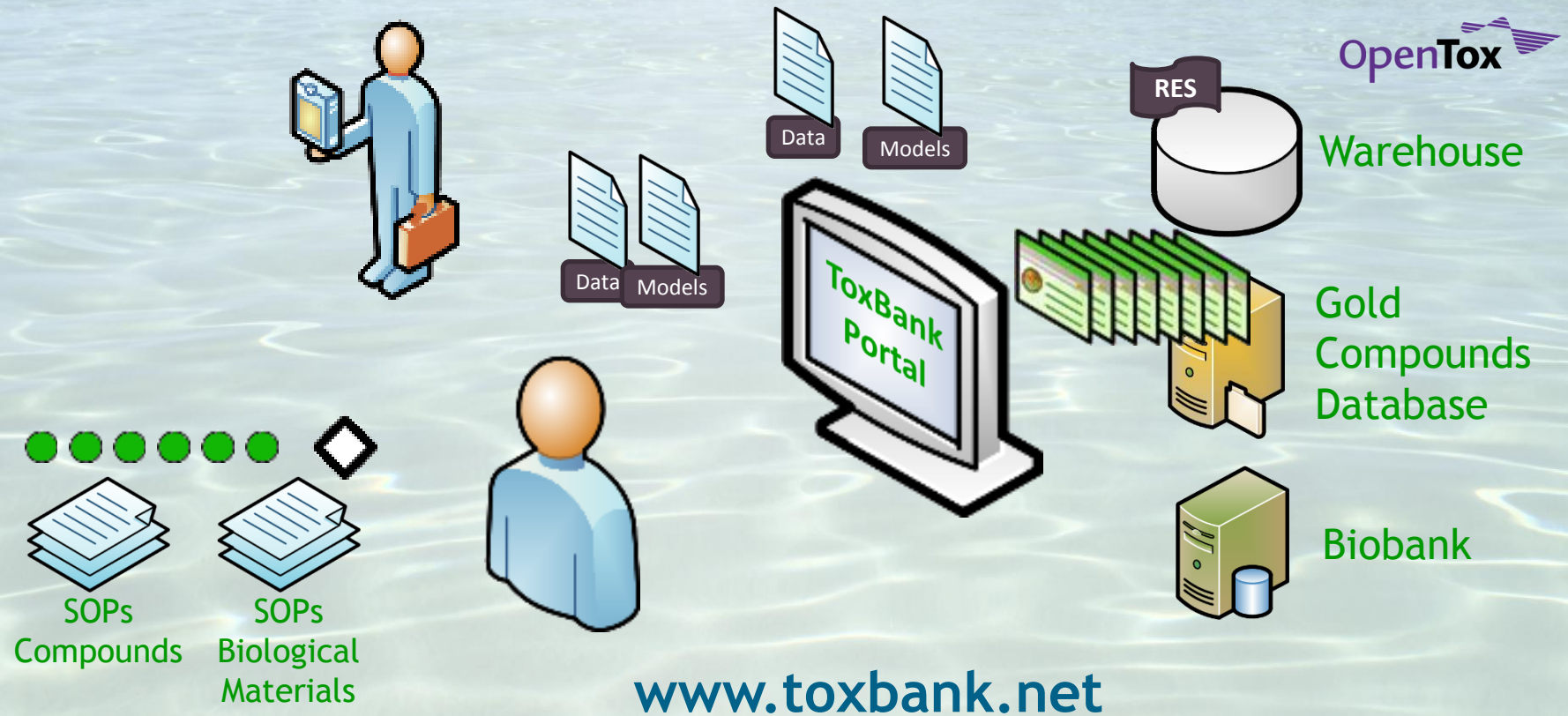
Our Infrastructure Vision for ToxBank supporting all steps of Predictive Toxicology Research based on Alternative Testing methods

Users access compounds, biological materials, data and models for experimental planning and integrated analysis of experimental results



www.toxbank.net

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SEVENTH FRAMEWORK PROGRAMME

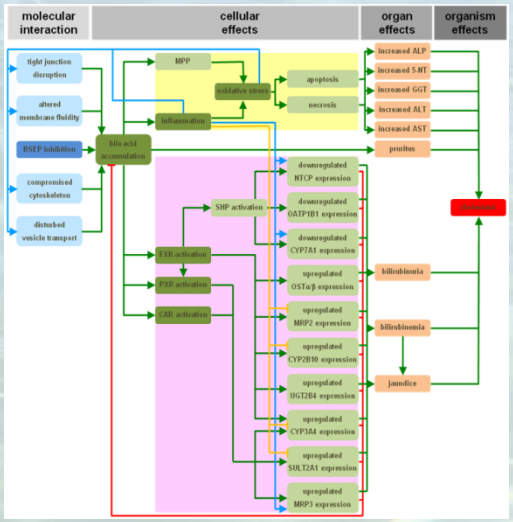
Compound Selection

- **Compound Assessment Team**: Dave Bower, Matthew Clark, Matthew Dent, Marina Goumenou, Gabrielle Hawksworth, Nina Jeliazkova, Brigitte Landesmann, Silvia Maggioni, Andrew White, Egon Willighagen, Jeffrey Wiseman
- **Gold Compound Working Group**: Roman Affentranger, Gordana Apic, Emilio Benfenati, Ian Cotgreave, Barry Hardy, Jan Hengstler, Susanne Bremer-Hoffmann, Paul Jennings, Giovanna Lazzari, Inge Mangelsdorf, Filomain Nguemo, Foozia Noor, Agapios Sachinidis, Michael Schwarz, Leo van Grunsven, Mathieu Vinken, Manfred Watzele, Jose-Manuel Zaldivar

Background Assumptions: Assay Readout Examples

- Hepatocellular necrosis: release of alanine aminotransferase and propidium iodide uptake without apoptosis
- Apoptosis: NF-κB/p53, caspase-3 activation , and Hoechst/annexin staining
- Inhibition of transporters, e.g. members of the ABC cassette transporter class
- Intra-hepatic cholestatis
- Steatosis and phospholipidosis: staining
- Hepatocyte function: urea synthesis, glycogen storage, albumin secretion, fibrinogen secretion, P450 transformation capacity
- Mitochondrial function: adenosine triphosphate (ATP) and membrane potential
- Oxidative stress: glutathione (GSH) levels & lipid peroxidation

Mapping Mechanism to Pathway



Consider adverse events relevant to cosmetics

Identify drugs demonstrated to exhibit these adverse events in humans

Add Mode of Action (MoA) standards with simpler profiles mapped against key events within Adverse Outcome Pathways (AOPs)

Add non-reactive analogues where needed

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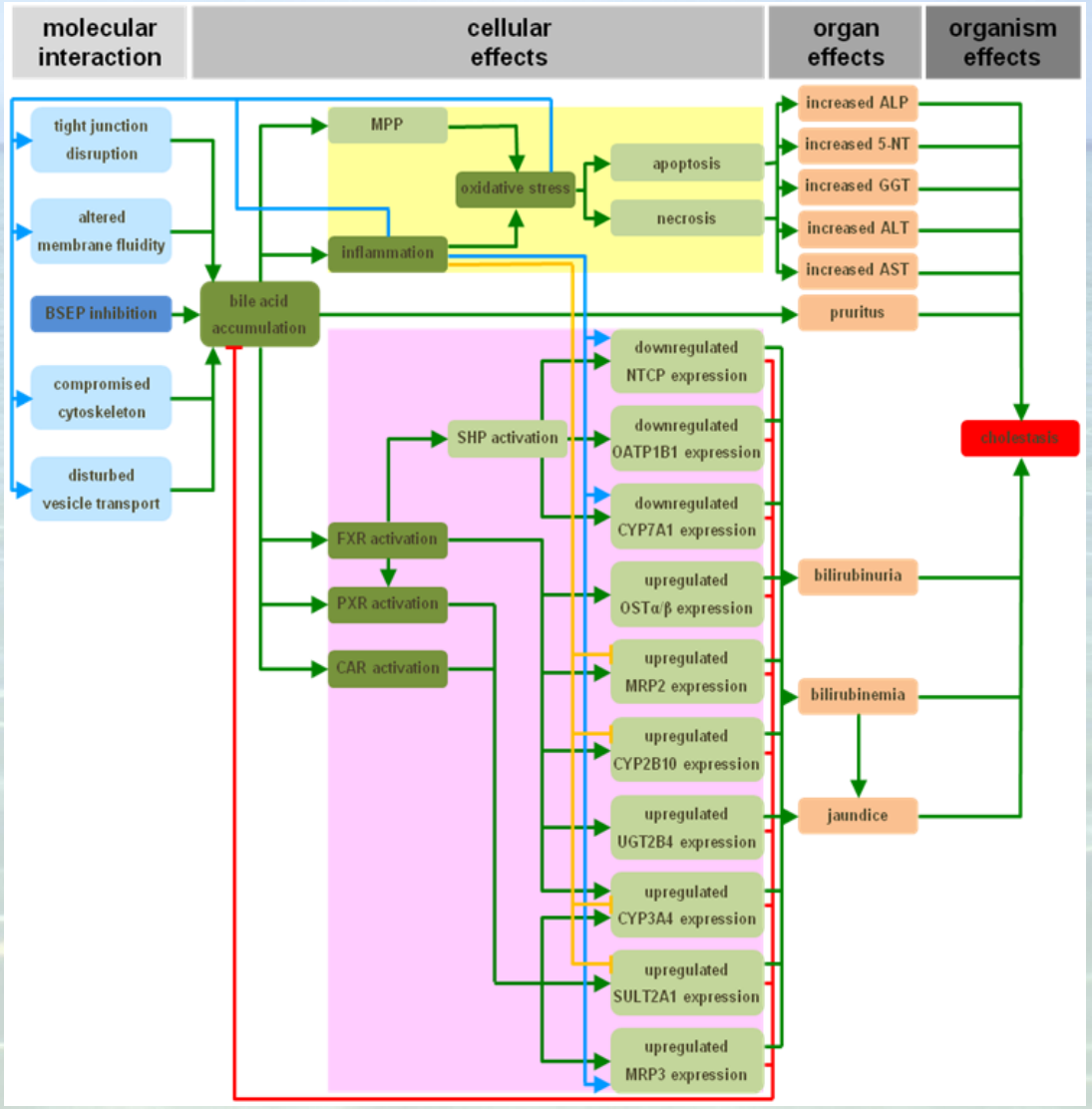
Adverse outcome pathway (AOP) : drug-induced cholestasis



Vinken M., Landesmann B., Goumenou M., Vinken S., Shah I., Jaeschke H., Willett C., Whelan M., Rogiers V. (2013) Development of an adverse outcome pathway from drug-mediated bile salt export pump inhibition to cholestatic liver injury. *Archives of Toxicology*: submitted .

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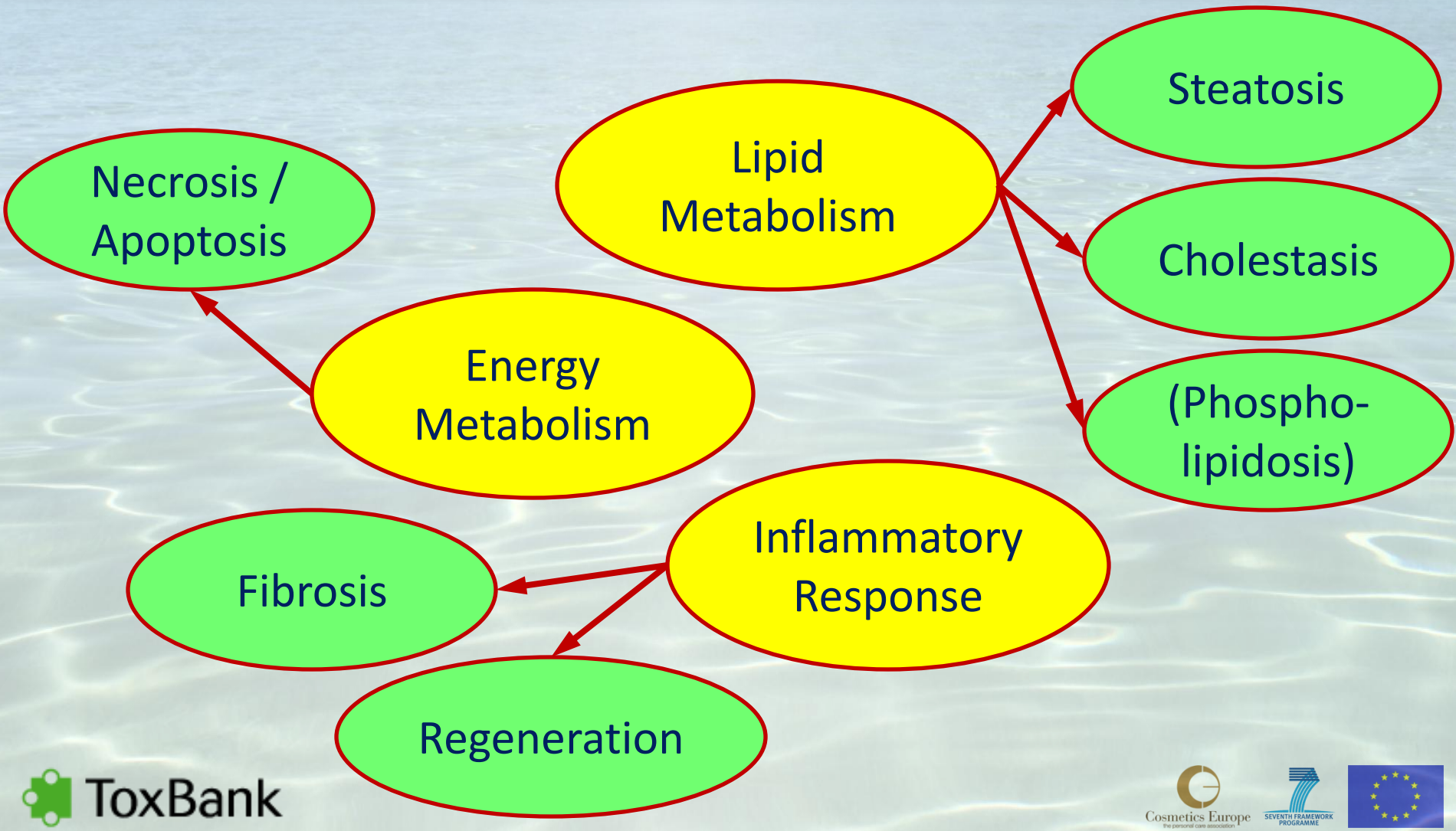
Compound Selection: Reference Toxicities to Biological Pathways



