

Integrated Analysis of Toxicology Data supported by ToxBank

OpenTox Euro 2013 Meeting

Mainz, Germany

October 1, 2013



Barry.Hardy –(at)- douglasconnect.com

18M

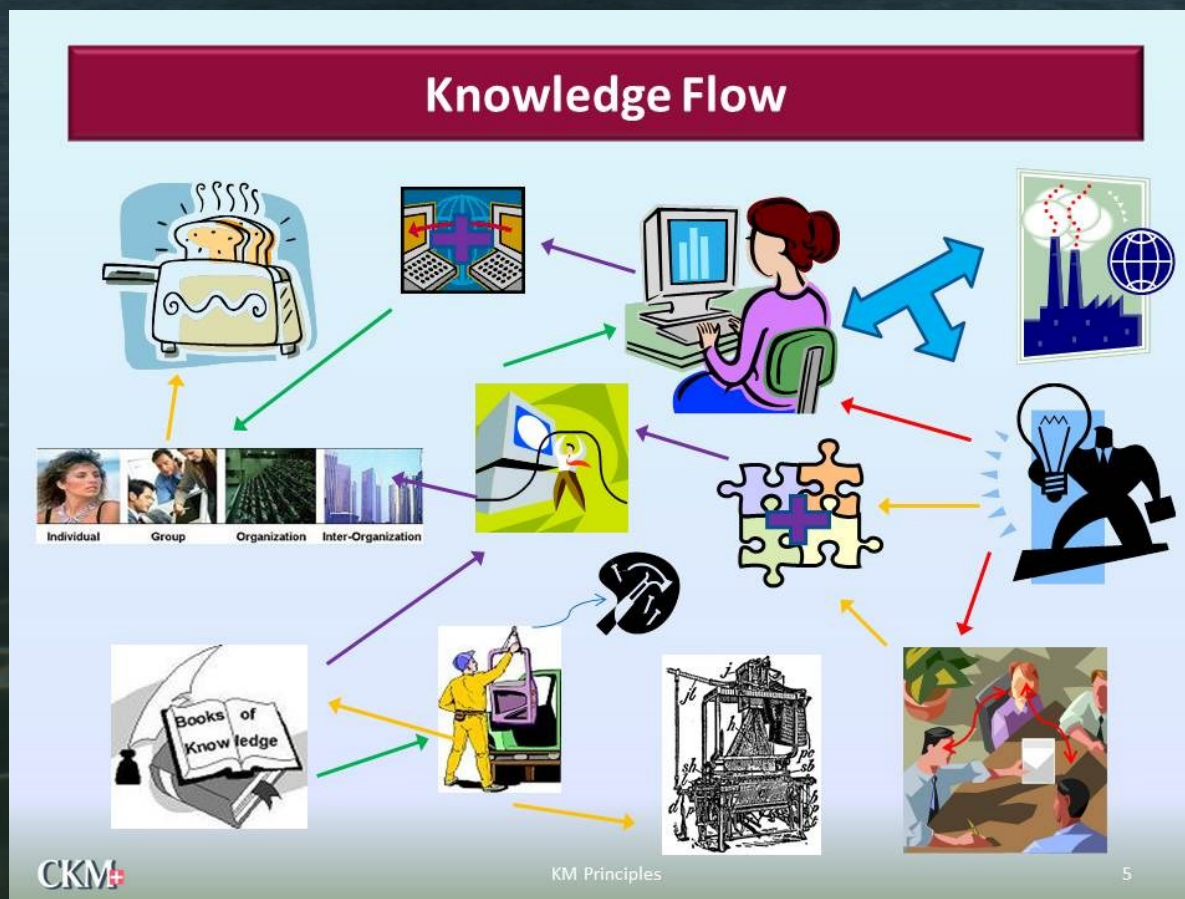
Open 



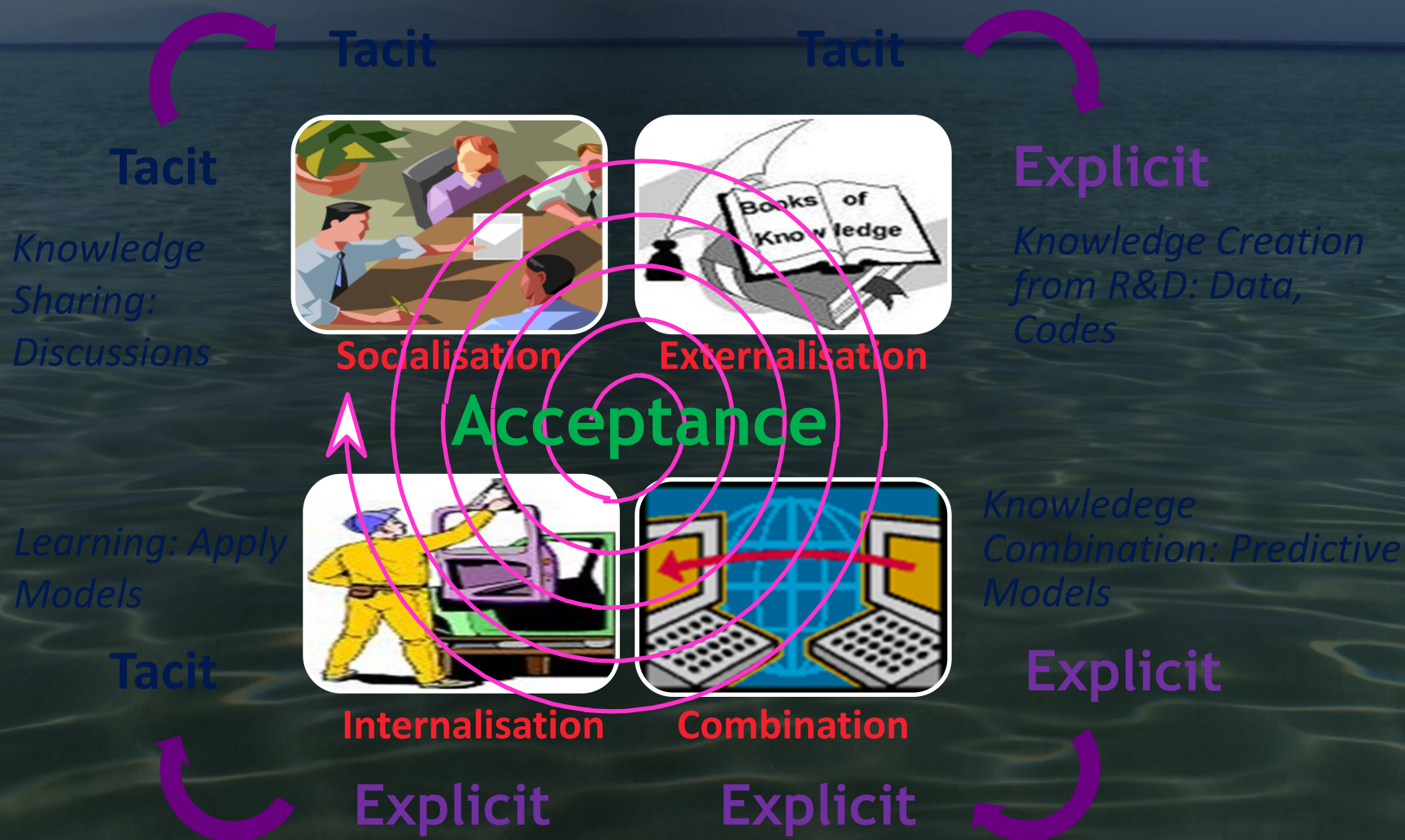
Islands



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



Knowledge-Oriented Framework



Knowledge Sharing



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.

OpenTox standards

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

Dataset

GET
POST
PUT
DELETE

Feature

GET
POST
PUT
DELETE

Compound

GET
POST
PUT
DELETE

AppDomain

GET
POST
PUT
DELETE

Model

GET
POST
PUT
DELETE

Algorithm

GET
POST
PUT
DELETE

Report

GET
POST
PUT
DELETE

Validation

GET
POST
PUT
DELETE

Ontology

GET
POST
PUT
DELETE

Plug In Components that solve Problems

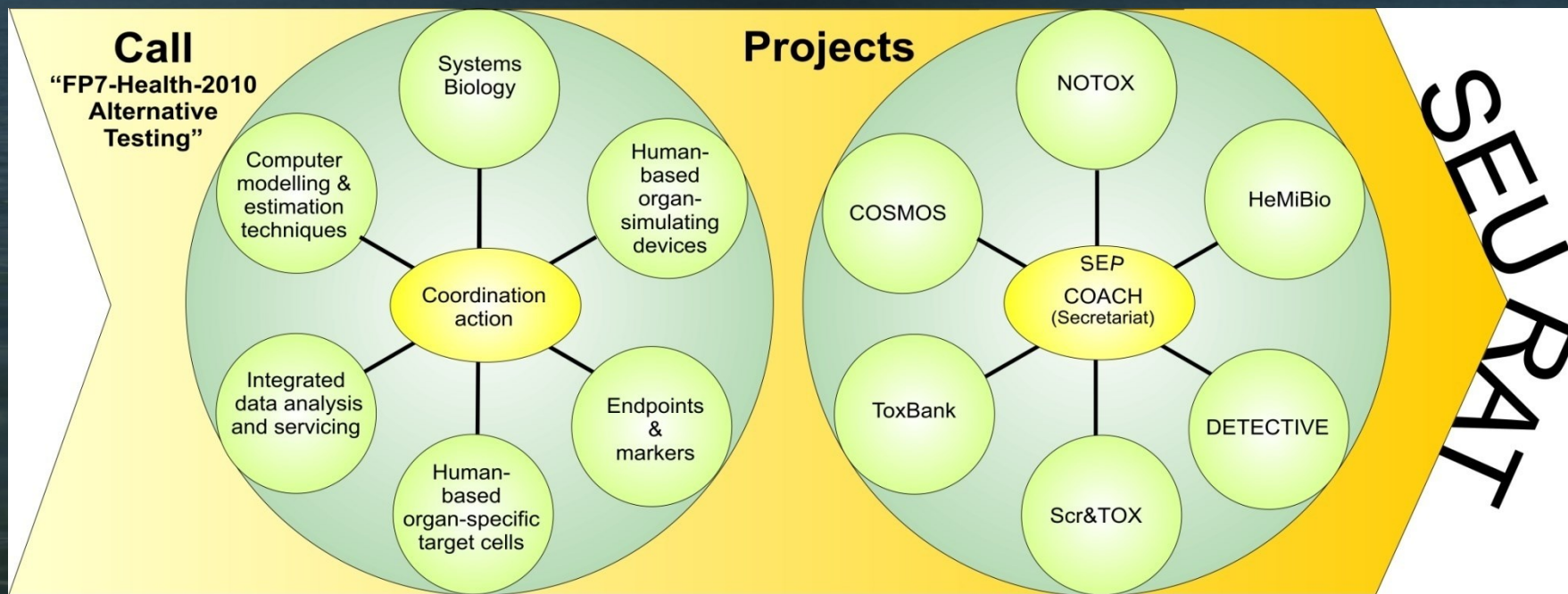


Open

ToxBank

Adaptor Solution in Jeddah, 2008

The Building Blocks of SEURAT-1

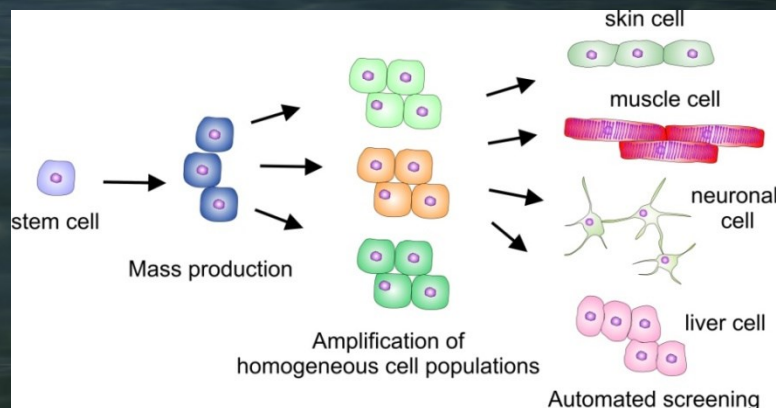


~ 70 research groups from European Universities, Public Research Institutes and Companies (more than 30% SMEs)