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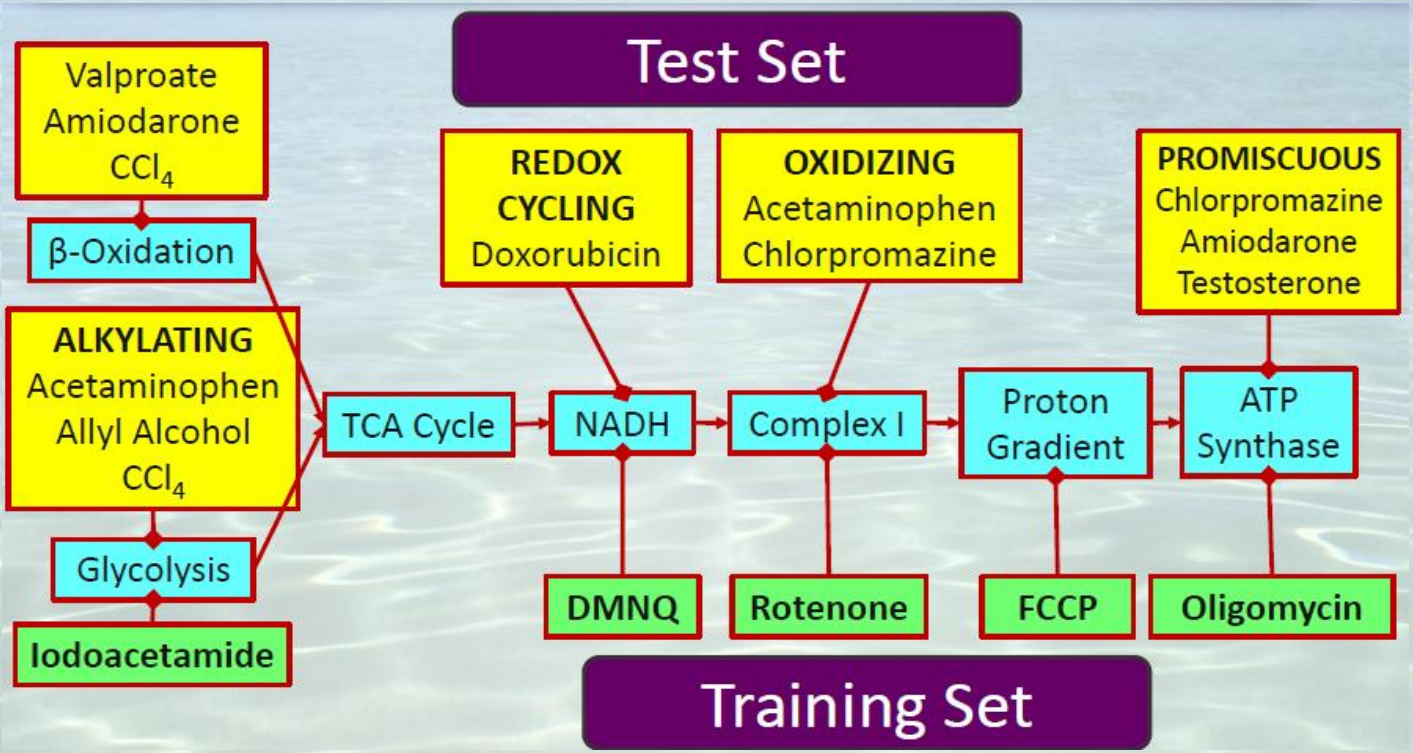
Compound Selection and Mechanistic Testing



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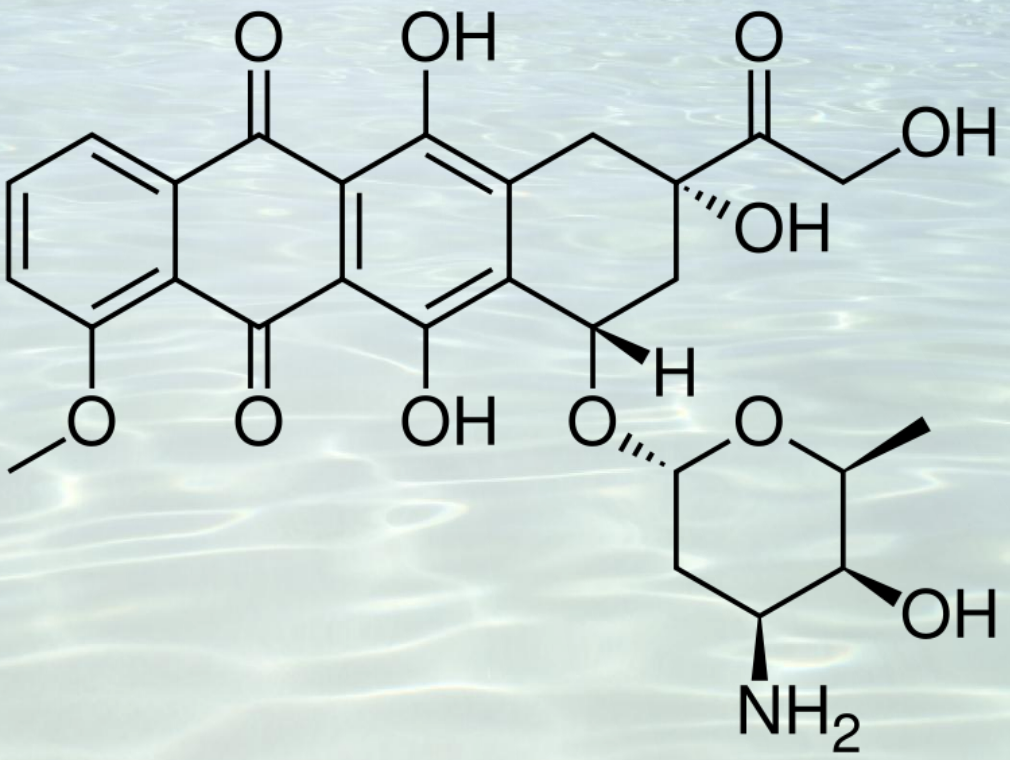
ToxBank Gold Compound - Doxorubicin



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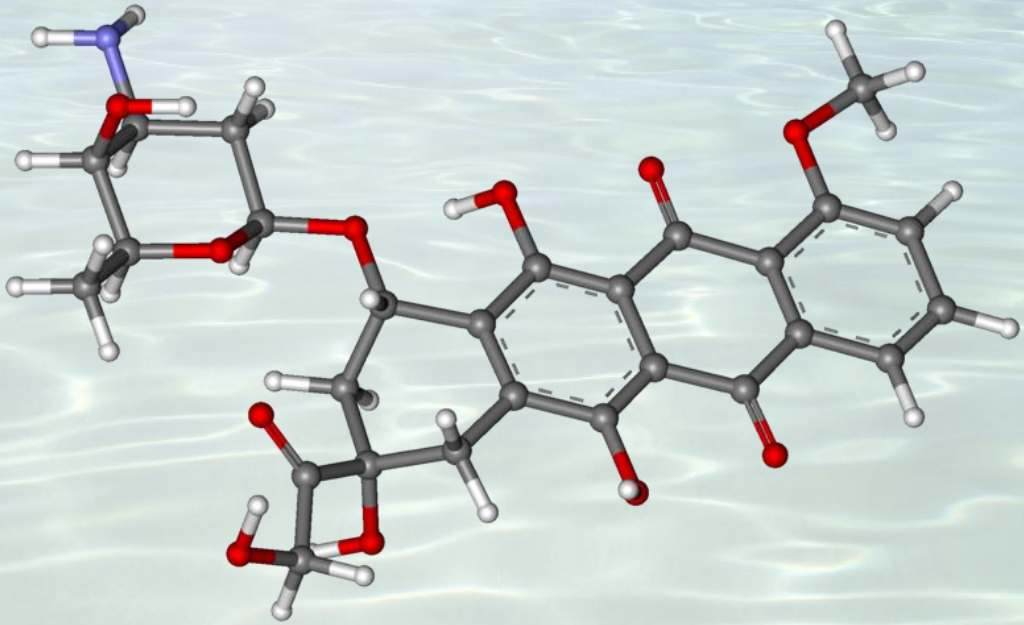
ToxBank Gold Compound - Doxorubicin



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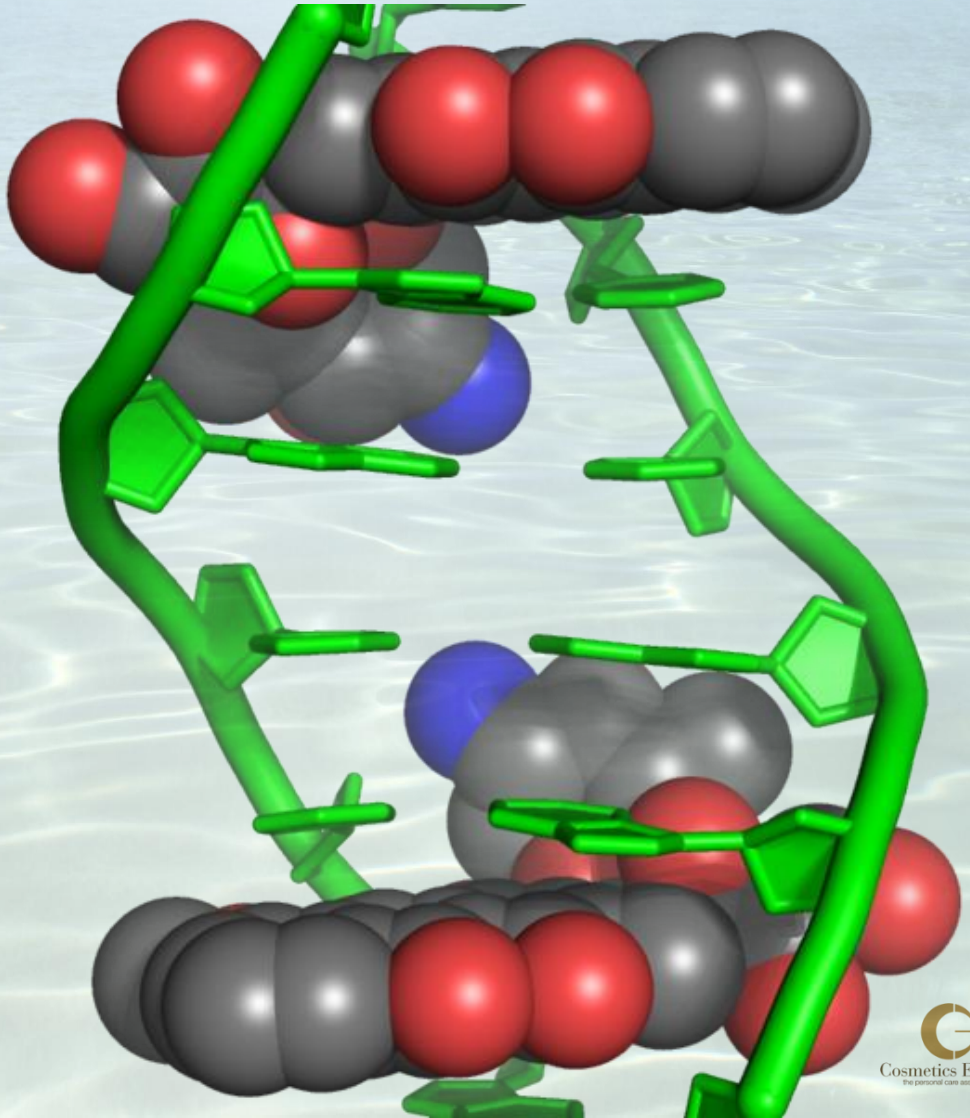
SEVENTH FRAMEWORK PROGRAMME

ToxBank Gold Compound - Doxorubicin



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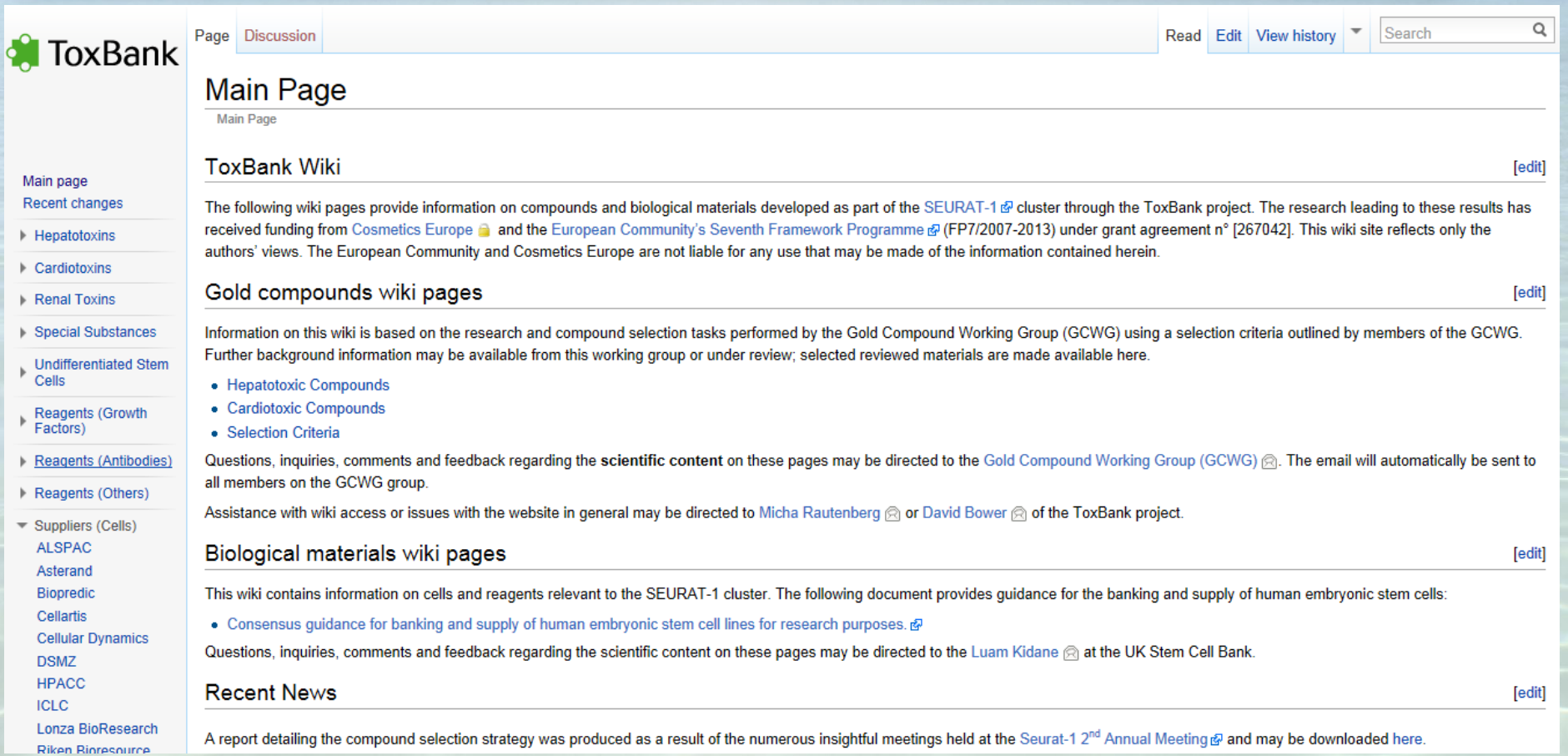
ToxBank Wiki Development