www.seurat-1.eu

Building block 1: Scr&Tox

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



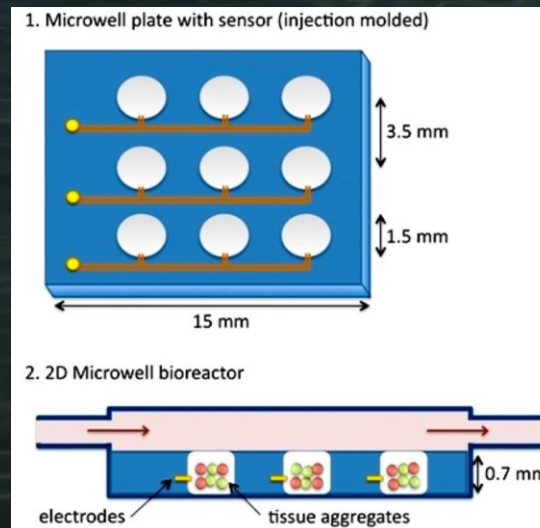
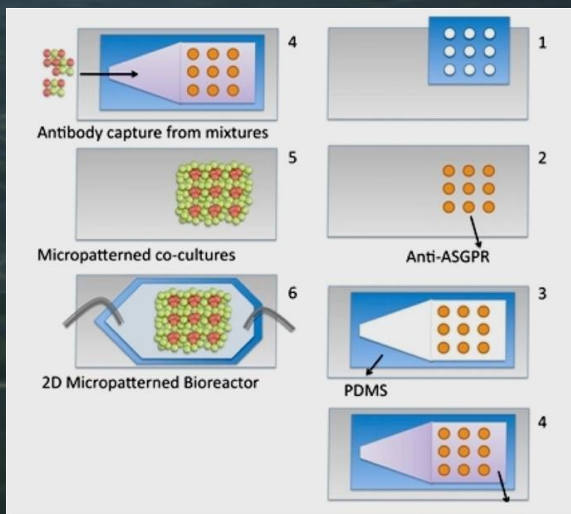
Coordinator:
Marc Peschanski
INSERM/i-STEM
France

website:
www.scrtox.eu

The cell factory

Building block 2: HeMiBio

Development of a hepatic microfluidic bioreactor



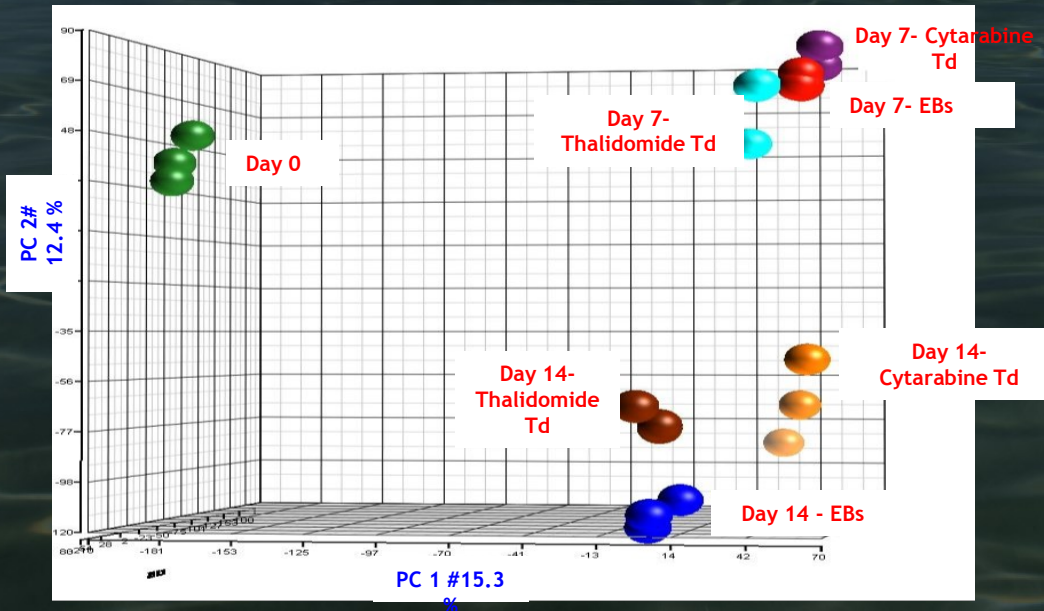
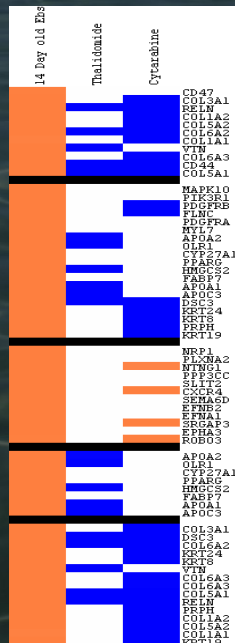
Coordinator:
Catherine Verfaillie
KU LEUVEN, Belgium

website:
www.hemibio.eu

The *in vitro* liver

Building block 3: DETECTIVE

• Identification of biomarkers for prediction of toxicity in humans



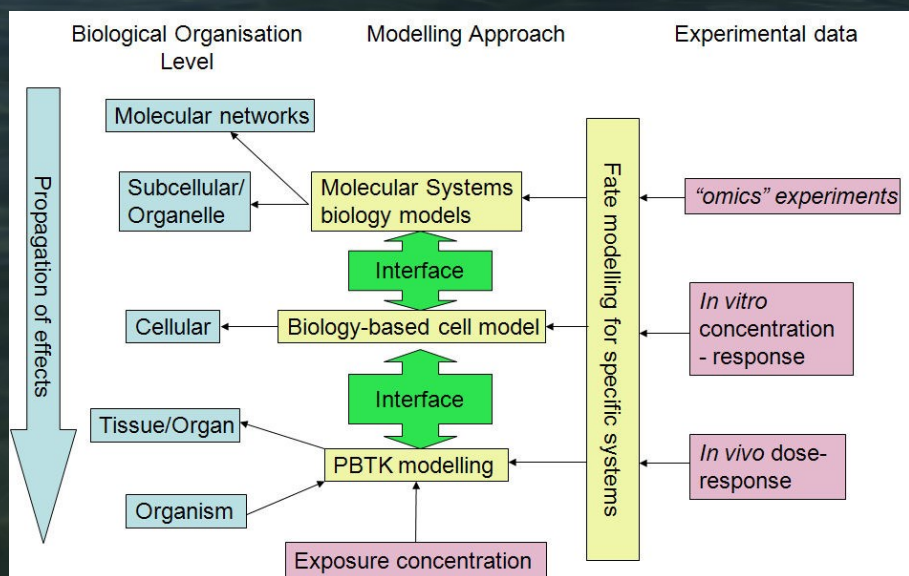
Coordinator:
Jürgen Hescheler
Klinikum der
Universität Köln,
Germany

website:
www.detect-iv-e.eu

Biomarkers and functional assays

Building block 4: COSMOS

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

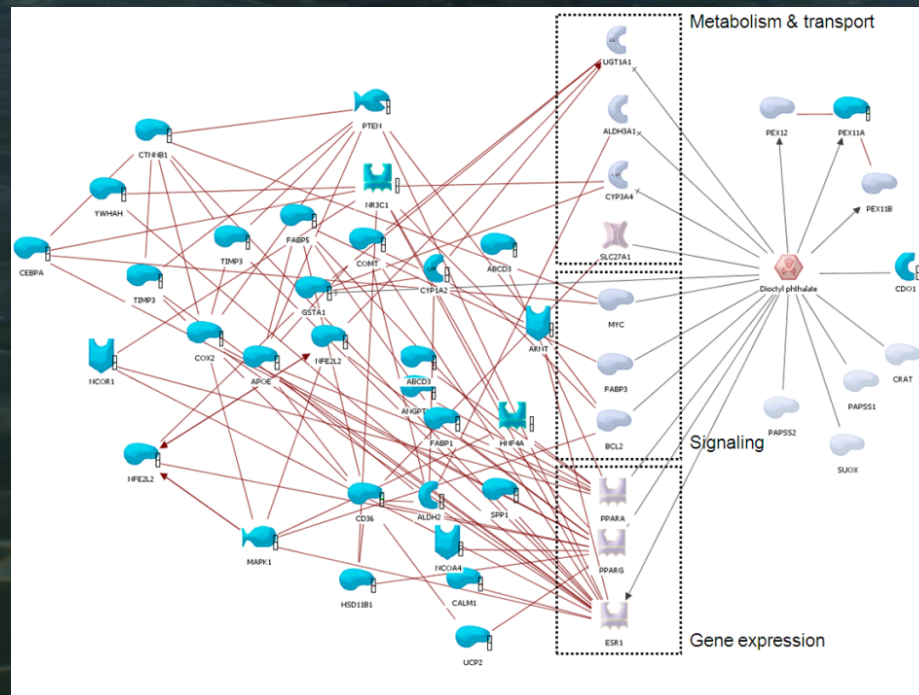


Coordinator:
Mark Cronin
Liverpool John
Moores University,
UK

website:
www.cosmos-tox.eu

Building block 5: NOTOX

- # Development of systems biological tools for organotypic human cell cultures



NOTOX

Coordinator:
Elmar Heinzle
Universität des
Saarlandes,
Germany

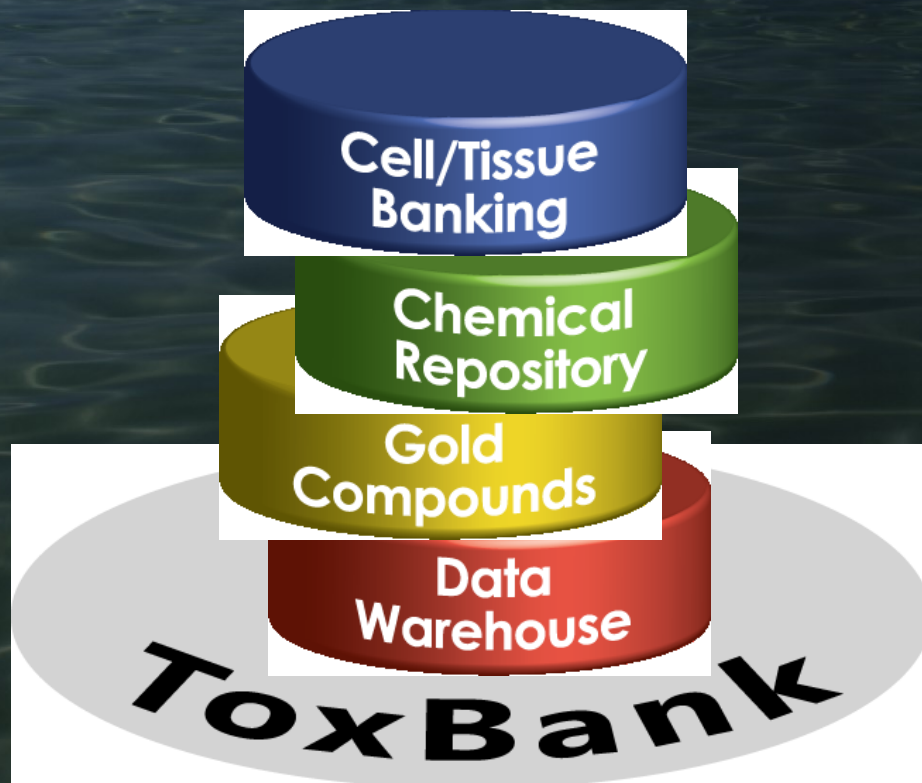
website:
www.notox-sb.eu

ToxBank Infrastructure Project

(started Jan 2011)

www.toxbank.net

Establishment of a ...



... cell and tissue banking
information resource

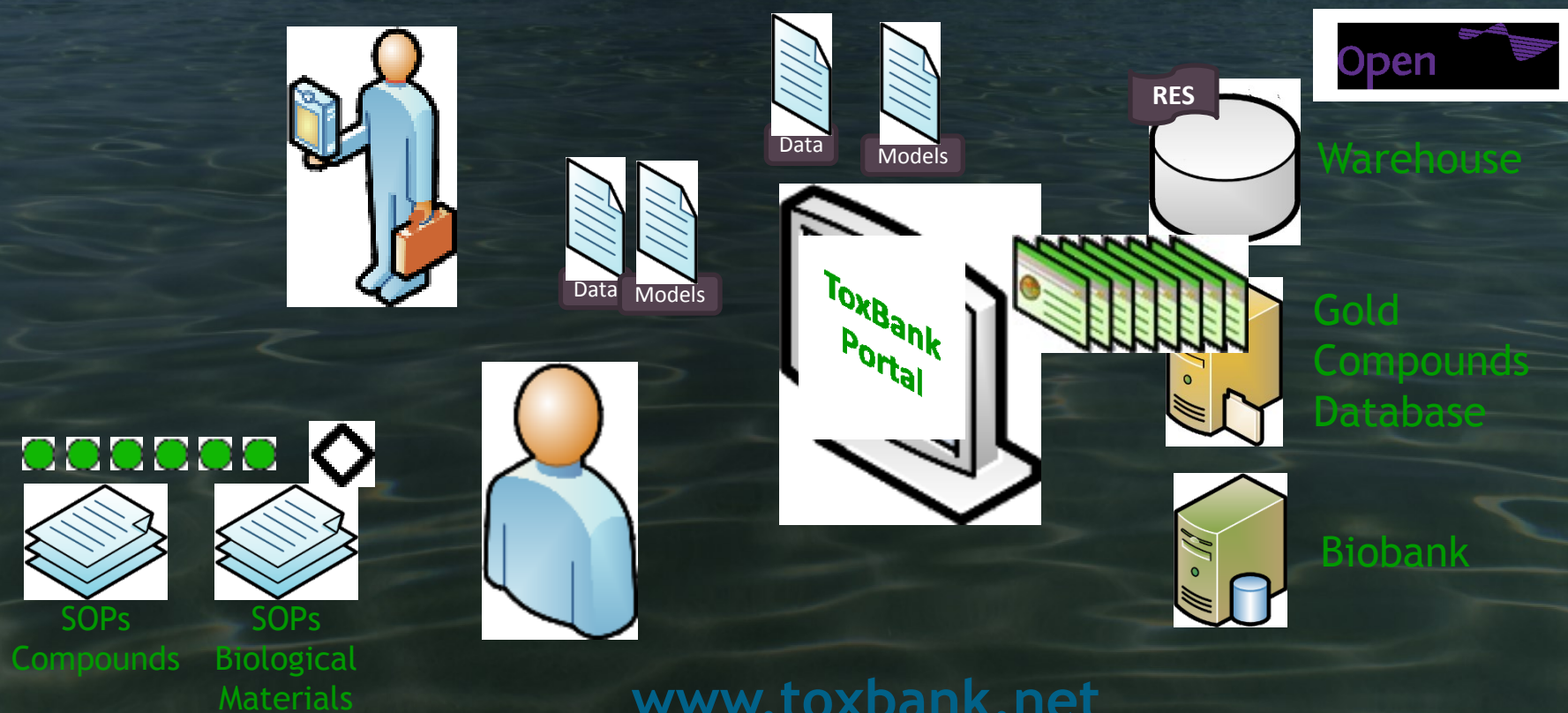
... repository for the selected
test compounds