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wiki.toxbank.net

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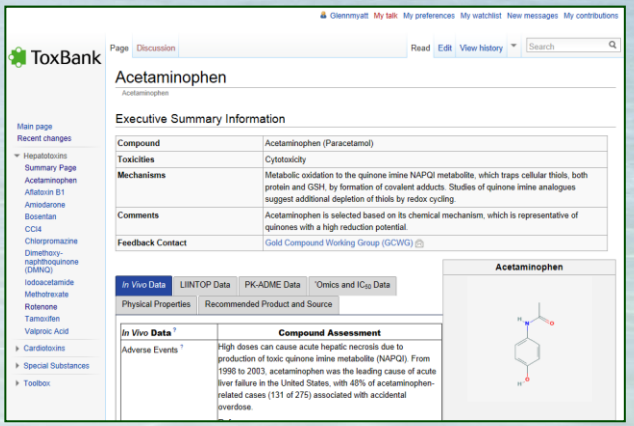
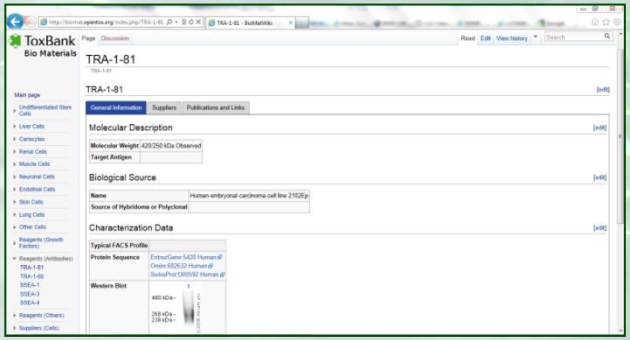
Information resources

- Gold compound wiki*
  - Information on selection criteria
  - In vivo, PB-PK data, ‘omics/IC50, physical data and sources
  - Discussion forum
- Biomaterials wiki
  - Information on cells (stem cells, hES/iPS-derived cells, primary cells), reagents (e.g. antibodies, growth factors) and suppliers
  - Discussion forum





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* See published Open Access materials at wiki.toxbank.net

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Organizing notes collected from interviews with SEURAT scientists

Hierarchically grouping the notes

Generating design ideas

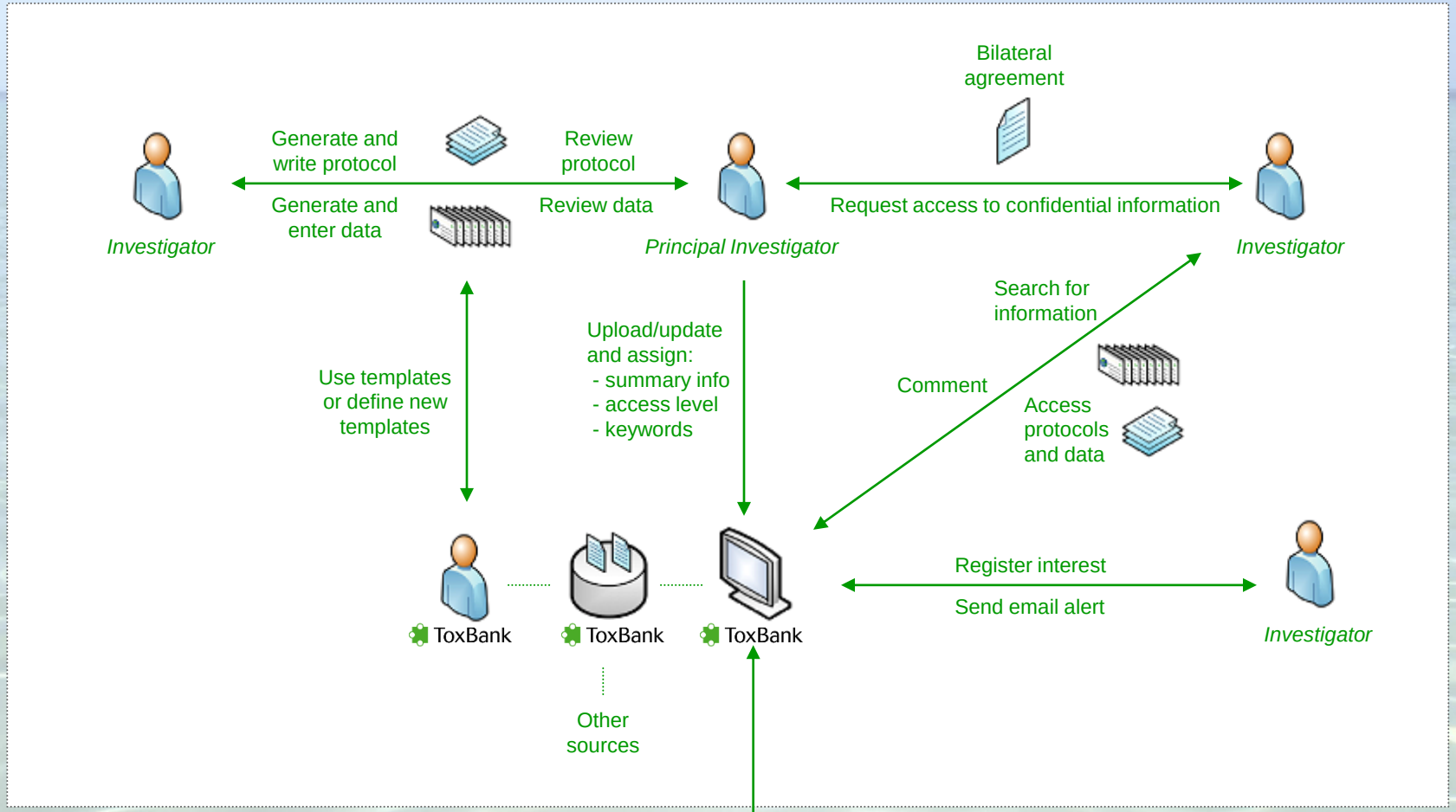
Reviewing use cases

Evaluating different approaches

Storyboarding different user interfaces

Outline of the ToxBank Data Warehouse

Phase 1: Unified data access



Phase 2: Integrated data analysis

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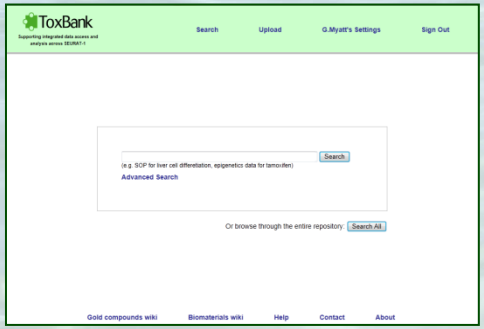
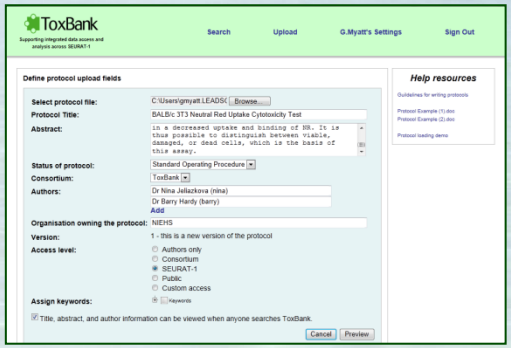
ToxBank – Initial Release & Testing

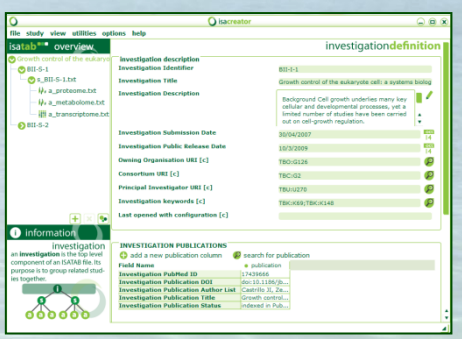
Main screen



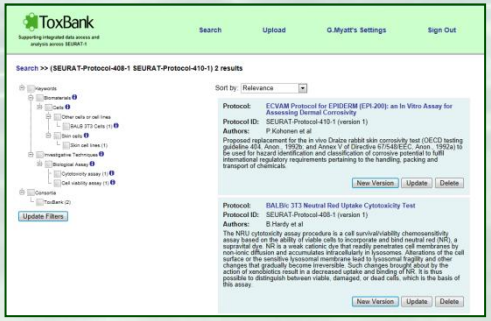
Upload protocols and data



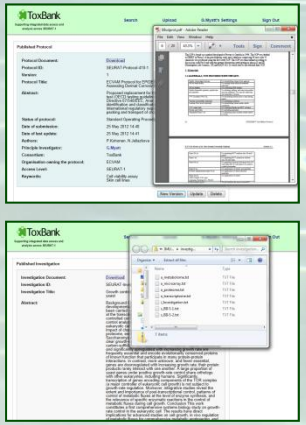
Preparing data



Browse search results



Download protocols and data



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SEVENTH FRAMEWORK PROGRAMME

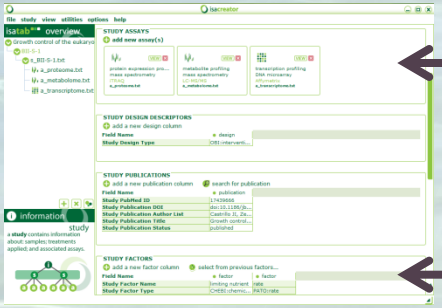
Use of SEURAT-configured ISAcreator to prepare datasets

Investigation information

SEURAT-1 information

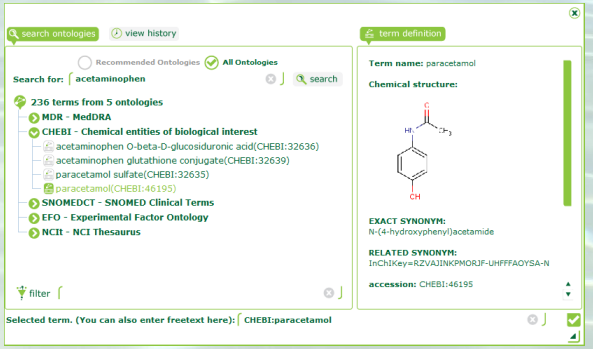
Publications

Each step linked to a SEURAT-1 protocol

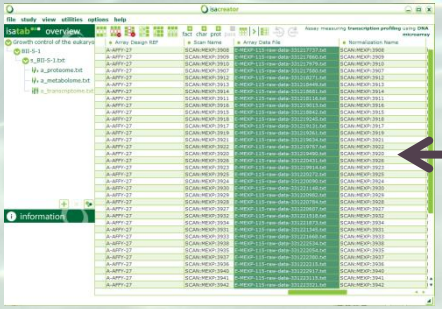


Templates for different assays

Specify experimental factors



Terms mapped to ontologies



Materials and results, with links to files containing the raw or processed data

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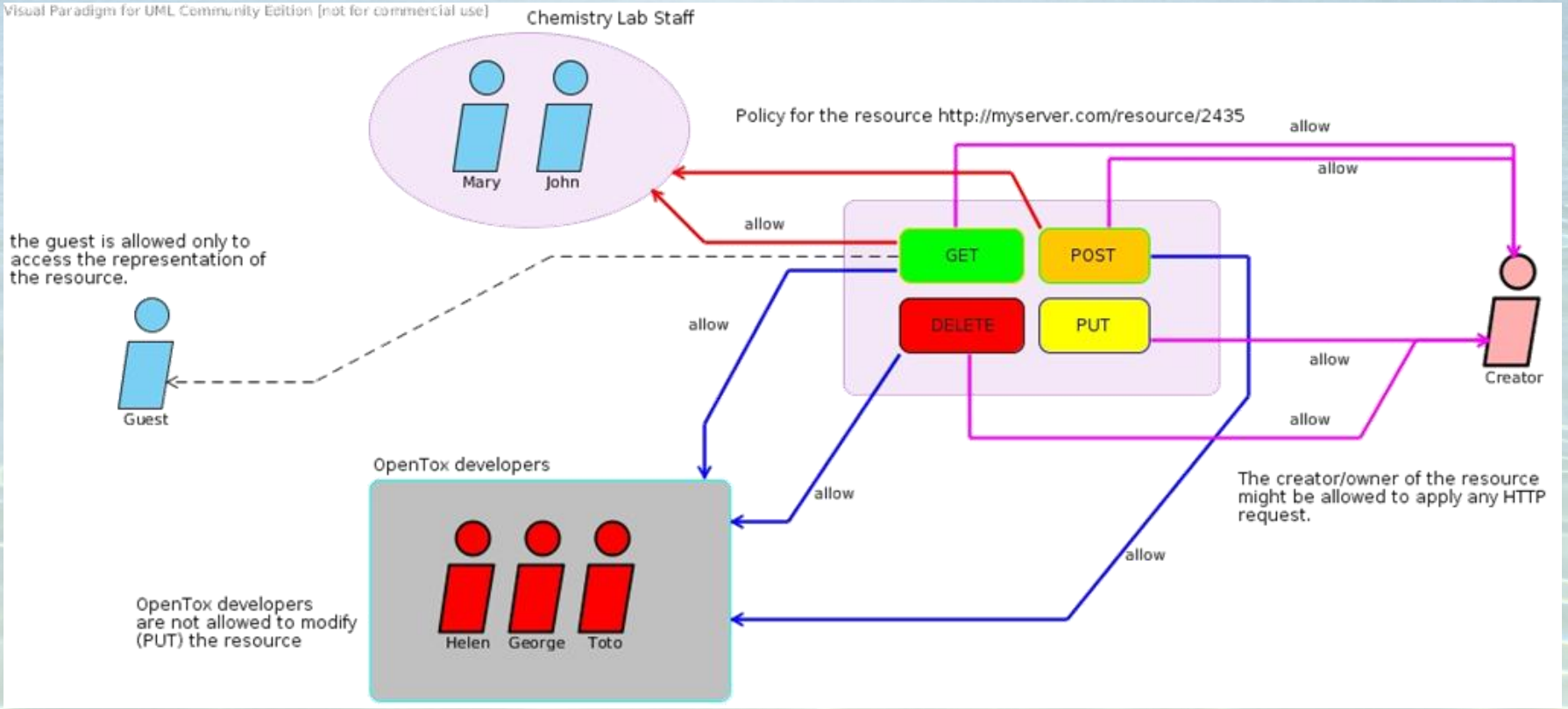
Security