... database of reference test
compounds

... dedicated web-based data
warehouse

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

Compound Selection

- ❖ **Compound Assessment Team:** Dave Bower, Matthew Clark, Matthew Dent, Marina Goumenou, Gabrielle Hawksworth, Nina Jeliaskova, 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- κ B/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

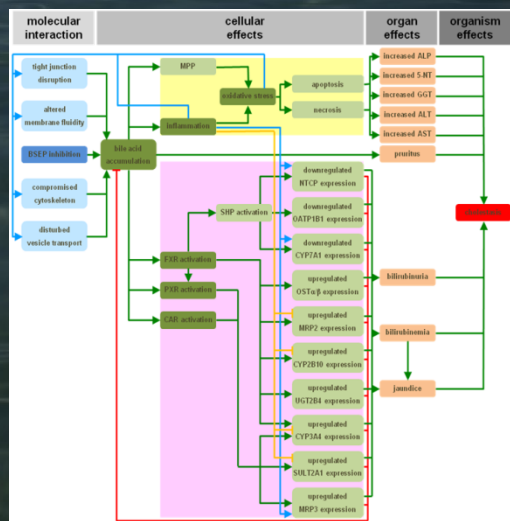
Mapping Mechanism to Pathway

Consider adverse events relevant to cosmetics

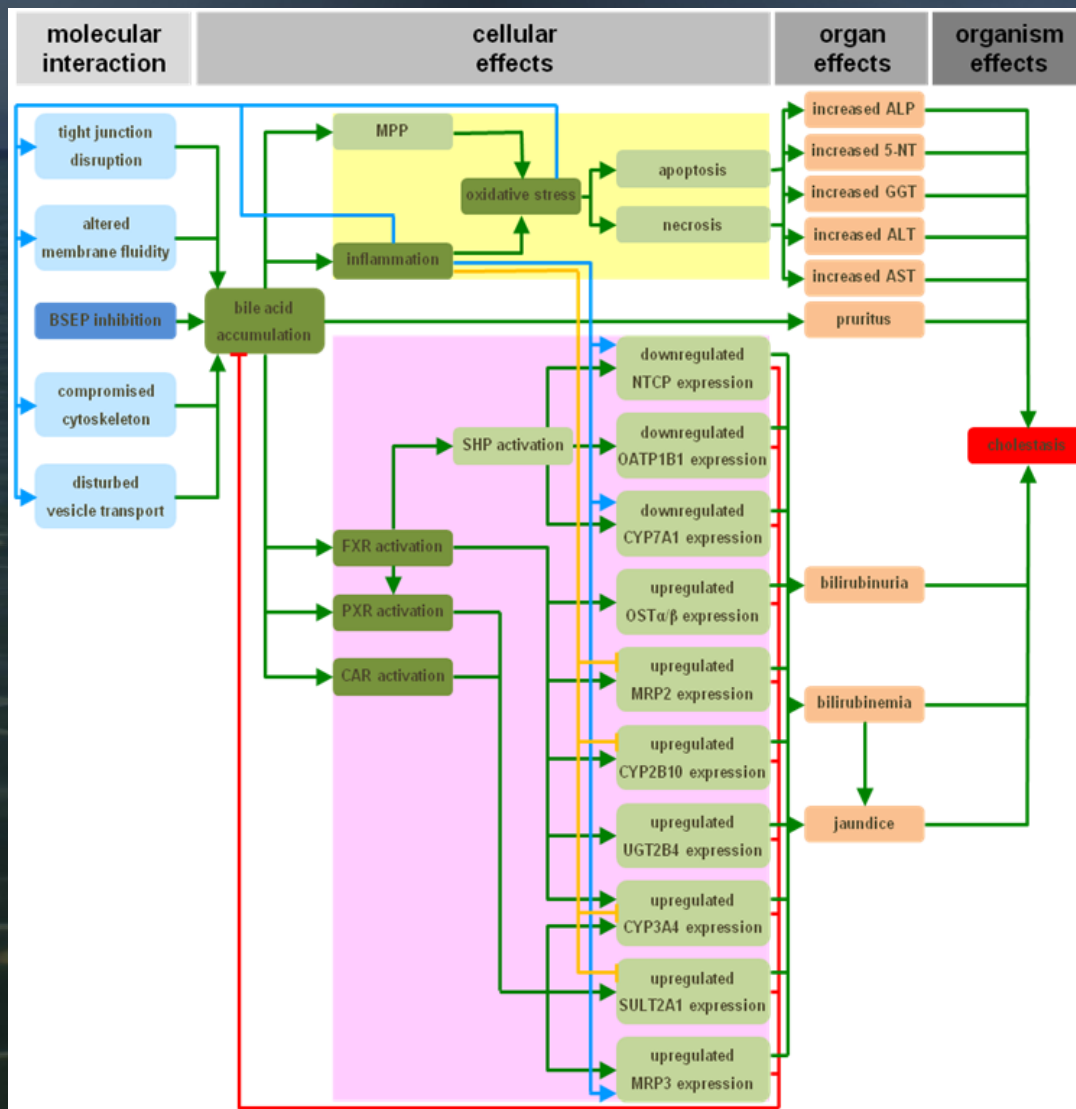
Identify drugs demonstrated to exhibit these adverse events in humans

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

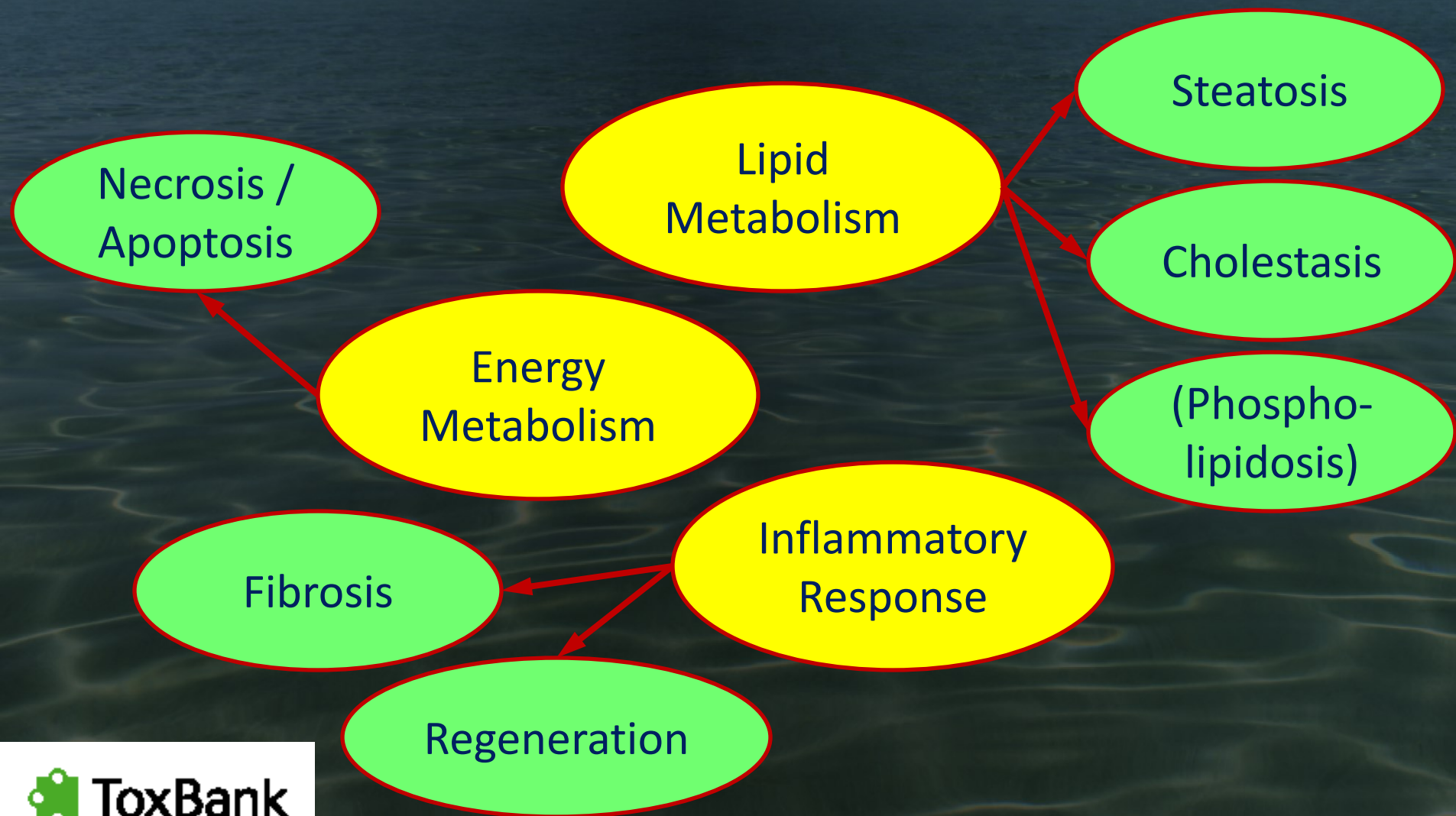
Add non-reactive analogues where needed



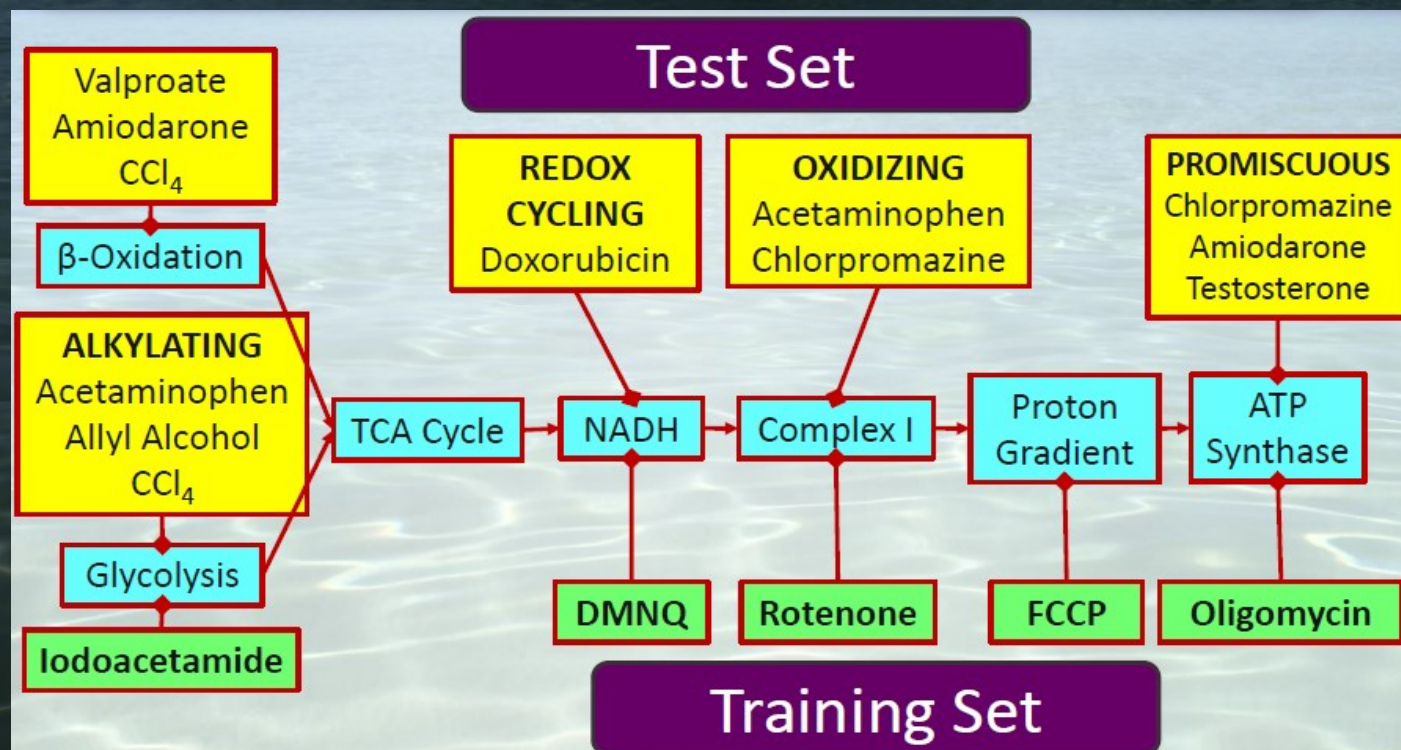
Adverse outcome pathway (AOP) : drug-induced cholestasis



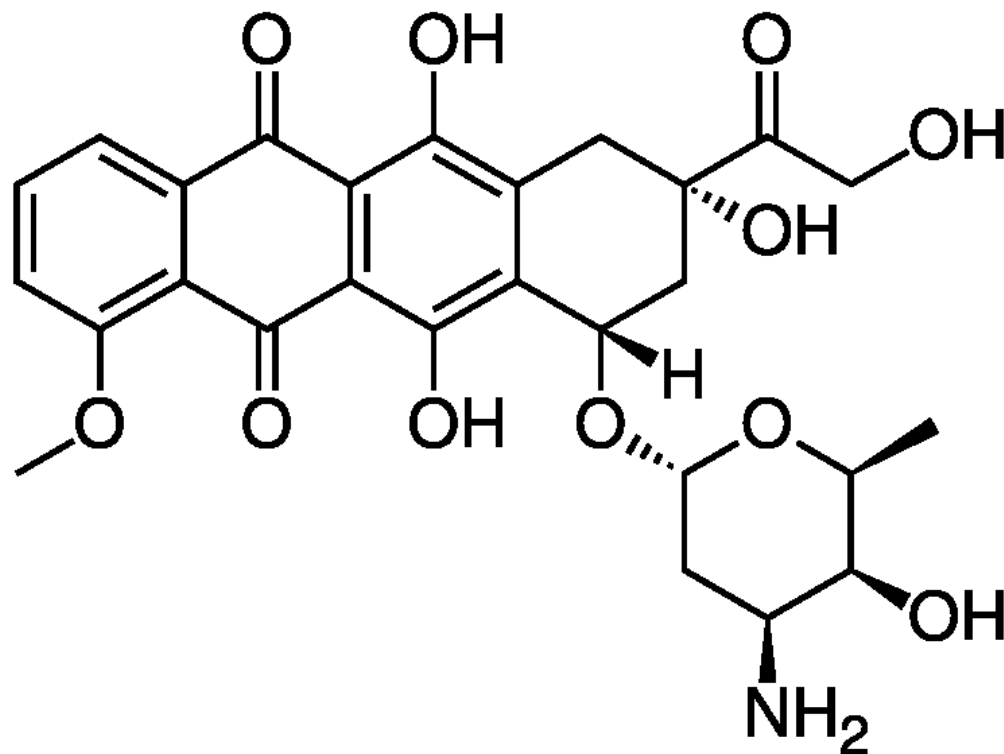
Compound Selection: Reference Toxicities to Biological Pathways



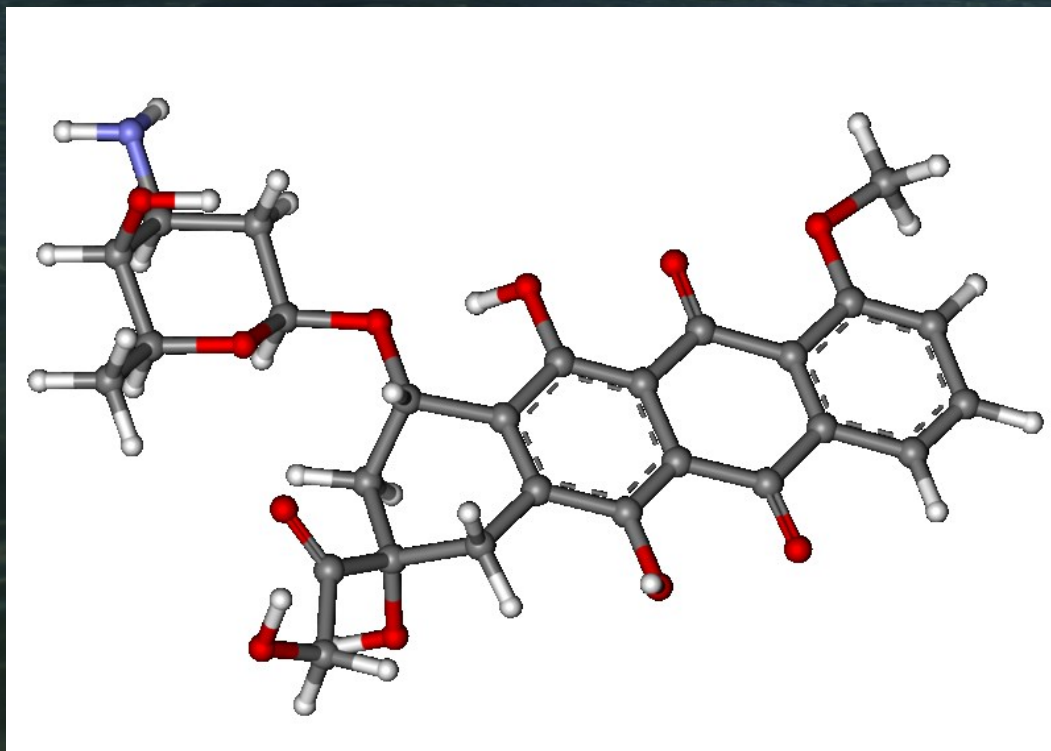
Compound Selection and Mechanistic Testing



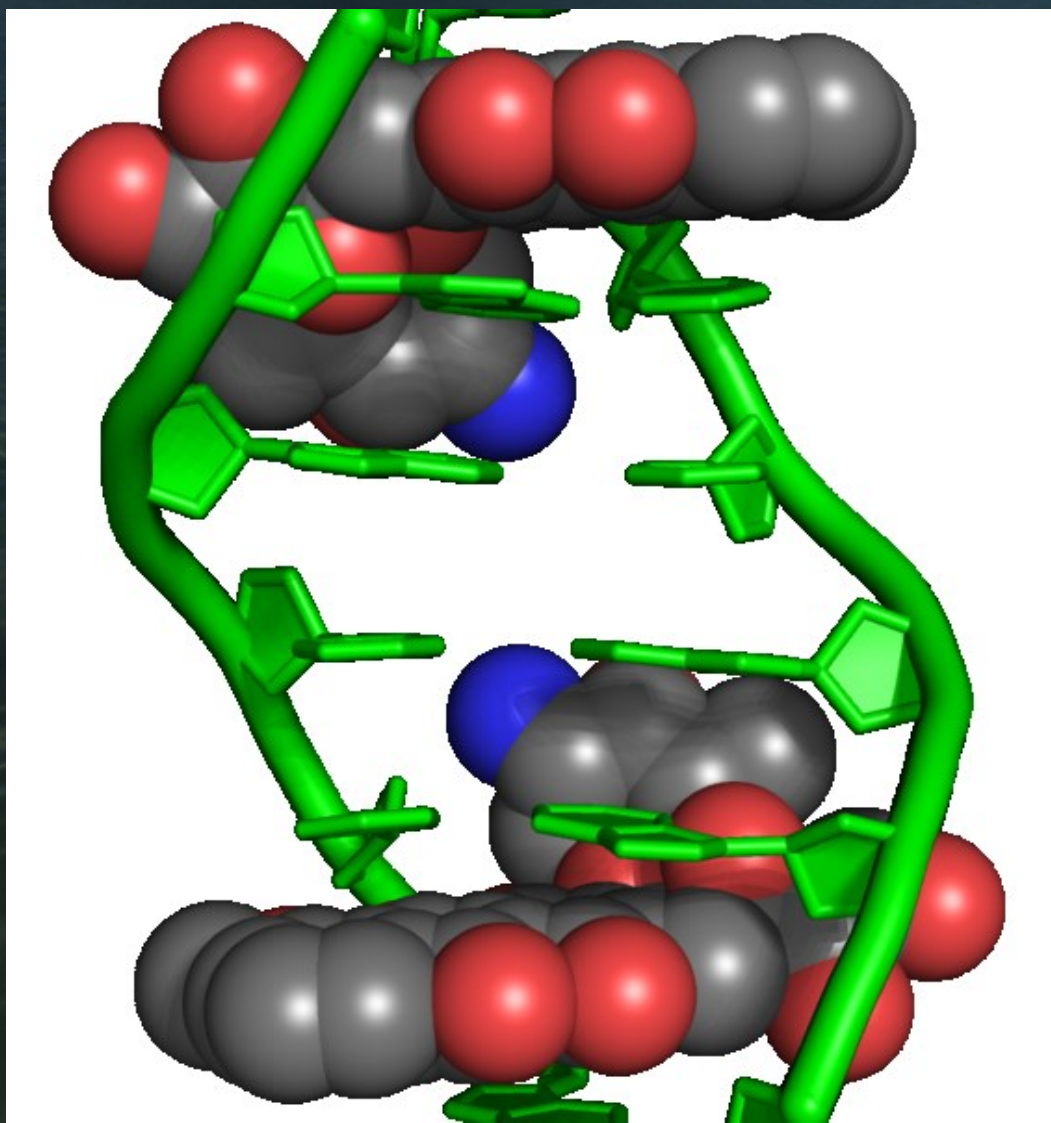
ToxBank Gold Compound - Doxorubicin




ToxBank Gold Compound - Doxorubicin



ToxBank Gold Compound - Doxorubicin



ToxBank Wiki Development

 **ToxBank**

Main page

Recent changes

Hepatotoxins

Cardiotoxins

Renal Toxins

Special Substances

Undifferentiated Stem Cells

Reagents (Growth Factors)

Reagents (Antibodies)

Reagents (Others)

Suppliers (Cells)

ALSPAC

Asterand

Biopredic

Cellartis

Cellular Dynamics

DSMZ

HPACC

ICLC

Lonza BioResearch

Riken Bioresource

Page

Discussion

Read

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Main Page

Main Page

ToxBank Wiki

[edit]

The following wiki pages provide information on compounds and biological materials developed as part of the [SEURAT-1](#) cluster through the ToxBank project. The research leading to these results has received funding from [Cosmetics Europe](#) and the [European Community's Seventh Framework Programme](#) (FP7/2007-2013) under grant agreement n° [267042]. This wiki site reflects only the authors' views. The European Community and Cosmetics Europe are not liable for any use that may be made of the information contained herein.

Gold compounds wiki pages

[edit]

Information on this wiki is based on the research and compound selection tasks performed by the Gold Compound Working Group (GCWG) using a selection criteria outlined by members of the GCWG. Further background information may be available from this working group or under review; selected reviewed materials are made available here.

- Hepatotoxic Compounds
- Cardiotoxic Compounds
- Selection Criteria

Questions, inquiries, comments and feedback regarding the **scientific content** on these pages may be directed to the [Gold Compound Working Group \(GCWG\)](#). The email will automatically be sent to all members on the GCWG group.

Assistance with wiki access or issues with the website in general may be directed to [Micha Rautenberg](#) or [David Bower](#) of the ToxBank project.

Biological materials wiki pages

[edit]

This wiki contains information on cells and reagents relevant to the SEURAT-1 cluster. The following document provides guidance for the banking and supply of human embryonic stem cells:

- [Consensus guidance for banking and supply of human embryonic stem cell lines for research purposes.](#)

Questions, inquiries, comments and feedback regarding the scientific content on these pages may be directed to the [Luam Kidane](#) at the UK Stem Cell Bank.

Recent News

[edit]

A report detailing the compound selection strategy was produced as a result of the numerous insightful meetings held at the [Seurat-1 2nd Annual Meeting](#) and may be downloaded [here](#).

Information resources

[Home](#)
[About Us](#)
[Privacy Policy](#)
[Terms of Service](#)
[Contact Us](#)
[Feedback](#)

ToxBank

[Main page](#)

- > [Recent changes](#)
- > [Hepatotoxicity](#)
- > [Summary Page](#)
- > [Acetaminophen](#)
- > [Adjuvant B1](#)
- > [Amiodarone](#)
- > [Bosentan](#)
- > [Cocaine](#)
- > [Chlorpromazine](#)
- > [Dimethyl-naphthalene \(DMN\)](#)
- > [Isoniazidamide](#)
- > [Methotrexate](#)
- > [Rufinamide](#)
- > [Tamoxifen](#)
- > [Valproic Acid](#)
- > [Cardiotoxics](#)
- > [Special Substances](#)
- > [Toolbox](#)

Page Discussion

Read
Edit
View history

Search

Acetaminophen

Acetaminophen

Executive Summary Information

Compound	Acetaminophen (Paracetamol)
Toxicities	Cytotoxicity
Mechanisms	Metabolic oxidation to the quinone imine NAPQI metabolite, which traps cellular thiols, both protein and GSH, by formation of covalent adducts. Studies of quinone imine analogues suggest additional depletion of thiols by redox cycling.
Comments	Acetaminophen is selected based on its chemical mechanism, which is representative of quinones with a high reduction potential.
Feedback Contact	Gold Compound Working Group (GCWG) @

In Vivo Data
LINTOP Data
PK-ADME Data
Omics and ToxCat Data

Physical Properties
Recommended Product and Source

In Vivo Data *

Adverse Events *

Compound Assessment

High doses can cause acute hepatic necrosis due to production of toxic quinone imine metabolite (NAPQI). From 1990 to 2003, acetaminophen was the leading cause of acute liver failure in the United States, with 40% of acetaminophen-related cases (131 of 275) associated with accidental overdose.