Use Open Standards on Resources but with extensive Authorisation and Authentication facilities accompanied by confidential data policies. e.g. *Validation against Confidential Data Case implemented Spring 2011*

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SEVENTH FRAMEWORK PROGRAMME

ToxBank System for Data and Protocol Management

Uploading protocols and data

Main screen

Upload and set email alerts

Upload protocols

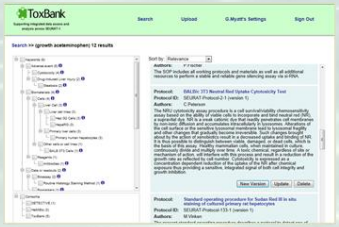
Upload data

Prepare datasets with ISAcreator

Searching

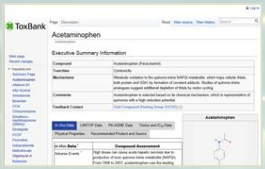
Main screen

Browse search results



Download protocols and data

Access related information



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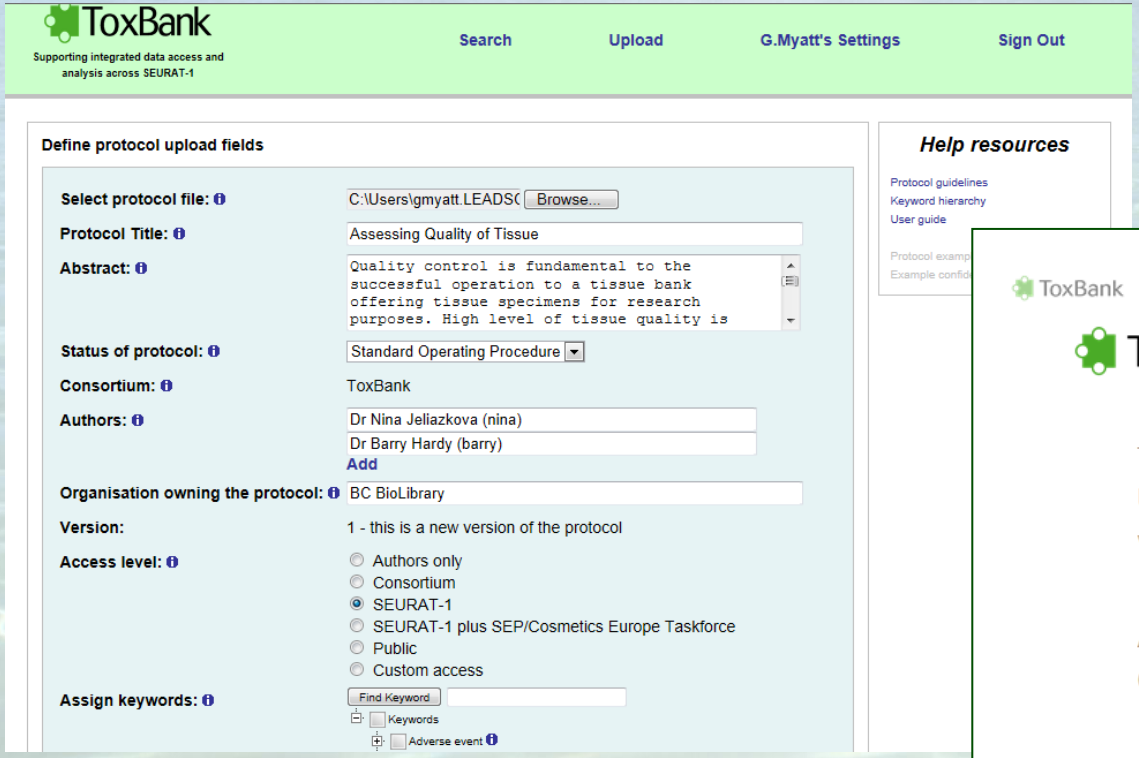
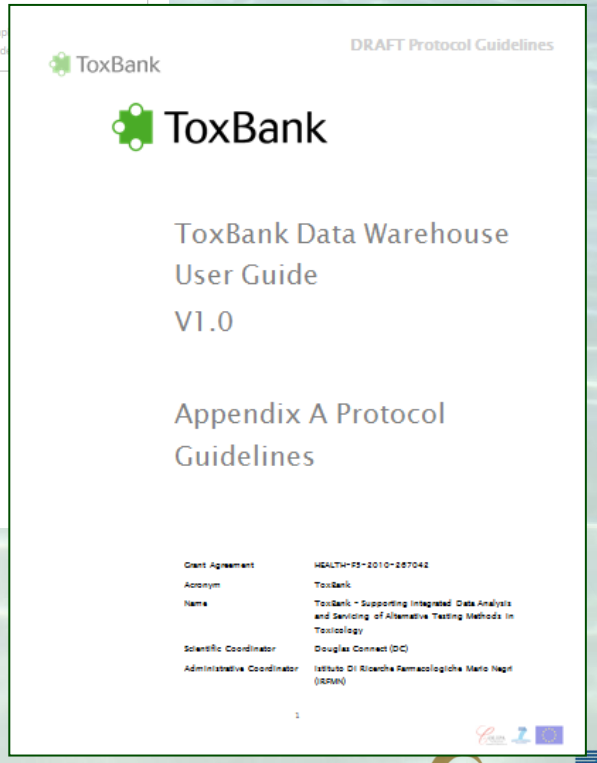
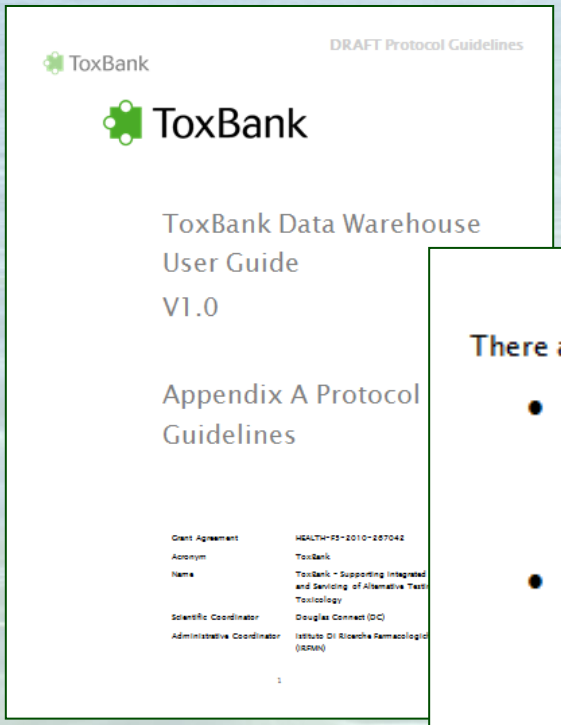
Uploading a protocol





Research Protocol vs. Standard Operating Procedure


DRAFT Protocol Guidelines

ToxBank

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ToxBank Data Warehouse
User Guide
V1.0

Appendix A Protocol
Guidelines

Grant Agreement	HEALTH-F5-2010-267042
Acronym	ToxBank
Name	ToxBank - Supporting Integrated and Servicing of Alternative Testi Toxicology
Scientific Coordinator	Douglas Connect (DC)
Administrative Coordinator	Istituto Di Ricerche Farmacologic (IRFMN)

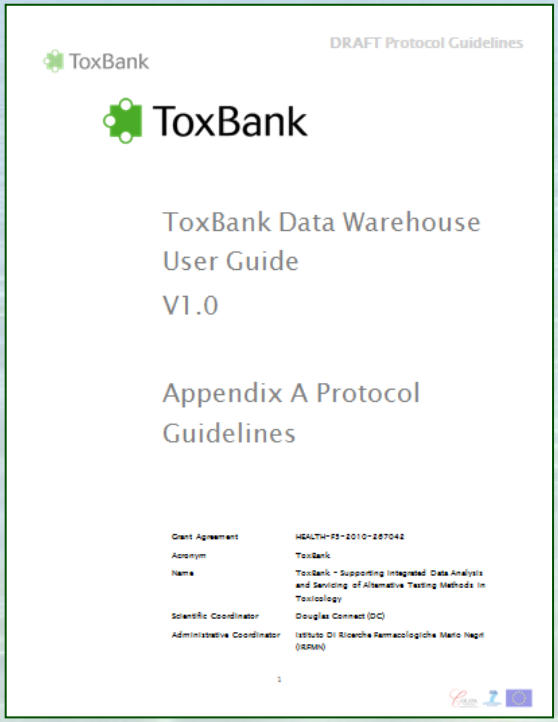
1

1.2. Types of Protocols

There are two types of protocols that can be uploaded into the ToxBank Data Warehouse:

- **Research protocols**: This is defined as documentation for procedures that are still in development; however, access to the method by other laboratories is considered useful. At a minimum the documentation should include a stepwise protocol, reagent list and key technical advice.
- **Standard operating procedures**: A Standard Operating Procedure or SOP should contain specific elements including: a stepwise protocol, reagent list/catalog numbers, supplementary procedures for reagent preparation, safety notes/COSHH assessment, and technical tips critical to method performance. Additional documentation which reports a series of results with the method including control and/or reference material values to demonstrate method performance should be provided within this structured SOP. This should enable the method to be transferred to other laboratories without the need for additional information. The procedure should be repeated by an independent group.

Guidelines provides suggestions on protocol outline and content



DRAFT Protocol Guidelines

ToxBank

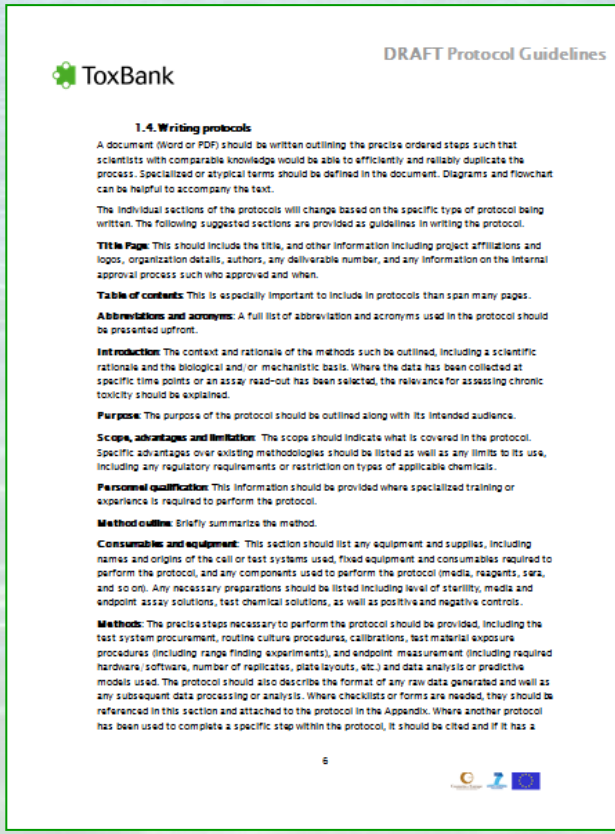
ToxBank

ToxBank Data Warehouse
User Guide
V1.0

Appendix A Protocol
Guidelines

Grant Agreement	HEALTH-F5-2010-267042
Acronym	ToxBank
Name	ToxBank - Supporting Integrated Data Analysis and Servicing of Alternative Testing Methods in Toxicology
Scientific Coordinator	Douglas Connect (DC)
Administrative Coordinator	Istituto Di Ricerche Farmacologiche Mario Negri (IRFMN)

1



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1.4. Writing protocols

A document (Word or PDF) should be written outlining the precise ordered steps such that scientists with comparable knowledge would be able to efficiently and reliably duplicate the process. Specialized or atypical terms should be defined in the document. Diagrams and flowchart can be helpful to accompany the text.

The individual sections of the protocols will change based on the specific type of protocol being written. The following suggested sections are provided as guidelines in writing the protocol.

Title Page: This should include the title, and other information including project affiliations and logos, organization details, authors, any deliverable number, and any information on the internal approval process such who approved and when.

Table of contents: This is especially important to include in protocols than span many pages.

Abbreviations and acronyms: A full list of abbreviation and acronyms used in the protocol should be presented upfront.

Introduction: The context and rationale of the methods such be outlined, including a scientific rationale and the biological and/or mechanistic basis. Where the data has been collected at specific time points or an assay read-out has been selected, the relevance for assessing chronic toxicity should be explained.

Purpose: The purpose of the protocol should be outlined along with its intended audience.

Scope, advantages and limitation: The scope should indicate what is covered in the protocol. Specific advantages over existing methodologies should be listed as well as any limits to its use, including any regulatory requirements or restriction on types of applicable chemicals.

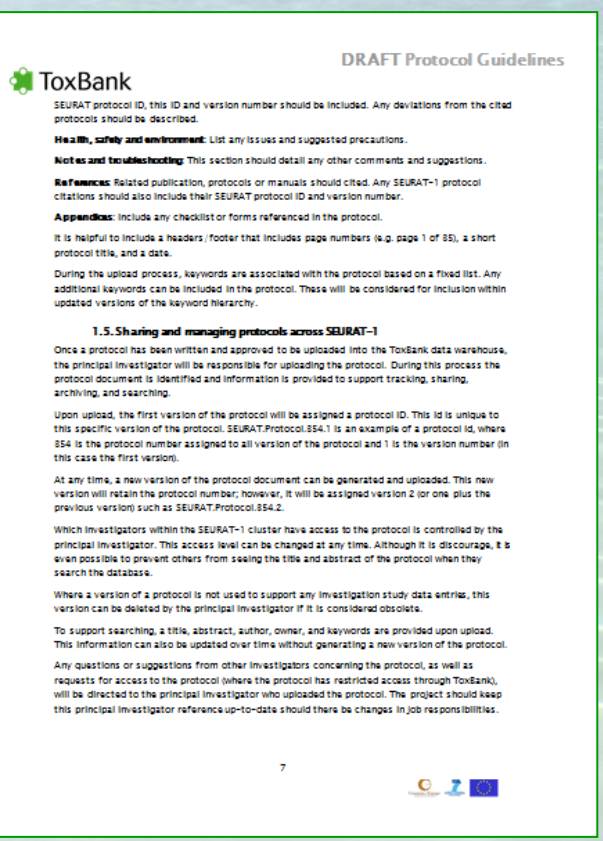
Personnel qualification: This information should be provided where specialized training or experience is required to perform the protocol.

Method outline: Briefly summarize the method.

Consumables and equipment: This section should list any equipment and supplies, including names and origins of the cell or test systems used, fixed equipment and consumables required to perform the protocol, and any components used to perform the protocol (media, reagents, sera, and so on). Any necessary preparations should be listed including level of sterility, media and endpoint assay solutions, test chemical solutions, as well as positive and negative controls.

Methods: The precise steps necessary to perform the protocol should be provided, including the test system procurement, routine culture procedures, calibrations, test material exposure procedures (including range finding experiments), and endpoint measurement (including required hardware/software, number of replicates, plate layouts, etc.) and data analysis or predictive models used. The protocol should also describe the format of any raw data generated and well as any subsequent data processing or analysis. Where checklists or forms are needed, they should be referenced in this section and attached to the protocol in the Appendix. Where another protocol has been used to complete a specific step within the protocol, it should be cited and if it has a

6



DRAFT Protocol Guidelines

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SEURAT protocol ID, this ID and version number should be included. Any deviations from the cited protocols should be described.

Health, safety and environment: List any issues and suggested precautions.

Notes and troubleshooting: This section should detail any other comments and suggestions.

References: Related publication, protocols or manuals should cited. Any SEURAT-1 protocol citations should also include their SEURAT protocol ID and version number.

Appendices: Include any checklist or forms referenced in the protocol.

It is helpful to include a header / footer that includes page numbers (e.g. page 1 of 85), a short protocol title, and a date.

During the upload process, keywords are associated with the protocol based on a fixed list. Any additional keywords can be included in the protocol. These will be considered for inclusion within updated versions of the keyword hierarchy.

1.5. Sharing and managing protocols across SEURAT-1

Once a protocol has been written and approved to be uploaded into the ToxBank data warehouse, the principal investigator will be responsible for uploading the protocol. During this process the protocol document is identified and information is provided to support tracking, sharing, archiving, and searching.

Upon upload, the first version of the protocol will be assigned a protocol ID. This id is unique to this specific version of the protocol. SEURAT.Protocol.854.1 is an example of a protocol id, where 854 is the protocol number assigned to all version of the protocol and 1 is the version number (in this case the first version).

At any time, a new version of the protocol document can be generated and uploaded. This new version will retain the protocol number; however, it will be assigned version 2 (or one plus the previous version) such as SEURAT.Protocol.854.2.

Which investigators within the SEURAT-1 cluster have access to the protocol is controlled by the principal investigator. This access level can be changed at any time. Although it is discourage, it is even possible to prevent others from seeing the title and abstract of the protocol when they search the database.

Where a version of a protocol is not used to support any investigation study data entries, this version can be deleted by the principal investigator if it is considered obsolete.

To support searching, a title, abstract, author, owner, and keywords are provided upon upload. This information can also be updated over time without generating a new version of the protocol.

Any questions or suggestions from other investigators concerning the protocol, as well as requests for access to the protocol (where the protocol has restricted access through ToxBank), will be directed to the principal investigator who uploaded the protocol. The project should keep this principal investigator reference up-to-date should there be changes in job responsibilities.

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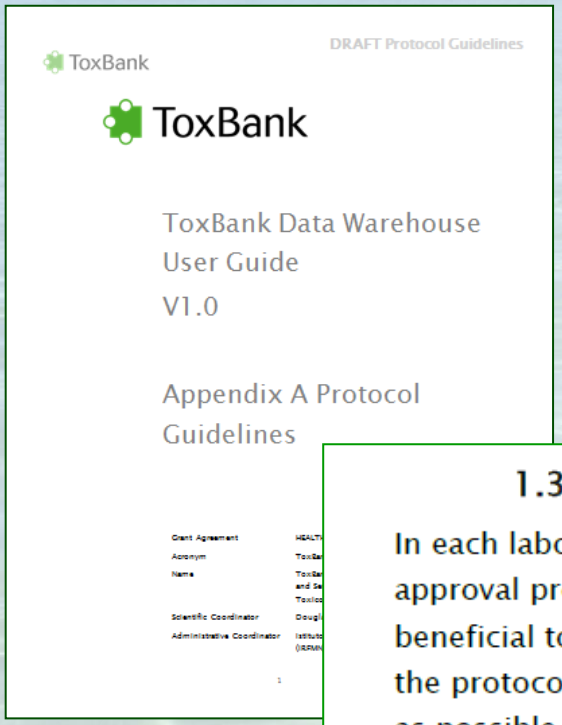
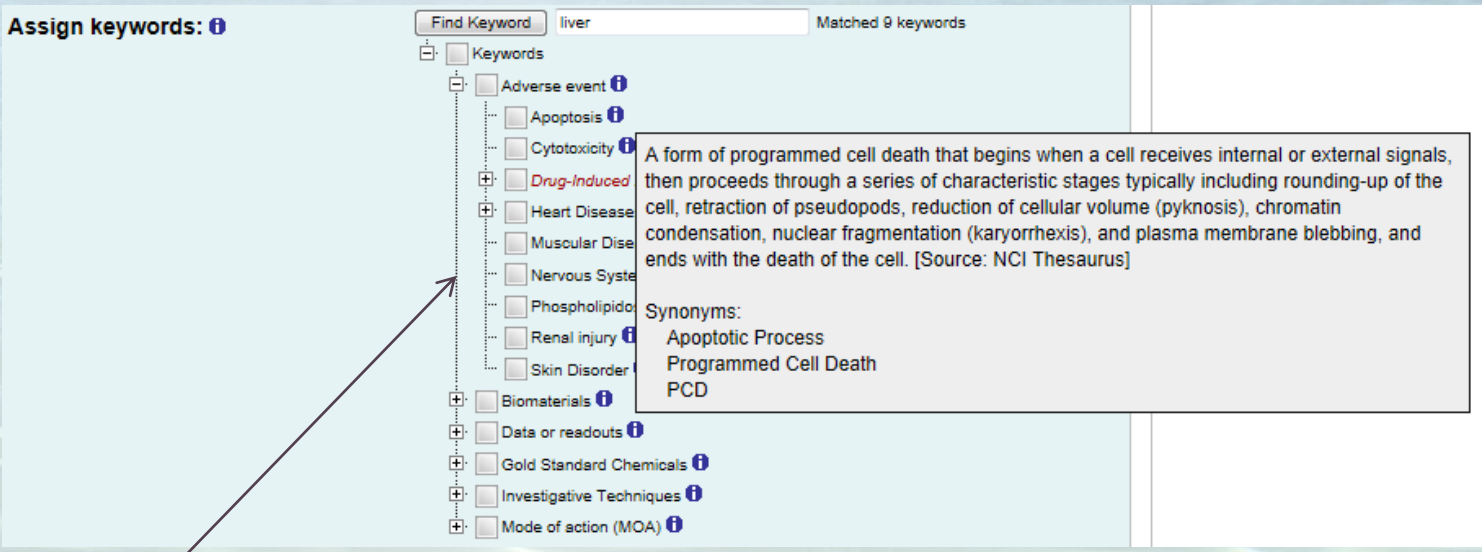
Protocol review



1.3. Protocol preparation and approval

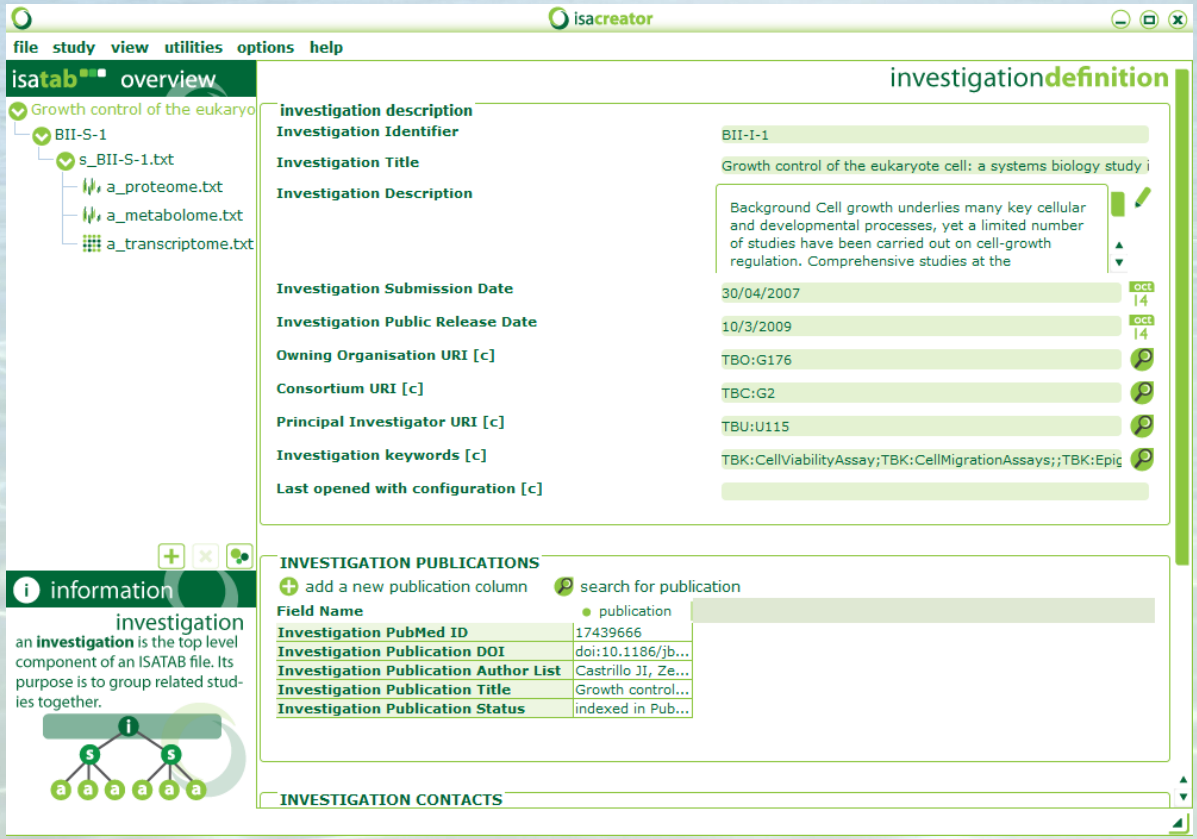
In each laboratory, it is important that a protocol is appropriately reviewed using any internal approval process prior to uploading the protocol into ToxBank. During the process, it would be beneficial to have someone inside the lab, not involved in writing the protocol document, to test the protocol prior to release. It is desirable to make the protocols available to as many scientists as possible in the cluster; however, there are reasons for restricting access to the protocol such as a pending publication or intellectual property issues. It is possible to upload a protocol and restrict access to the protocol, which can be changed over time.

Protocols are indexed using a keyword hierarchy



Set keywords to support searching, browsing and linking

Use of SEURAT-configured ISAcreator to prepare datasets



Investigation information

SEURAT-1 information

Publications

Templates are available for different experiments

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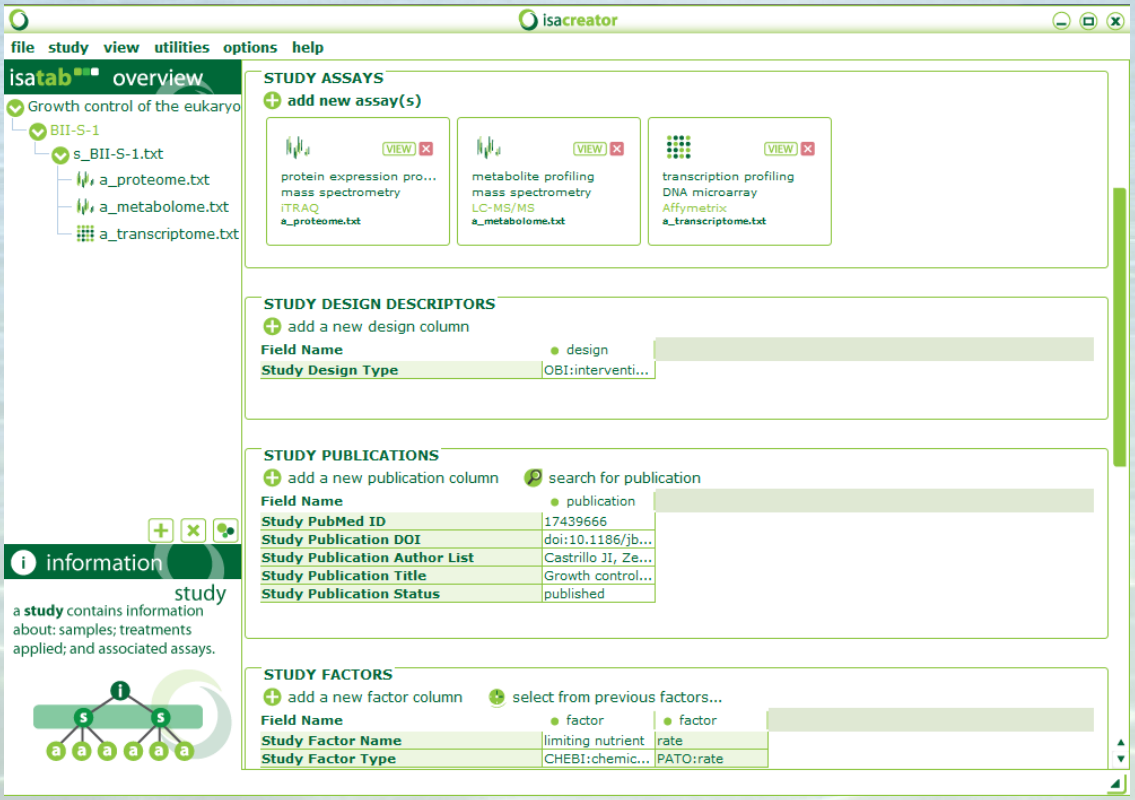
Use of SEURAT-configured ISAcreator to prepare datasets