Acetaminophen

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed 10.1006/j.mol.2001.3500

TaxBank
Bio Materials

Page: Discussion Read Edit View history Search

TR-1-81
TR-1-81 [info]

Main page

Unfractionated Stem Cells Liver Cells Carcinomas Neural Cells Muscle Cells Neuronal Cells Endothelial Cells Stem Cells Lung Cells Other Cells

Respiratory (Alveolar Epithelial)

Respiratory (Antibodies)

TR-1-81
TR-1-80
TR-1-1
TR-1-2
TR-1-4

Respiratory (Others)

Respiratory (Cilia)

Respiratory (Cilia)

Characterization Data

Typical FACS Profile

Protein Sequence

Enter/View 1420 Human
Enter/View 1422 Human
Enter/View 1423 Human
Enter/View 1424 Human

Western Blot

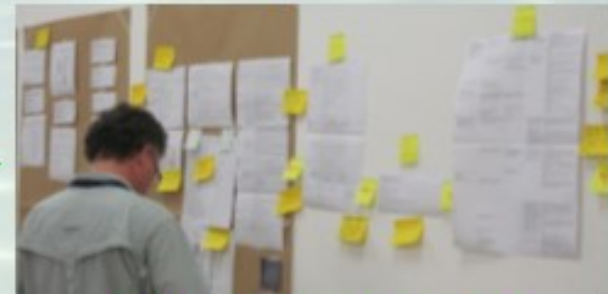
Organizing notes collected from interviews with SEURAT scientists



Hierarchically grouping the notes



Generating design ideas



Reviewing use cases



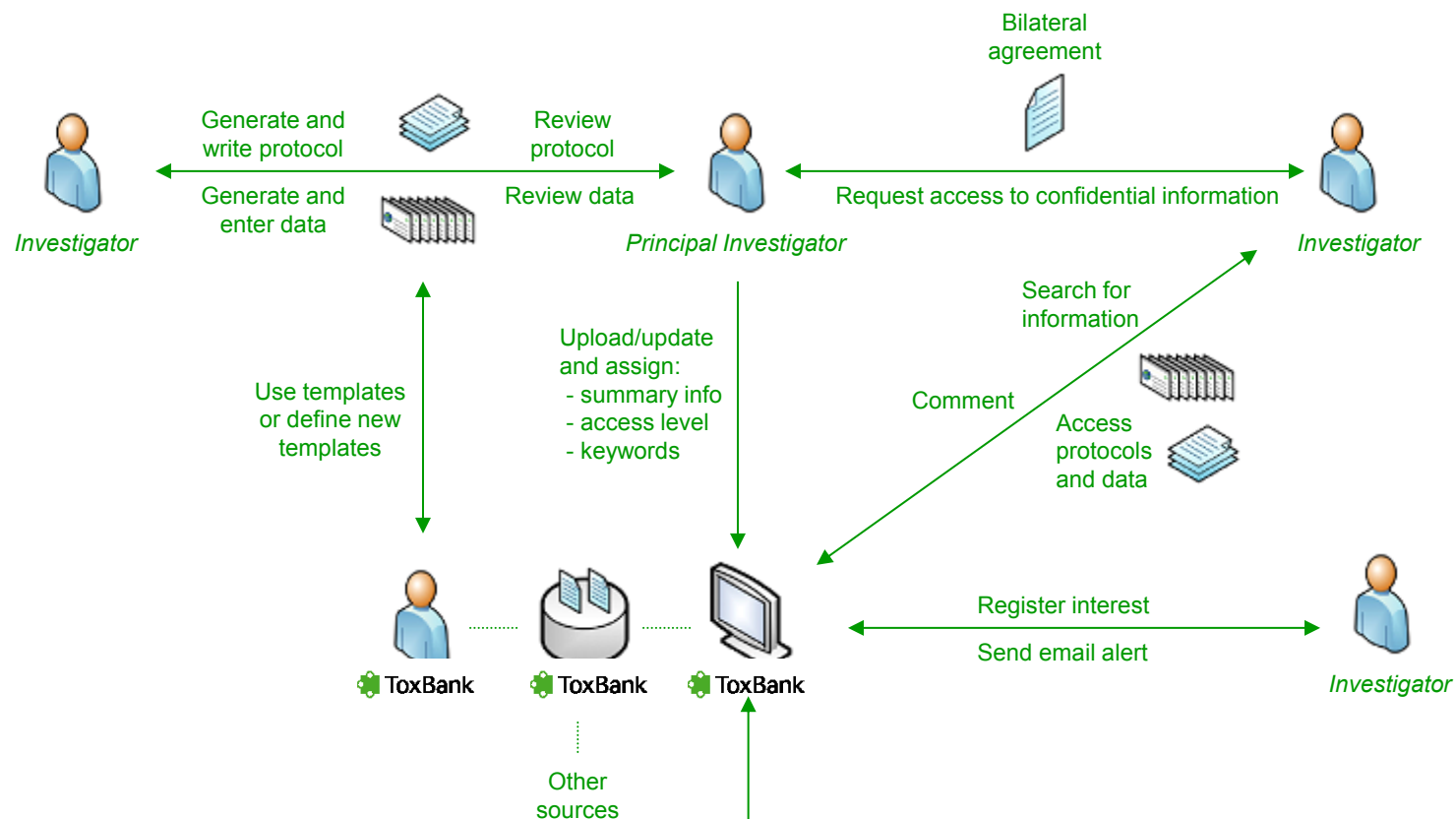
Evaluating different approaches



Storyboarding different user interfaces

Outline of the ToxBank Data Warehouse

Phase 1: Unified data access



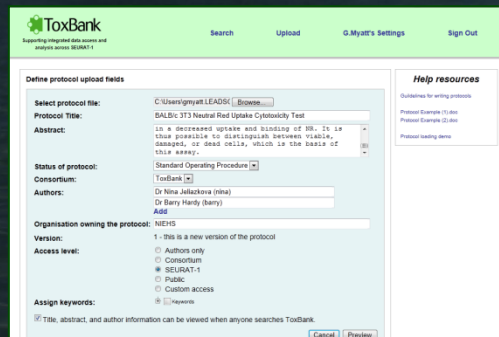
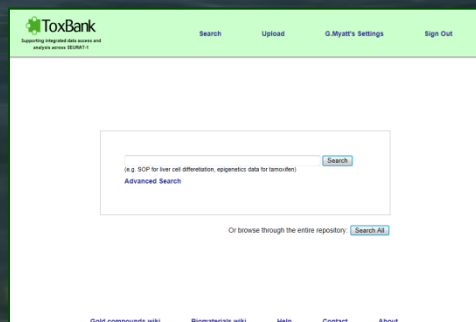
Phase 2: Integrated data analysis

ToxBank – Initial Release & Testing

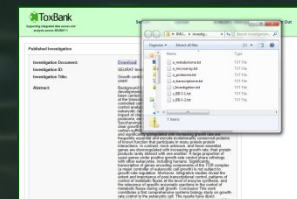
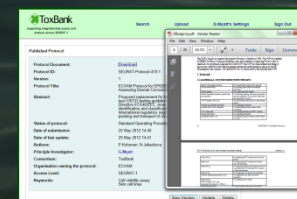
Upload protocols and data

Preparing data

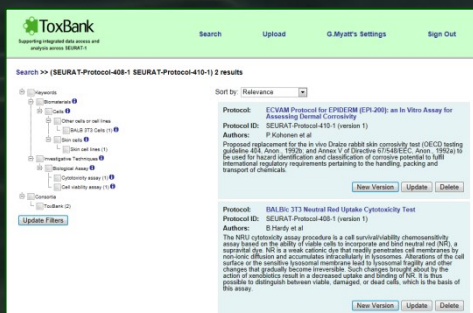
Main screen



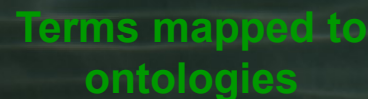
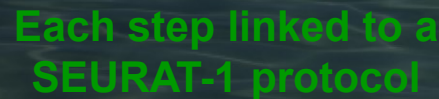
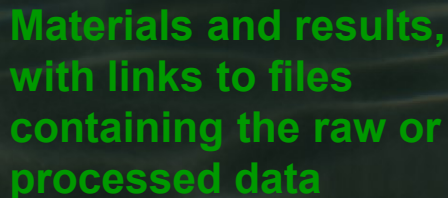
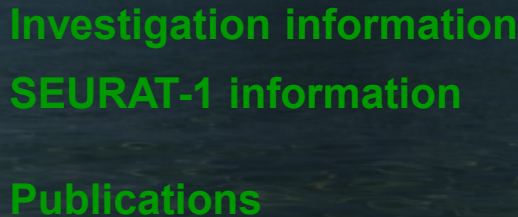
Download protocols and data