Templates for different assays

Specify experimental factors

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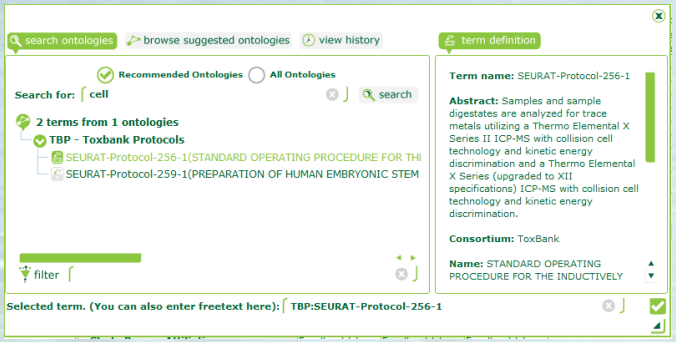
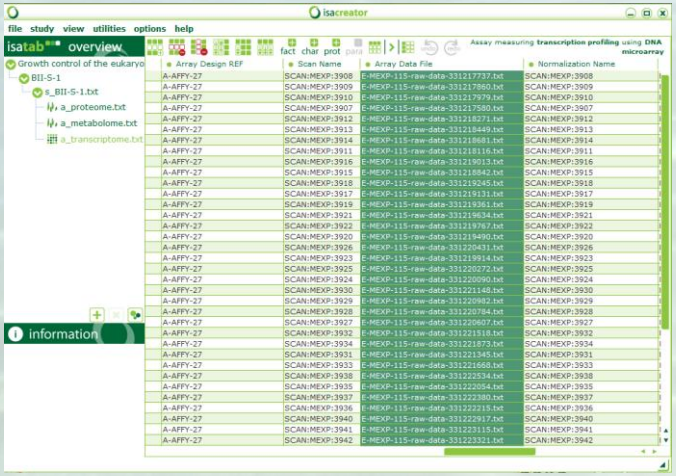


Results, with each step linked to a SEURAT-1 protocol



Results, with links to files containing the raw or processed data

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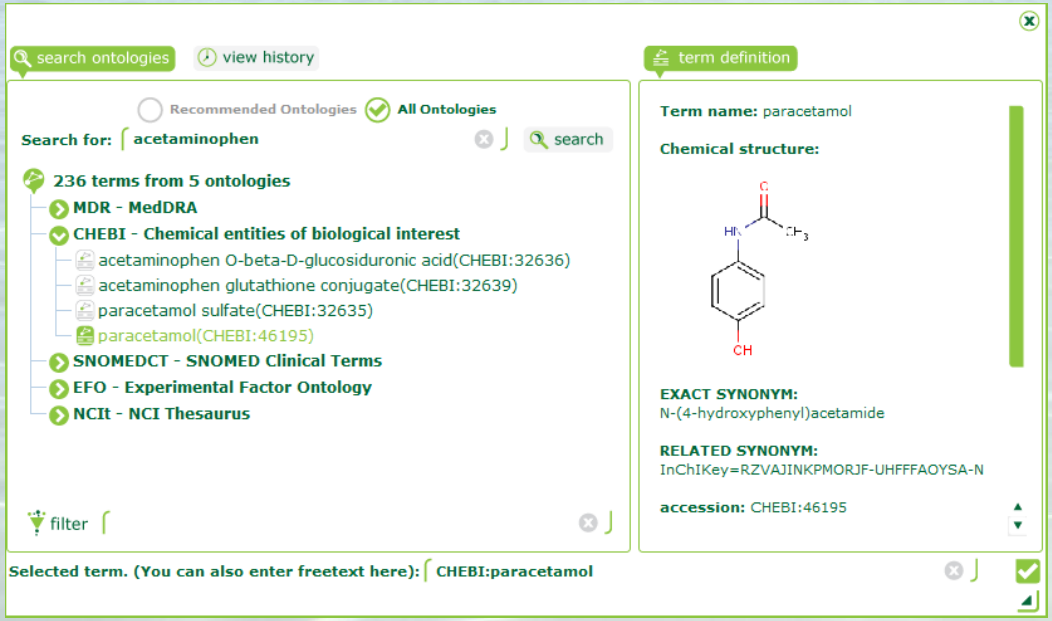
Use of SEURAT-configured ISAcreator to prepare datasets



Mapped to terms in ontologies

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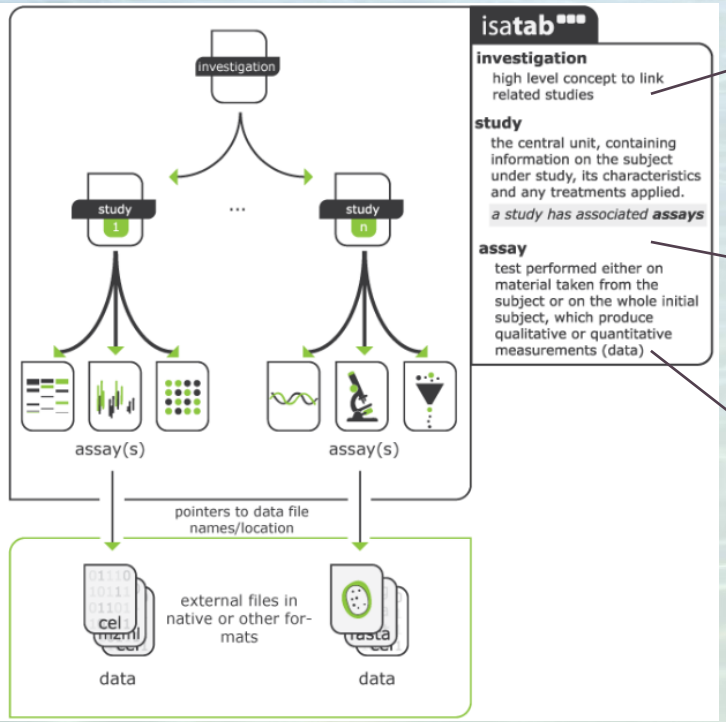
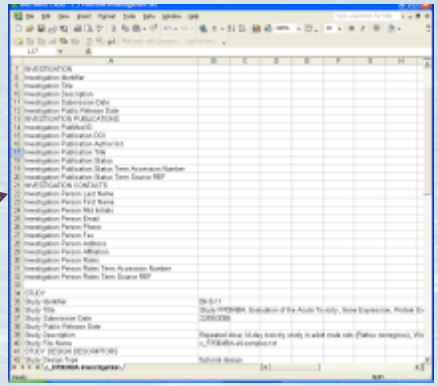
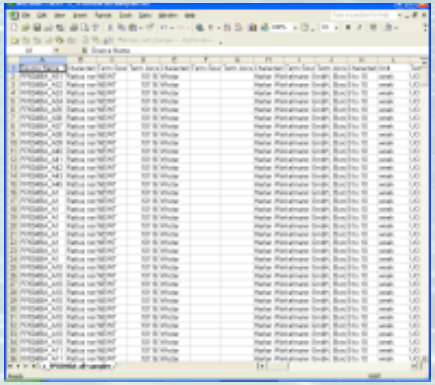
Create an ISATAB zip archive for each investigation

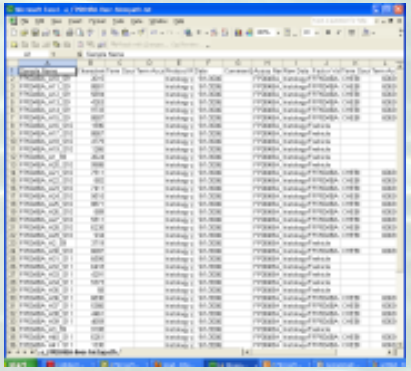




Overall investigation design and information (i… files)



Study description (s… files)



Test results (a… files) with links to data table or native file (e.g. CEL files)

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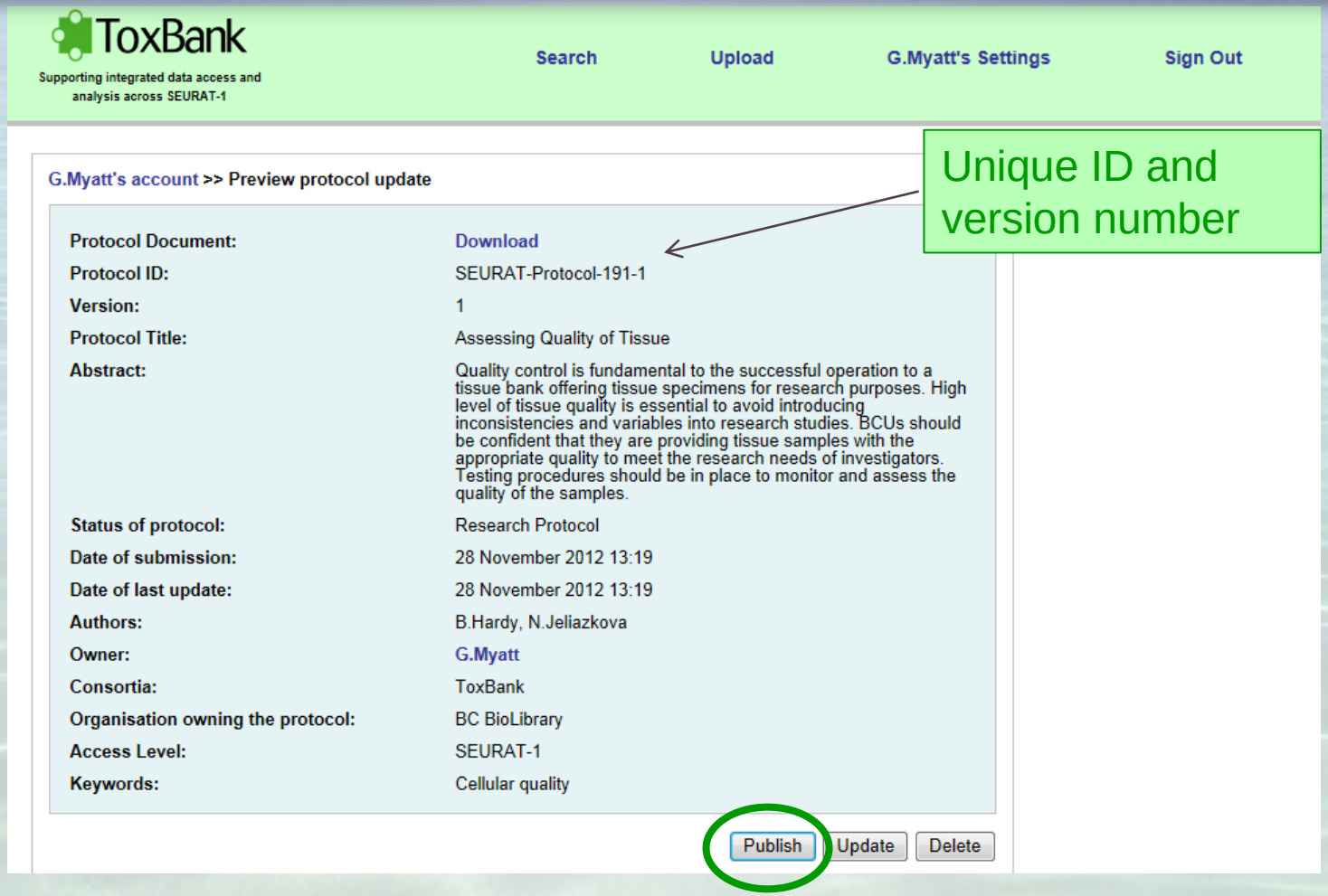
Publishing a protocol



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Viewing the investigation record

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Supporting integrated data access and analysis across SEURAT-1

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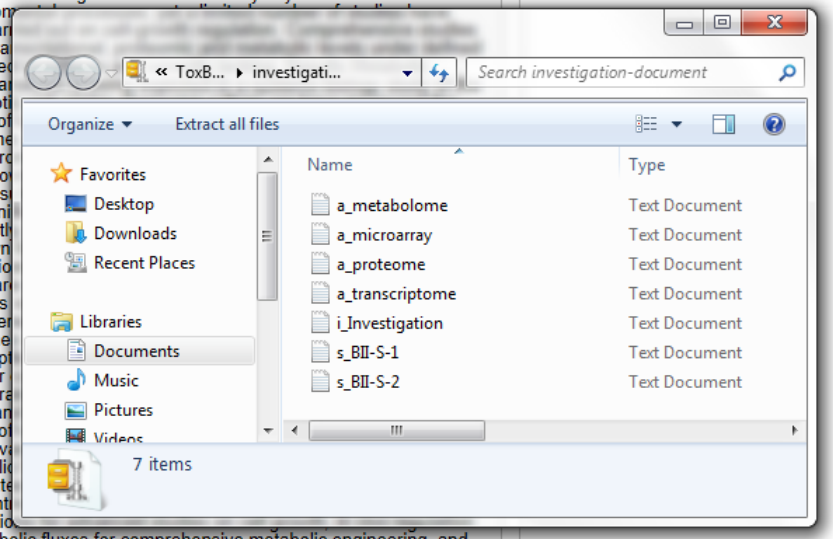
Published Investigation

Investigation Document: Download

Investigation Title: Growth control of the eukaryote cell: a systems biology study in yeast