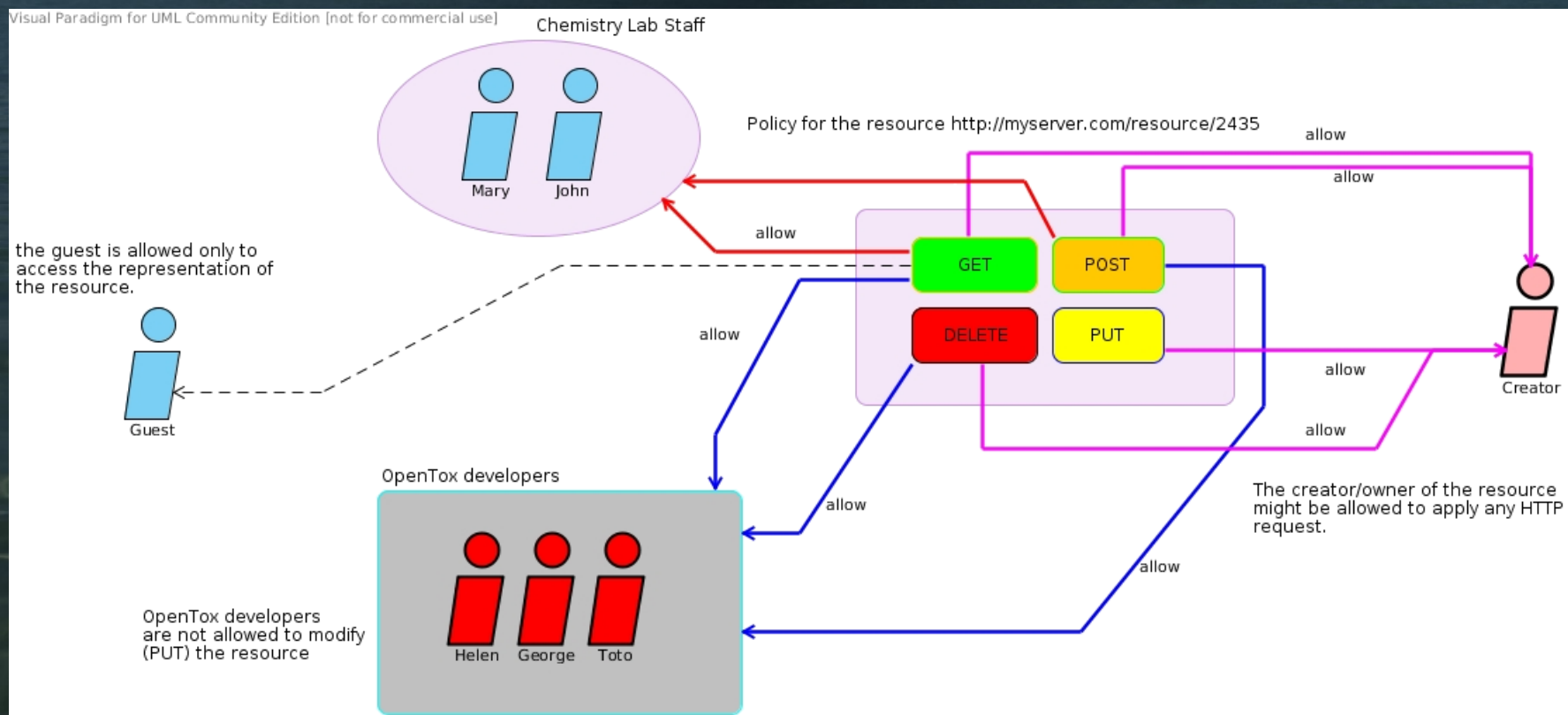
Browse search results



Use of SEURAT-configured ISAcreeator to prepare datasets



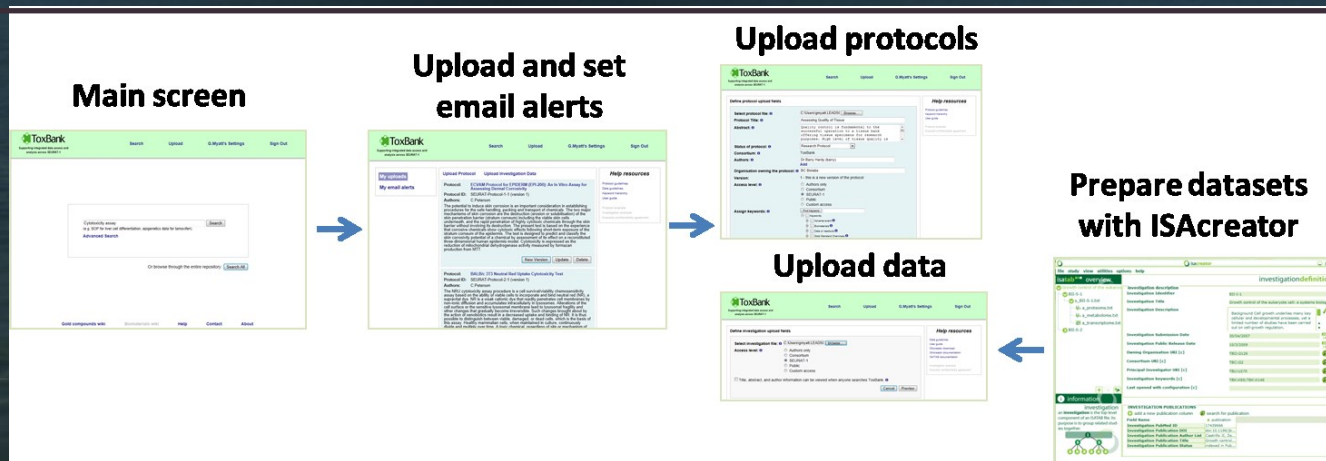
Security



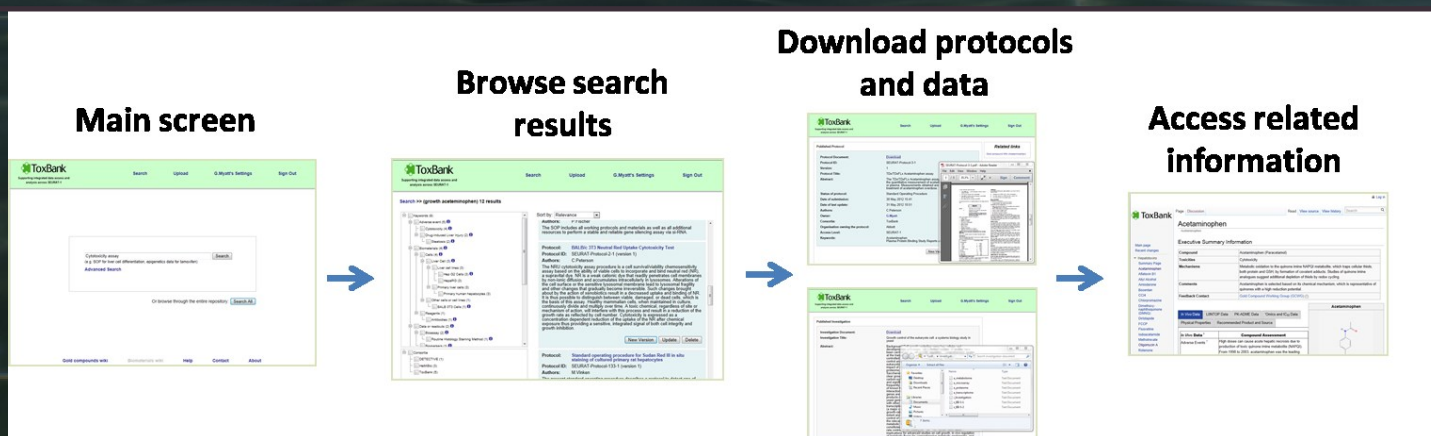
Use Open Standards on Resources but with extensive Authorisation and Authentication facilities accompanied by confidential data policies. e.g. *Validation against Confidential Data Case implemented Spring 2011*

ToxBank System for Data and Protocol Management

Uploading
protocols
and data



Searching



Uploading a protocol

ToxBank
Supporting integrated data access and analysis across SEURAT-1

Search Upload G.Myatt's Settings Sign Out

Define protocol upload fields

Select protocol file: C:\Users\gmyatt\LEADS\ Browse...

Protocol Title: Assessing Quality of Tissue

Abstract: Quality control is fundamental to the successful operation to a tissue bank offering tissue specimens for research purposes. High level of tissue quality is

Status of protocol: Standard Operating Procedure

Consortium: ToxBank

Authors: Dr Nina Jelliazkova (nina)
Dr Barry Hardy (barry)
Add

Organisation owning the protocol: BC BioLibrary

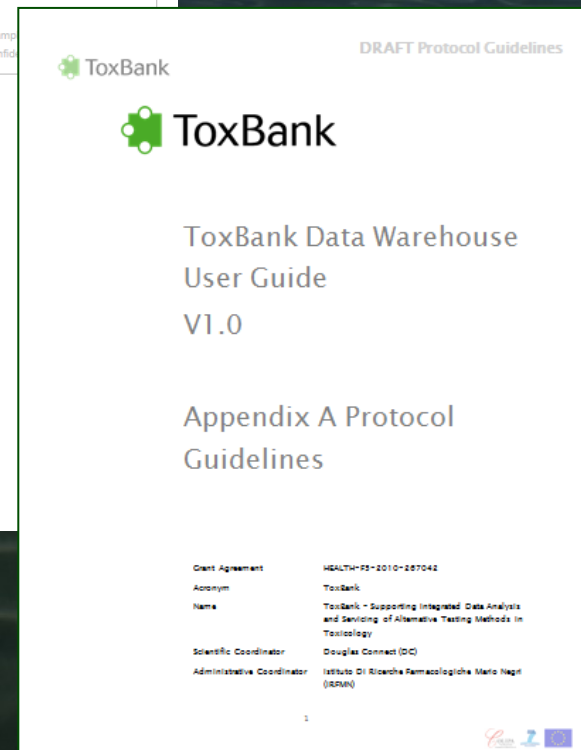
Version: 1 - this is a new version of the protocol

Access level:
☐ Authors only
☐ Consortium
☒ SEURAT-1
☐ SEURAT-1 plus SEP/Cosmetics Europe Taskforce
☐ Public
☐ Custom access

Assign keywords: Find Keyword
☐ Keywords
☐ Adverse event

Help resources

Protocol guidelines
Keyword hierarchy
User guide
Protocol example
Example config



Research Protocol vs. Standard Operating Procedure



DRAFT Protocol Guidelines



ToxBank Data Warehouse
User Guide
V1.0

Appendix A Protocol
Guidelines

Grant Agreement	HEALTH-95-2010-287042
Acronym	ToxBank
Name	ToxBank - Supporting Integrated and Servicing of Alternative Test Toxicology
Scientific Coordinator	Douglas Connect (DC)
Administrative Coordinator	Istituto DI Ricerche Farmacologiche (IRFAR)

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 Data Warehouse User Guide V1.0

Appendix A Protocol Guidelines

Grant Agreement	HEALTH-F5-2010-287042
Acronym	ToxBank
Name	ToxBank - Supporting Integrated Data Analysis and Servicing of Alternative Testing Methods in Toxicology
Scientific Coordinator	Douglas Connors (DC)
Administrative Coordinator	Istituto Di Ricerche Farmacologiche Mario Negri (IRFM)

1



DRAFT Protocol Guidelines

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

5



DRAFT Protocol Guidelines

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.

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

It is helpful to include a headers/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.Protecol.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.Protecol.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 discouraged, 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.

7



Protocol review



ToxBank

DRAFT Protocol Guidelines



ToxBank

ToxBank Data Warehouse
User Guide
V1.0

Appendix A Protocol
Guidelines

Grant Agreement	HEALTH
Acronym	ToxBa
Name	ToxBa
	and Se
	Toxic
Scientific Coordinator	Dougl
Administrative Coordinator	Institu
	(ORCID)

1

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

Assign keywords:

Find Keyword Matched 9 keywords

Keywords

- ☐ Adverse event
- ☐ Apoptosis
- ☐ Cytotoxicity
- ☒ Drug-Induced
- ☒ Heart Disease
- ☐ Muscular Disease
- ☐ Nervous System
- ☐ Phospholipids
- ☐ Renal injury
- ☐ Skin Disorder
- ☒ Biomaterials
- ☒ Data or readouts
- ☒ Gold Standard Chemicals
- ☒ Investigative Techniques
- ☒ Mode of action (MOA)

A form of programmed cell death that begins when a cell receives internal or external signals, then proceeds through a series of characteristic stages typically including rounding-up of the cell, retraction of pseudopods, reduction of cellular volume (pyknosis), chromatin condensation, nuclear fragmentation (karyorrhexis), and plasma membrane blebbing, and ends with the death of the cell. [Source: NCI Thesaurus]

Synonyms:
Apoptotic Process
Programmed Cell Death
PCD

Set keywords to support searching, browsing and linking

Use of SEURAT-configured ISAcreeator to prepare datasets

The screenshot displays the ISAcreeator web application interface. The top navigation bar includes 'file', 'study', 'view', 'utilities', 'options', and 'help'. The main content area is titled 'investigationdefinition' and is divided into two main sections: 'Investigation description' and 'INVESTIGATION PUBLICATIONS'.

Investigation description

Investigation Identifier	BII-I-1
Investigation Title	Growth control of the eukaryote cell: a systems biology study
Investigation Description	Background Cell growth underlies many key cellular and developmental processes, yet a limited number of studies have been carried out on cell-growth regulation. Comprehensive studies at the
Investigation Submission Date	30/04/2007
Investigation Public Release Date	10/3/2009
Owning Organisation URI [c]	TBO:G176
Consortium URI [c]	TBC:G2
Principal Investigator URI [c]	TBU:U115
Investigation keywords [c]	TBK:CellViabilityAssay;TBK:CellMigrationAssays;;TBK:Epig
Last opened with configuration [c]	

INVESTIGATION PUBLICATIONS

add a new publication column search for publication

Field Name	publication
Investigation PubMed ID	17439666
Investigation Publication DOI	doi:10.1186/jb...
Investigation Publication Author List	Castrillo JI, Ze...
Investigation Publication Title	Growth control...
Investigation Publication Status	indexed in Pub...

INVESTIGATION CONTACTS

Investigation information

an **investigation** is the top level component of an ISATAB file. Its purpose is to group related studies together.

Publications

Investigation information

SEURAT-1 information

Publications

Use of SEURAT-configured ISAcceptor to prepare datasets

isatab overview

✓ Growth control of the eukaryo...

✓ BII-S-1

✓ s_BII-S-1.txt

✓ a_proteome.txt

✓ a_metabolome.txt

✓ a_transcriptome.txt

STUDY ASSAYS

+ add new assay(s)

protein expression pro...
mass spectrometry
ITRAQ
a_proteome.txt

metabolite profiling
mass spectrometry
LC-MS/MS
a_metabolome.txt

transcription profiling
DNA microarray
Affymetrix
a_transcriptome.txt

STUDY DESIGN DESCRIPTORS

+ add a new design column

Field Name

Study Design Type

STUDY PUBLICATIONS

+ add a new publication column search for publication

Field Name

Study PubMed ID	17439666
Study Publication DOI	doi:10.1186/jb...
Study Publication Author List	Castrillo JI, Ze...
Study Publication Title	Growth control...
Study Publication Status	published

STUDY FACTORS

+ add a new factor column select from previous factors...

Field Name

Study Factor Name	limiting nutrient	rate
Study Factor Type	CHEBI:chemic...	PATO:rate

information

study

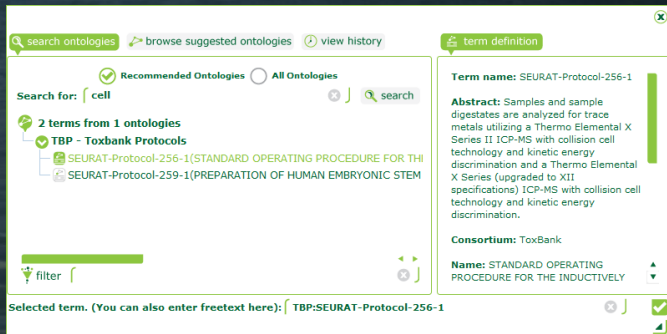
a study contains information about: samples; treatments applied; and associated assays.

```
graph TD
    I((I)) --- S1((S))
    I --- S2((S))
    S1 --- A1((a))
    S1 --- A2((a))
    S1 --- A3((a))
    S2 --- A4((a))
    S2 --- A5((a))
    S2 --- A6((a))
```

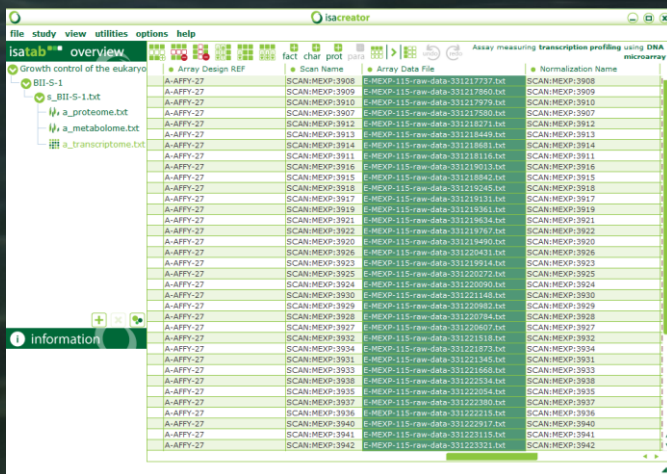
Templates for different assays

Specify experimental factors

Use of SEURAT-configured ISAcreeator to prepare datasets



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



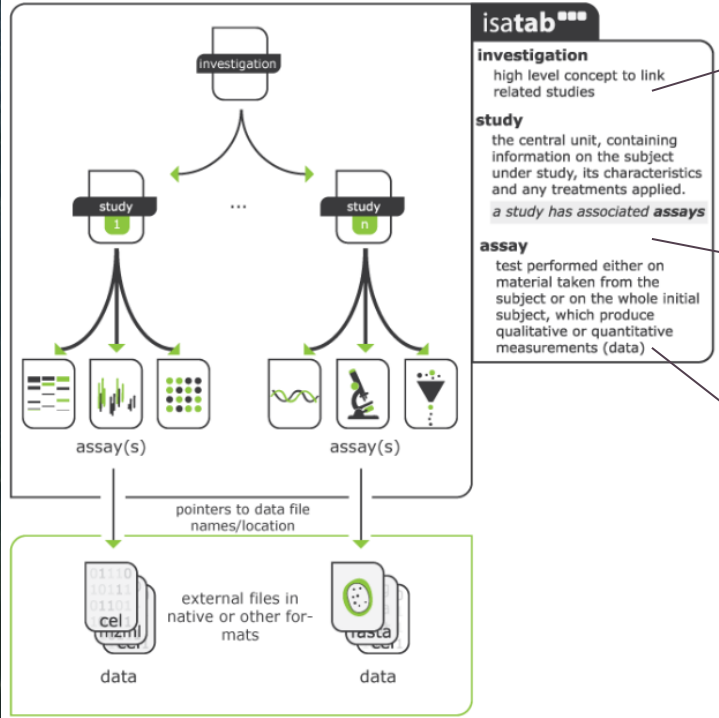
Results, with links to files containing the raw or processed data

Use of SEURAT-configured ISAcreeator to prepare datasets

The screenshot displays the ISAcreeator web interface. At the top, there are tabs for 'search ontologies' and 'view history'. Below these, a search bar contains 'acetaminophen'. The results show '236 terms from 5 ontologies', including MDR - MedDRA, CHEBI - Chemical entities of biological interest (with sub-entries for acetaminophen O-beta-D-glucosiduronic acid, acetaminophen glutathione conjugate, paracetamol sulfate, and paracetamol), SNOMEDCT - SNOMED Clinical Terms, EFO - Experimental Factor Ontology, and NCIt - NCI Thesaurus. A 'filter' button is at the bottom left. On the right, the 'term definition' panel for 'paracetamol' is shown, featuring its chemical structure, exact synonym 'N-(4-hydroxyphenyl)acetamide', related synonym 'InChIKey=RZVAJINKPMORJF-UHFFFAOYSA-N', and accession 'CHEBI:46195'. A 'Selected term' bar at the bottom shows 'CHEBI:paracetamol'.


Mapped to terms in ontologies

Create an ISATAB zip archive for each investigation



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

Publishing a protocol

 **ToxBank**
Supporting integrated data access and
analysis across SEURAT-1

SearchUploadG.Myatt's SettingsSign Out

G.Myatt's account >> Preview protocol update

Protocol Document:	Download
Protocol ID:	SEURAT-Protocol-191-1
Version:	1
Protocol Title:	Assessing Quality of Tissue
Abstract:	Quality control is fundamental to the successful operation to a tissue bank offering tissue specimens for research purposes. High level of tissue quality is essential to avoid introducing inconsistencies and variables into research studies. BCUs should be confident that they are providing tissue samples with the appropriate quality to meet the research needs of investigators. Testing procedures should be in place to monitor and assess the quality of the samples.
Status of protocol:	Research Protocol
Date of submission:	28 November 2012 13:19
Date of last update:	28 November 2012 13:19
Authors:	B.Hardy, N.Jeliazkova
Owner:	G.Myatt
Consortia:	ToxBank
Organisation owning the protocol:	BC BioLibrary
Access Level:	SEURAT-1
Keywords:	Cellular quality

[Publish](#) [Update](#) [Delete](#)

Unique ID and version number

Viewing the investigation record

The screenshot displays the ToxBank website interface. At the top, the ToxBank logo is on the left, and navigation links for Search, Upload, G.Myatt's Settings, and Sign Out are on the right. Below the header, the 'Published Investigation' section is visible. It includes fields for 'Investigation Document:', 'Investigation Title:', and 'Abstract:'. The 'Investigation Title:' field contains the text 'Growth control of the eukaryote cell: a systems biology study in yeast'. The 'Abstract:' field contains a longer text starting with 'Background Cell growth underlies many key cellular and...'. A 'Download' link is present next to the title. Overlaid on the right side of the page is a file explorer window titled '<< ToxB... >> investigati...'. The window shows a list of files with columns for Name and Type. The files listed are: a_metabolome (Text Document), a_microarray (Text Document), a_proteome (Text Document), a_transcriptome (Text Document), i_Investigation (Text Document), s_BII-S-1 (Text Document), and s_BII-S-2 (Text Document). The window also shows a sidebar with 'Favorites' and 'Libraries' sections, and a status bar at the bottom indicating '7 items'.

ToxBank
Supporting integrated data access and analysis across SEURAT-1

[Search](#) [Upload](#) [G.Myatt's Settings](#) [Sign Out](#)

Published Investigation

Investigation Document:

Investigation Title: [Download](#)
Growth control of the eukaryote cell: a systems biology study in yeast

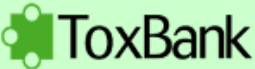
Abstract:
Background Cell growth underlies many key cellular and...
development...
been car...
at the tra...
controlled...
control at...
eukaryote...
impact of...
proteome...
Saccharo...
clear gro...
carbon-s...
and sign...
frequentl...
of known...
interacti...
genes ar...
products...
yeast ge...
with othe...
transcrip...
(a major...
growth-ra...
extent an...
control of...
the relev...
metabolic...
constitute...
rate cont...
implicatio...
of metabolic fluxes for comprehensive metabolic engineering, and
for the design of non-ense... scale systems biology models of the

File Explorer Window: << ToxB... >> investigati...
Search investigation-document

Name	Type
a_metabolome	Text Document
a_microarray	Text Document
a_proteome	Text Document
a_transcriptome	Text Document
i_Investigation	Text Document
s_BII-S-1	Text Document
s_BII-S-2	Text Document

7 items

Linking to wikis



Supporting integrated data access and analysis across SEURAT-1

[Search](#) [Upload](#) [G.Myatt's Settings](#) [Sign Out](#)

Published Protocol

Protocol Document:

Protocol ID:

Version:

Protocol Title:

Abstract:

Email the owner to request access: [U.Summer school](#)

SEURAT-Protocol-38-1


1

In vitro test for py...

Parenteral pharm... pyrogenic (fever... general be define... pyrogens that alm... pharmaceuticals... LPS) from Gram... 1979b). There are... contamination: the... amoebocyte lysat... detects LPS and... body temperature... a sterile solution... LAL test detects... the bacterial endo... that LPS causes... (haemolymph) of... & Page 1964) A...

Related links

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



Main page
Recent changes

- Hepatotoxins
 - Summary Page
 - Acetaminophen
 - Aflatoxin B1
 - Amiodarone
 - Bosentan
 - CCl4
 - Chlorpromazine
 - Dimethoxy-naphthoquinone (DMNQ)
 - Iodoacetamide
 - Methotrexate
 - Rotenone
 - Tamoxifen
 - Valproic Acid
- Cardiotoxins
- Special Substances
- Toolbox

Page [Discussion](#)

Acetaminophen

Acetaminophen

Executive Summary Information

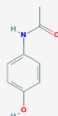
Compound	Acetaminophen (Paracetamol)
Toxicities	Cytotoxicity
Mechanisms	Metabolic oxidation to the quinone imine NAPQI metabolite, which traps cellular thiols, both protein and GSH, by formation of covalent adducts. Studies of quinone imine analogues suggest additional depletion of thiols by redox cycling.
Comments	Acetaminophen is selected based on its chemical mechanism, which is representative of quinones with a high reduction potential.
Feedback Contact	Gold Compound Working Group (GCWG)

[In Vivo Data](#) [LIINTOP Data](#) [PK-ADME Data](#) [Omics and IC₅₀ Data](#) [Physical Properties](#)


Recommended Product and Source

In Vivo Data ?	Compound Assessment
Adverse Events ?	High doses can cause acute hepatic necrosis due to production of toxic quinone imine metabolite (NAPQI). From 1998 to 2003, acetaminophen was the leading cause of acute liver failure in the United States, with 48% of acetaminophen-related cases (131 of 275) associated with accidental

Acetaminophen



ToxBank Wiki Development

 **ToxBank**

Main page

Recent changes

Hepatotoxins

Cardiotoxins

Renal Toxins

Special Substances

Undifferentiated Stem Cells

Reagents (Growth Factors)

Reagents (Antibodies)

Reagents (Others)

Suppliers (Cells)

ALSPAC

Asterand

Biopredic

Cellartis

Cellular Dynamics

DSMZ

HPACC

ICLC

Lonza BioResearch

Riken Bioresource

Page

Discussion

Read

Edit

View history

Search

Main Page

Main Page

ToxBank Wiki

The following wiki pages provide information on compounds and biological materials developed as part of the [SEURAT-1](#) cluster through the ToxBank project. The research leading to these results has received funding from [Cosmetics Europe](#) and the [European Community's Seventh Framework Programme](#) (FP7/2007-2013) under grant agreement n° [267042]. This wiki site reflects only the authors' views. The European Community and Cosmetics Europe are not liable for any use that may be made of the information contained herein.

Gold compounds wiki pages

Information on this wiki is based on the research and compound selection tasks performed by the Gold Compound Working Group (GCWG) using a selection criteria outlined by members of the GCWG. Further background information may be available from this working group or under review; selected reviewed materials are made available here.

- Hepatotoxic Compounds
- Cardiotoxic Compounds
- Selection Criteria

Questions, inquiries, comments and feedback regarding the **scientific content** on these pages may be directed to the [Gold Compound Working Group \(GCWG\)](#). The email will automatically be sent to all members on the GCWG group.

Assistance with wiki access or issues with the website in general may be directed to [Micha Rautenberg](#) or [David Bower](#) of the ToxBank project.

Biological materials wiki pages

This wiki contains information on cells and reagents relevant to the SEURAT-1 cluster. The following document provides guidance for the banking and supply of human embryonic stem cells:

- [Consensus guidance for banking and supply of human embryonic stem cell lines for research purposes.](#)

Questions, inquiries, comments and feedback regarding the scientific content on these pages may be directed to the [Luam Kidane](#) at the UK Stem Cell Bank.

Recent News

A report detailing the compound selection strategy was produced as a result of the numerous insightful meetings held at the [Seurat-1 2nd Annual Meeting](#) and may be downloaded [here](#).

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. Grafström,^[a] Lyn Healy,^[d] Christoph Helma,^[e] Nina Jeliaskova,^[f] Vedrin Jeliaskov,^[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] Pharmatrop, 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

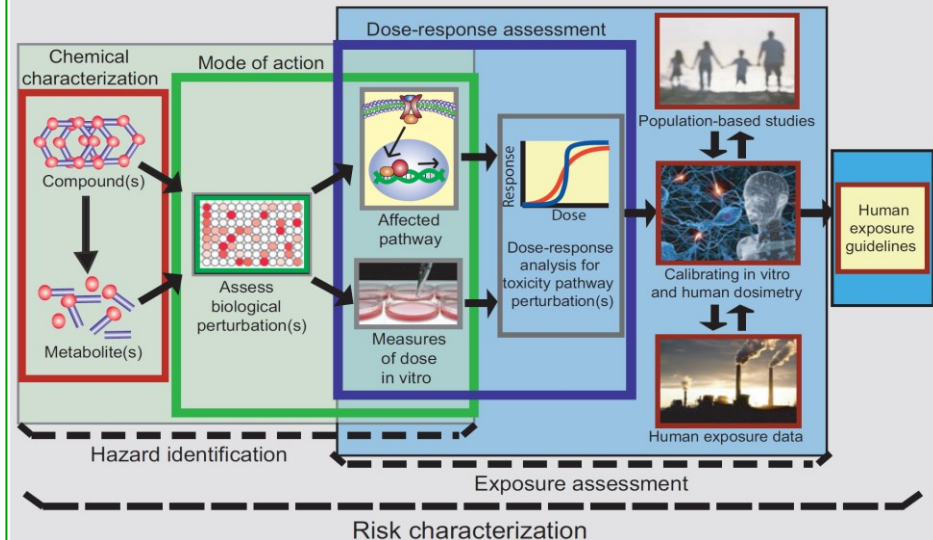
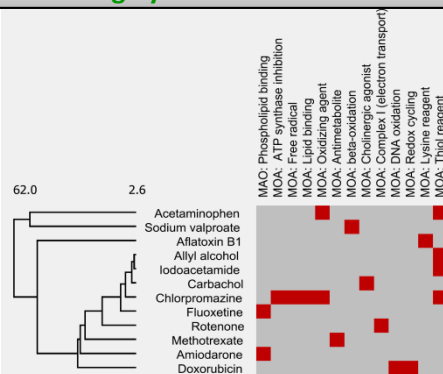


Figure 1. Multiple tools will be, **step by step**, implemented into an **innovative toxicity testing** strategy based on **mode-of-action**.