Abstract: Background Cell growth underlies many key cellular and

of metabolic fluxes for comprehensive metabolic engineering, and



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Linking to wikis

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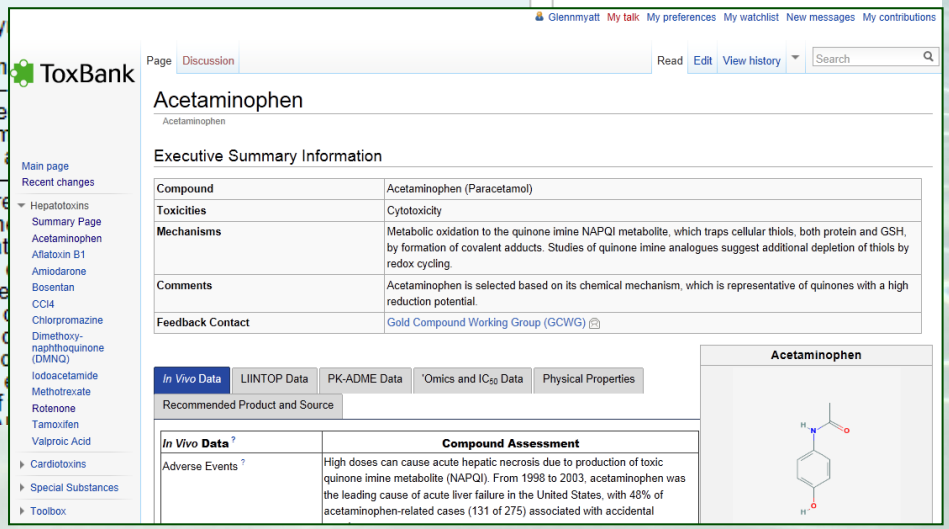
Published Protocol

Protocol Document:	Email the owner to request access: U.Summer school
Protocol ID:	SEURAT-Protocol-38-1
Version:	1
Protocol Title:	In vitro test for py
Abstract:	Parenteral pharm… pyrogenic (fever– general be define… pyrogens that alm… pharmaceuticals … LPS) from Gram– 1979b). There are… contamination: th… amoebocyte lysat… detects LPS and … body temperature… a sterile solution … LAL test detects … the bacterial endo… that LPS causes … (haemolymph) of …

Related links

- Gold compound Wiki (Acetaminophen)
- Search PubMed for related terms
- Subscribe for updates to this protocol



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wiki.toxbank.net

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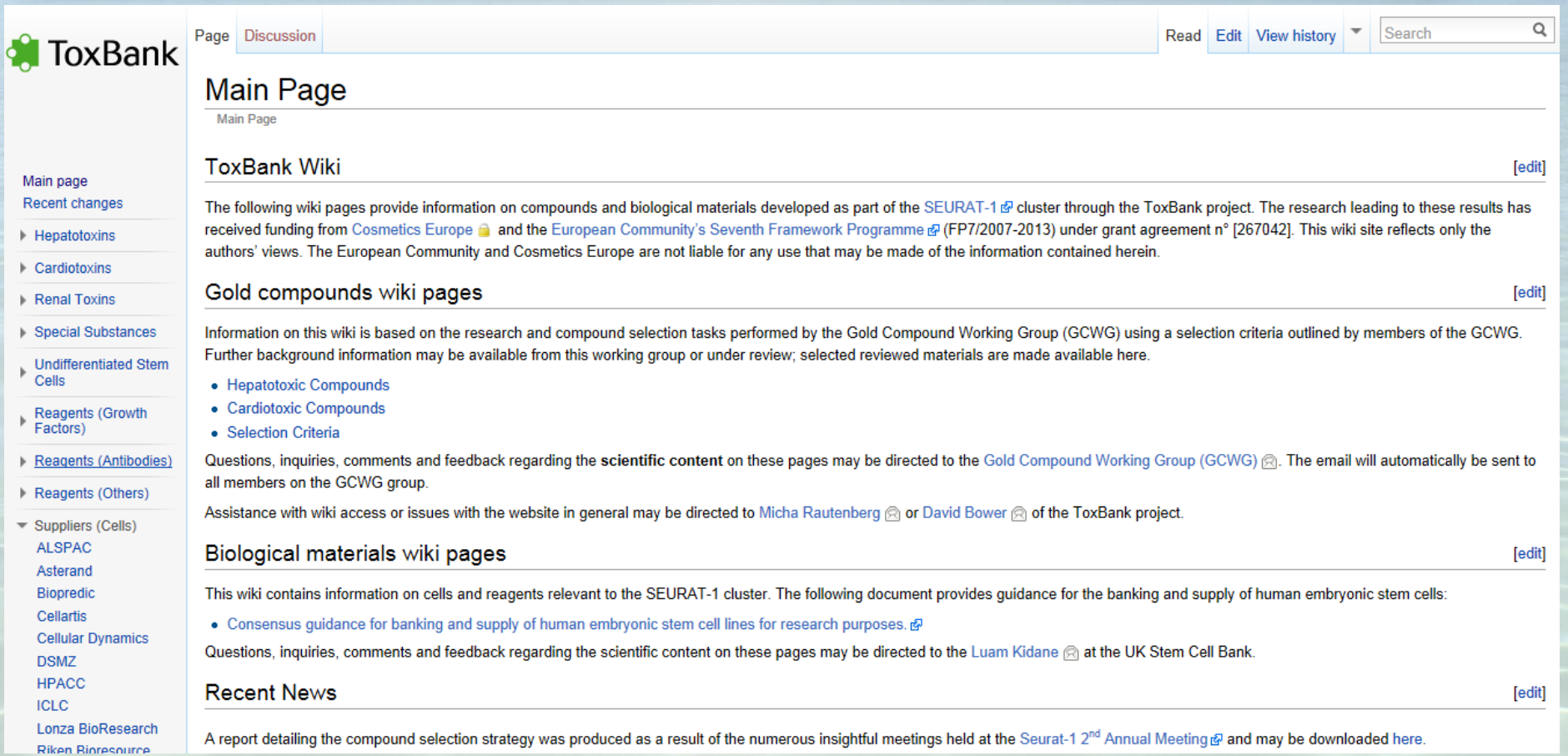
ToxBank Wiki Development



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SEVENTH FRAMEWORK PROGRAMME

ToxBank integrates systems biology concepts into toxicological assessment

Pekka Kohonen,[a] Emilio Benfenati,[b] David Bower,[c] Rebecca Ceder,[a] Michael Crump,[c] Kevin Cross,[c] Roland C. Grafstrçm,[a] Lyn Healy,[d] Christoph Helma,[e] Nina Jeliazkova,[f] Vedrin Jeliazkov,[f] Silvia Maggioni,[b] Scott Miller,[c] Glenn Myatt,[c] Michael Rautenberg,[e] Glyn Stacey,[d] Egon Willighagen,[a] Jeff Wiseman,[g] and Barry Hardy*[h];

[a]Karolinska Institutet, Institute for Environmental Medicine, Molecular Toxicology,Stockholm, Sweden; [b], Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy; [c] Leadscope, Columbus, USA; [d] National Institute for Biological Standards and Control, Potters Bar, UK; [e]In silico toxicology, Basel, Switzerland; [f]Ideaconsult, Sofia, Bulgaria; [g]Pharmatrope,Wayne, USA; [h]Douglas Connect, Zeiningen, Switzerland.

Conclusions - *great potential to contribute to*

- ❖ toxicity evaluation based on **Mode-of-Action**
- ❖ **decreased need for animal experiments**

Systems toxicology - *principles*

Understanding the **toxicological interactions** in *biological systems under compound challenges*

Based on developments in **high-throughput biology**

- ❖ *'Omics* profiling: *gene expression, proteins, metabolites and others*
- ❖ *cell-based screening:* High-Throughput and High-Content analyses

Risk assessment carried out primarily using

- ❖ *in vitro*
- ❖ *In silico* methods

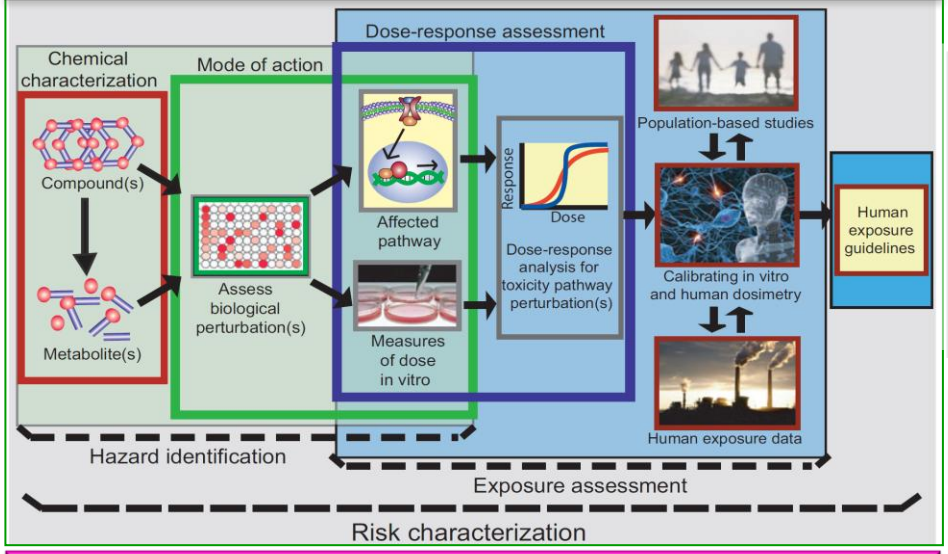


Figure 1. Multiple tools will be, **step by step**, implemented into an **innovative toxicity testing** strategy based on **mode-of-action.**

Kohonen P. et al. The ToxBank Data Warehouse: Supporting the Replacement of In Vivo Repeated Dose Systemic Toxicity Testing. Molecular Informatics. 17 JAN 2013, DOI: 10.1002/minf.201200114.

Clustering by Gene **Clustering by Gene Ontology**

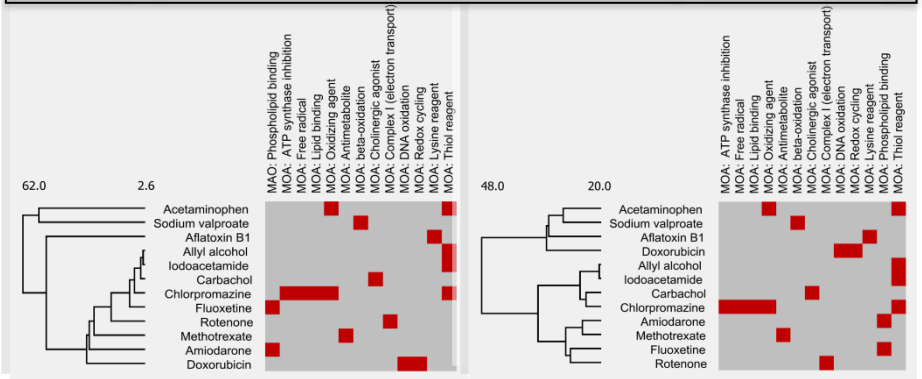


Figure 2. Clustering of ToxBank Gold Compounds by **biological similarity** using chemical-genome links from Comparative Toxicogenomics Database (CTD). Compounds with similar Mode-of-Action cluster together.

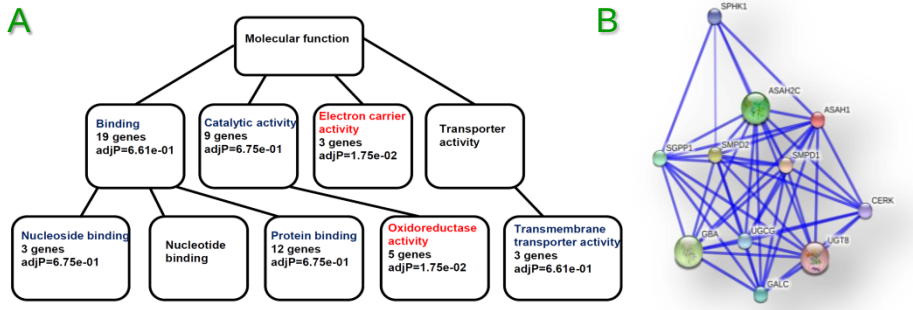


Figure 3. A) Enriched gene ontology (GO) categories of genes associated with the oxidizing agent mode-of-action (MOA) B) Protein-protein association network around the Asah1 protein. Associated with phospholipid binding MOA.

ToxBank builds *databases and data management solutions* to aid in **systems toxicology-based** risk assessment

Cancer- och Allergifonden
cancer - allergi - miljö

Cosmetics Europe
the personal care association

ToxBank

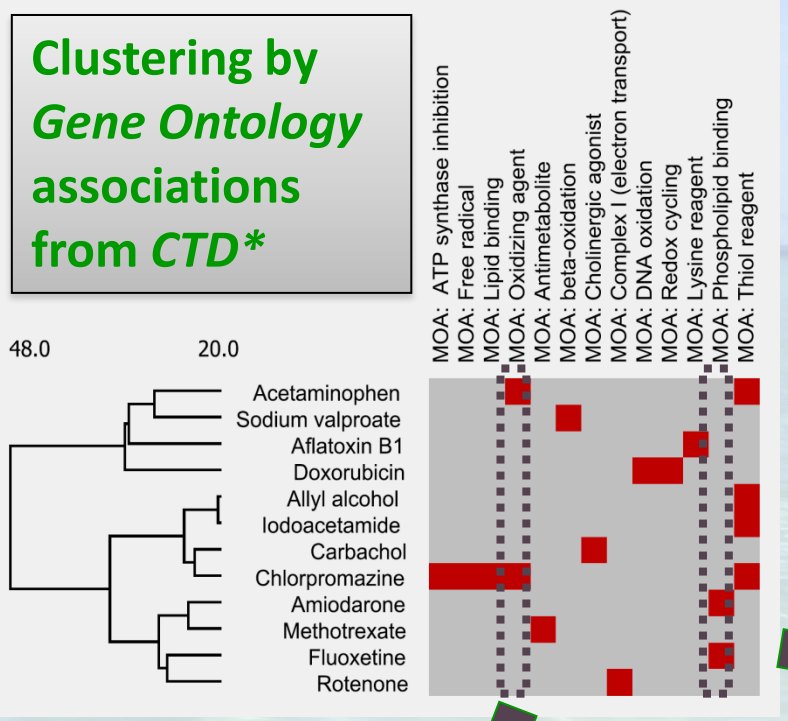
Seventh Framework Programme

Karolinska Institutet
Anno 1810

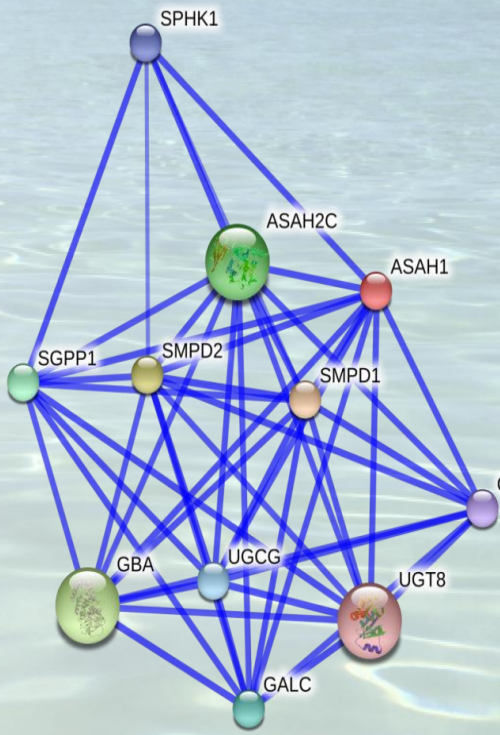
IMM Institute of Environmental Medicine
Institutet för Miljömedicin

Public Data Analysis

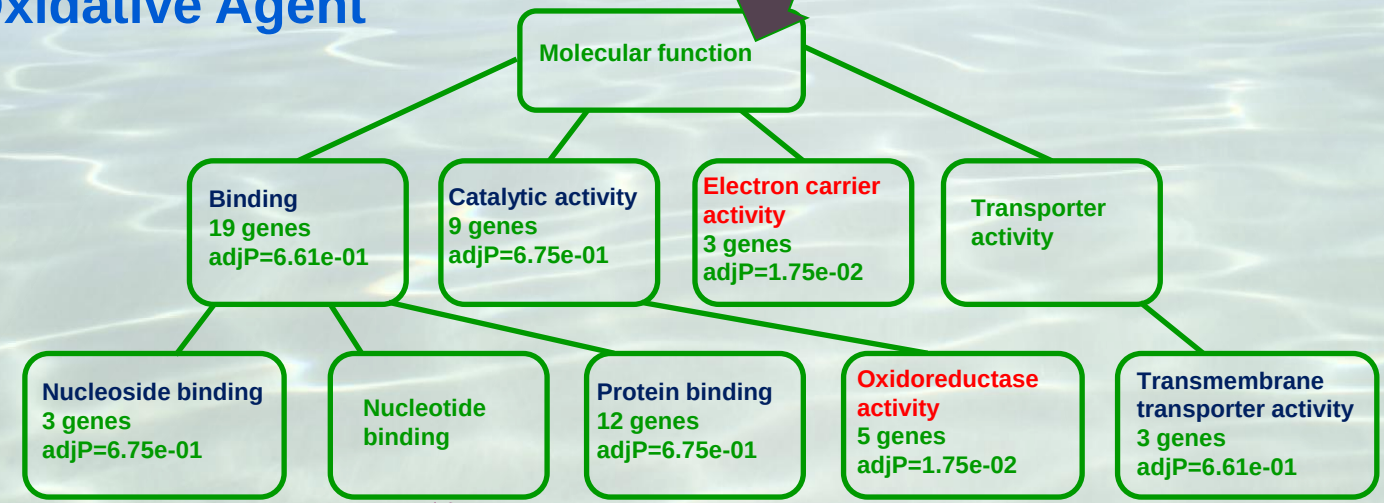
Clustering by *Gene Ontology* associations from *CTD**



Phospholipid Binding



Oxidative Agent



**CTD = Comparative Toxicogenomics Database (www.ctd.org)*

Karolinska Institutet

Kohonen P. et al. The ToxBank Data Warehouse: Supporting the Replacement of In Vivo Repeated Dose Systemic Toxicity Testing. Mol. Inf.17 JAN 2013.

Web Resources - Open Access

http://onlinelibrary.wiley.com/doi/10.1002/minf.201200114/full

The ToxBank Data

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ABOUT THIS JOURNAL

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Full Paper

The ToxBank Data Warehouse: Supporting the Replacement o Repeated Dose Systemic Toxicity Testing

Pekka Kohonen[1], Emilio Benfenati[2], David Bower[3], Rebecca Ceder[1], Michael Crump[3], Kevin Cross[3], Roland C. Grafström[1], Lyn Healy[4], Christoph Helma[5], Nina Jeliazkova[6], Vedrin Jeliazkov[6], Silvia Maggioni[2], Scott Miller[3], Glenn Myatt[3], Michael Rautenberg[5], Glyn Stacey[4], Egon Willighagen[1], Jeff Wiseman[7], Barry Hardy[8,*]

Article first published online: 17 JAN 2013

DOI: 10.1002/minf.201200114

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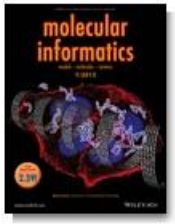
Issue



Molecular Informatics

Special Issue: Advances in Computational Toxicology

Volume 32, Issue 1, pages 47 –63, January 2013

Additional Information **(Show All)**

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Abstract | Article | References | Supporting Information | Cited By

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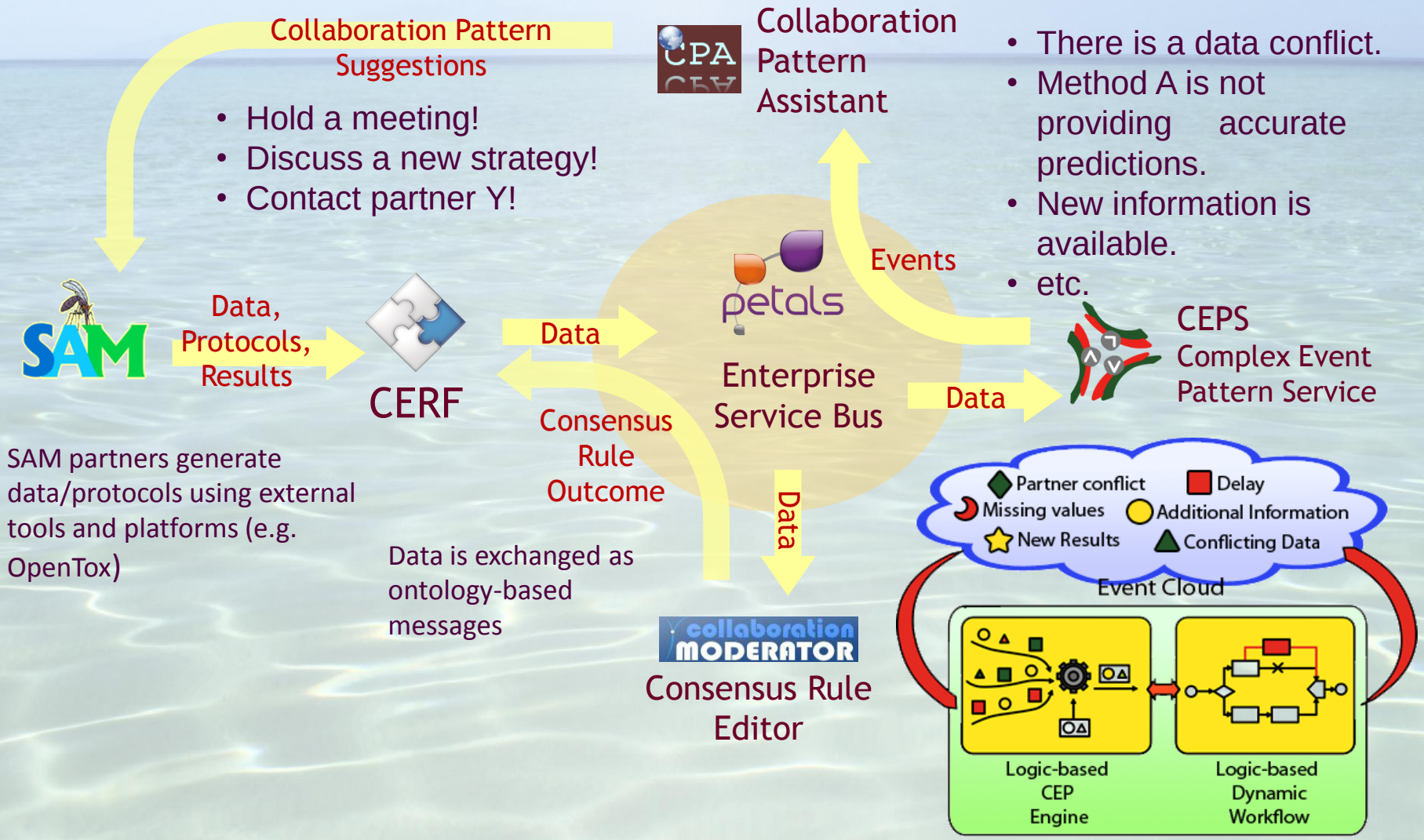
SAM ICT Architecture



SAM partners generate data/protocols using external tools and platforms (e.g. OpenTox)

Data is exchanged as ontology-based messages

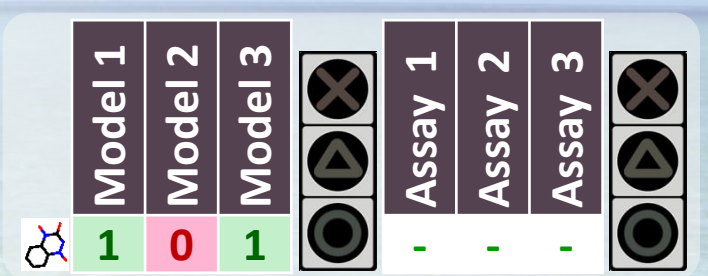
Hardy and Affentranger, Drug Discovery Today. 2013 Jul;18(13-14):681-6.

Event Driven Weight of Evidence

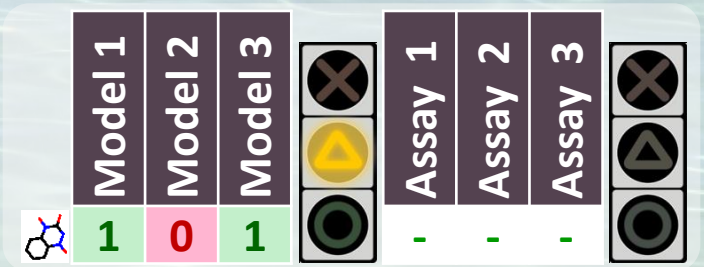
collaboration MODERATOR

Consensus Rule Editor

Recommendation Rules:

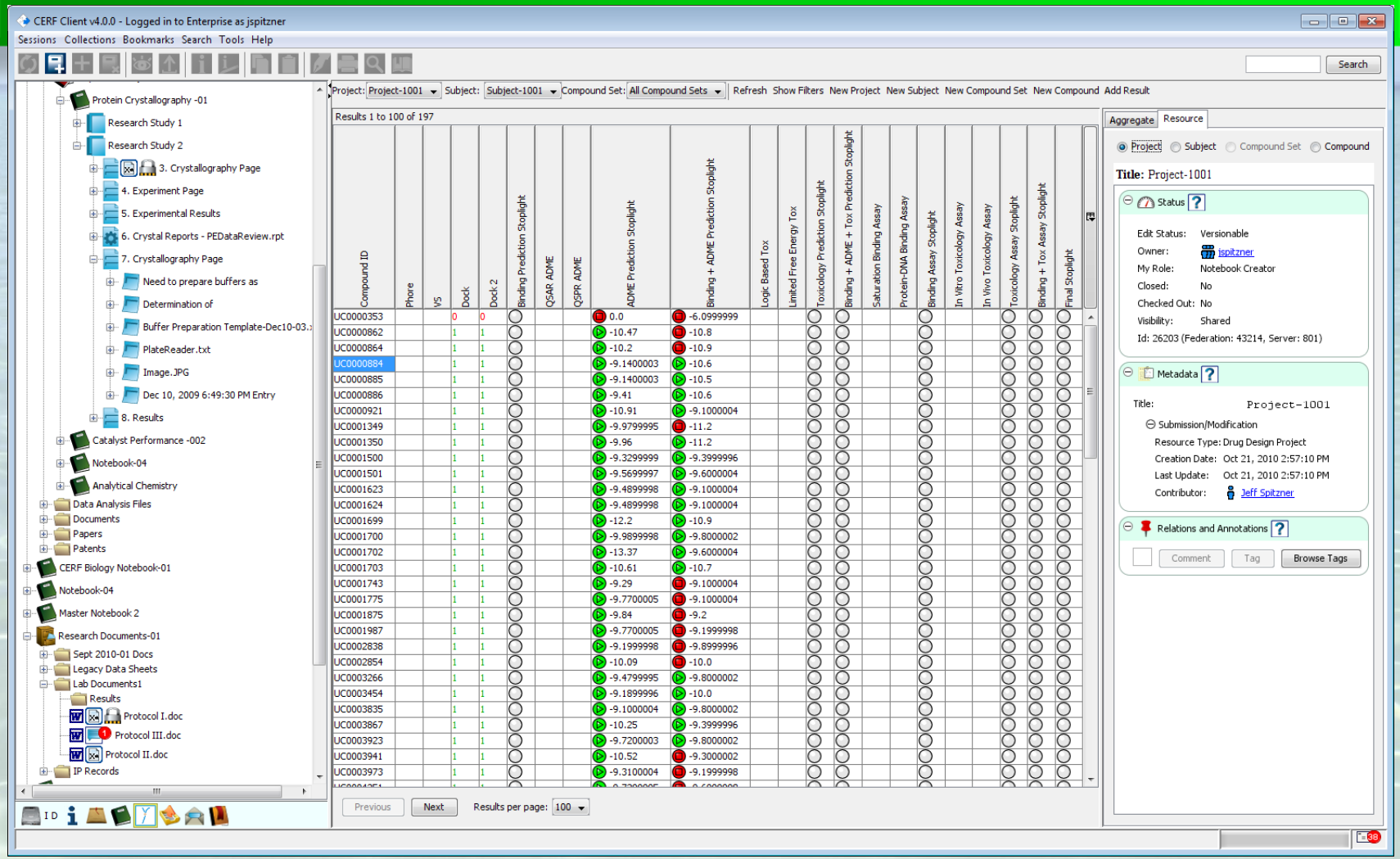


Synergy



OpenTox

Event-driven Weight of Evidence



[Hardy and Affentranger, Drug Discovery Today. 2013 Jul;18(13-14):681-6.]

ToxBank Acknowledgements

DouglasConnect

in silico toxicology

Karolinska Institutet

Leadscope®

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MARIO NEGRI
ISTITUTO DI RICERCHE FARMACOLOGICHE

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