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

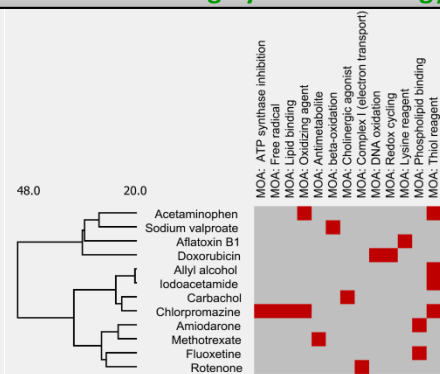
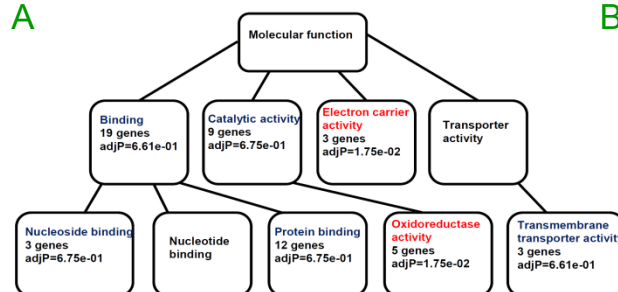


Figure 2. Clustering of ToxBank Gold Compounds by **biological similarity** using chemical-genome links from Comparative Toxicogenomics Database (CTD). Compounds with similar Mode-of-Action cluster together.

A



B

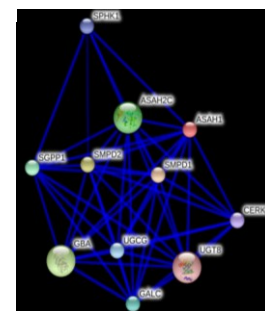


Figure 3. A) Enriched gene ontology (GO) categories of genes associated with the oxidizing agent mode-of-action (MOA) B) Protein-protein association network around the Asah1 protein. Associated with phospholipid binding MOA

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



CANCER- OCH
ALLERGIFONDEN
cancer - allergi - miljö



Cosmetics Europe
International Cosmetics Federation



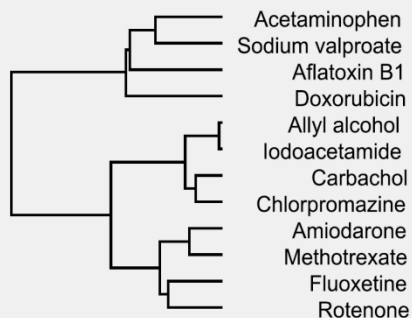
Karolinska
Institutet



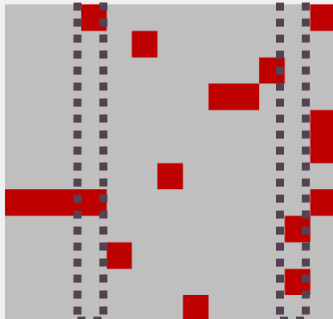
IMM Institute of Environmental Medicine
Institutet för Miljömedicin

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

48.0 20.0

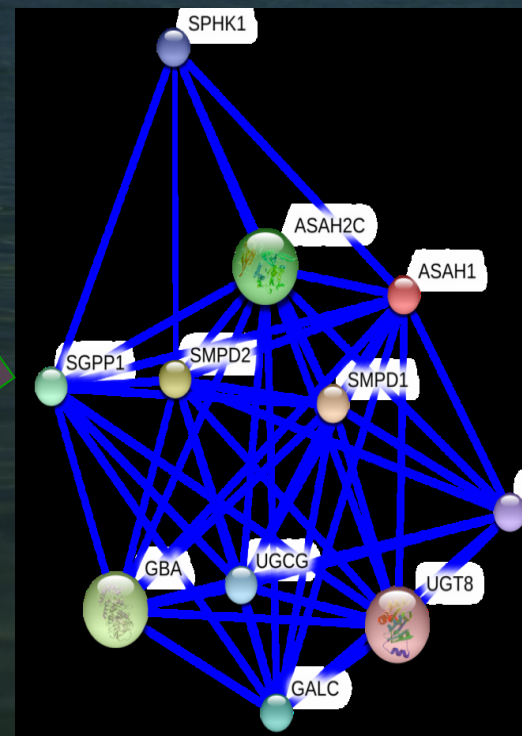


MOA: ATP synthase inhibition
MOA: Free radical
MOA: Lipid binding
MOA: Oxidizing agent
MOA: Antimetabolite
MOA: beta-oxidation
MOA: Cholinergic agonist
MOA: Complex I (electron transport)
MOA: DNA oxidation
MOA: Redox cycling
MOA: Lysine reagent
MOA: Phospholipid binding
MOA: Thiol reagent



Public Data Analysis

Phospholipid Binding



Oxidative Agent

Molecular function

Binding

19 genes
adjP=6.61e-01

Catalytic activity

9 genes
adjP=6.75e-01

Electron carrier activity

3 genes
adjP=1.75e-02

Transporter activity

Nucleoside binding

3 genes
adjP=6.75e-01

Nucleotide binding

Protein binding

12 genes
adjP=6.75e-01

Oxidoreductase activity

5 genes
adjP=1.75e-02

Transmembrane transporter activity

3 genes
adjP=6.61e-01

*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 browser address bar: <http://onlinelibrary.wiley.com/doi/10.1002/minf.201200114/full>

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ABOUT THIS JOURNAL

molecular informatics

models – molecules – systems

Full Paper

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

Pekka Kohonen¹, Emilio Benfenati², David Bower³, Rebecca Ceder¹, Michael Crump³, Kevin Cross³, Roland C. Grafström¹, Lyn Healy⁴, Christoph Helma⁵, Nina Jeliaskova⁶, Vedrin Jeliaskov⁶, Silvia Maggioni², Scott Miller³, Glenn Myatt³, Michael Rautenberg⁵, Glyn Stacey⁴, Egon Willighagen¹, Jeff Wiseman⁷, 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)

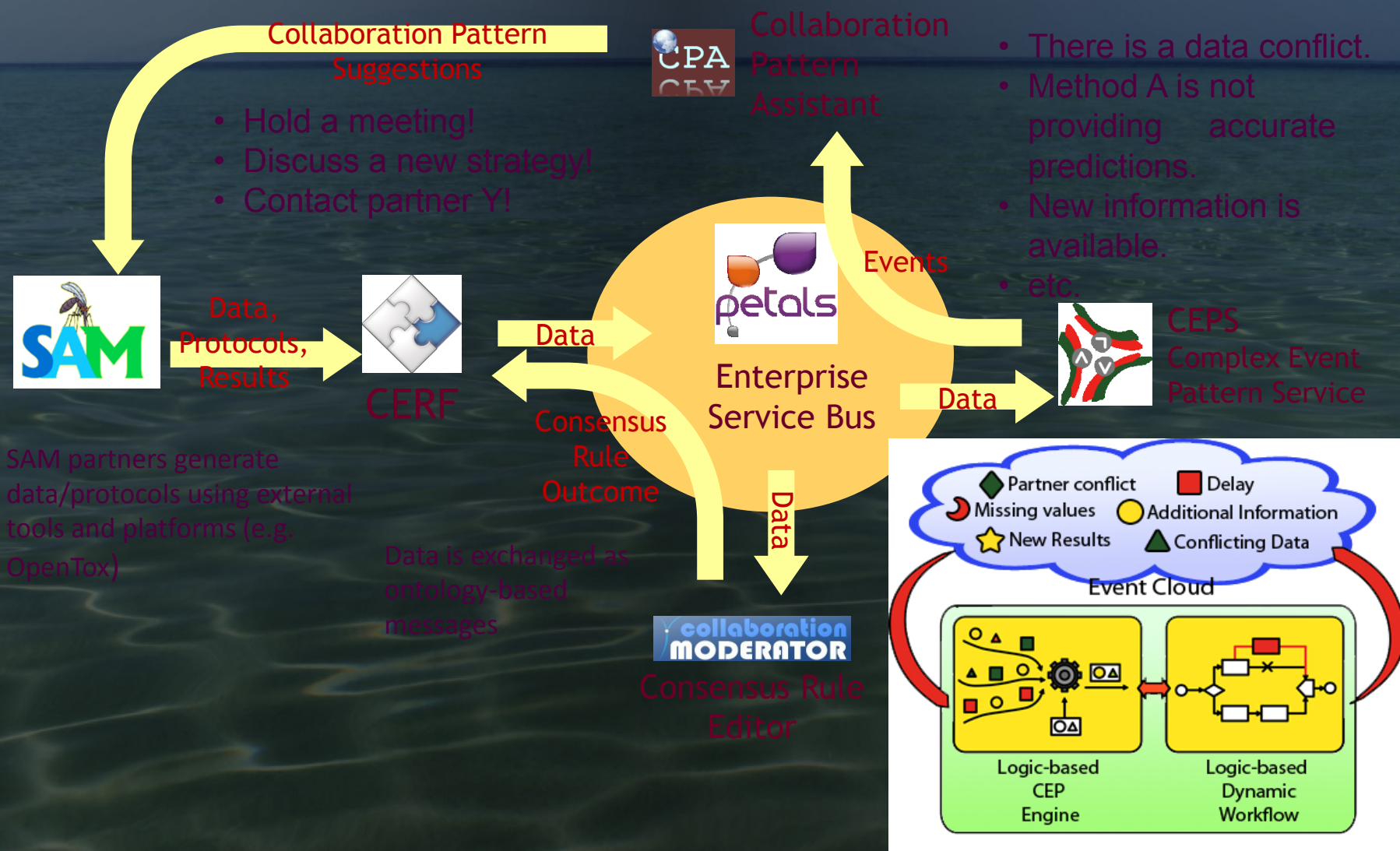
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Abstract | **Article** | References | Supporting Information | Cited By

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SAM ICT Architecture



Hardy and Affentranger, Drug Discovery Today.

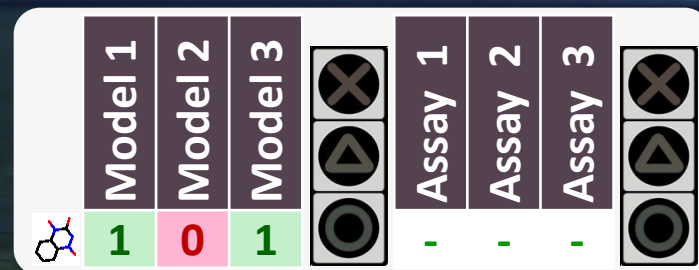
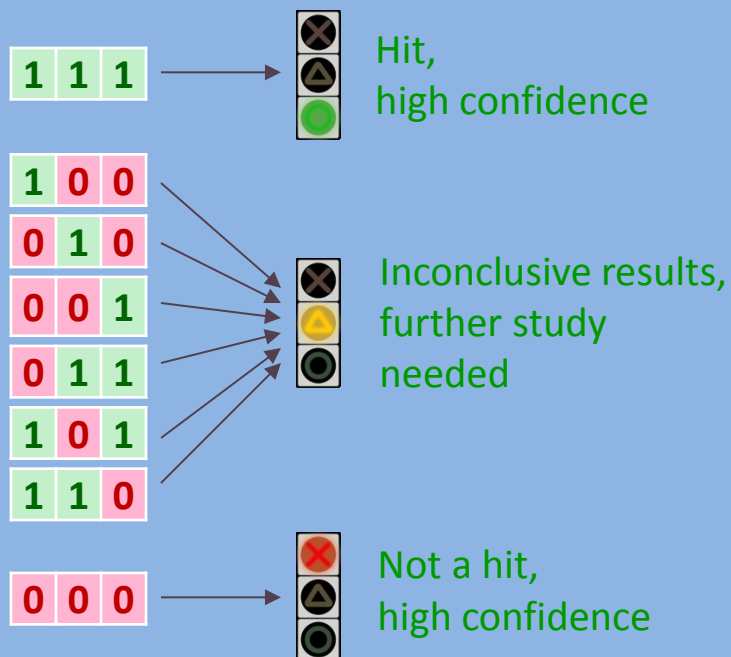
2013 Jul;18(13-14):681-6.

Event Driven Weight of Evidence

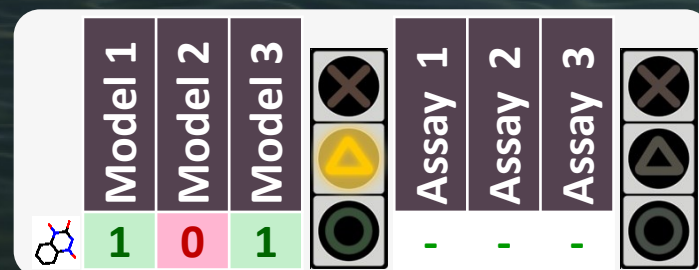
collaboration
MODERATOR

Consensus Rule
Editor

Recommendation Rules:



Synergy



OpenTox



Event-driven Weight of Evidence

CERF Client v4.0.0 - Logged in to Enterprise as jspitzner

Sessions Collections Bookmarks Search Tools Help

Project: Project-1001 Subject: Subject-1001 Compound Set: All Compound Sets Refresh Show Filters New Project New Subject New Compound Set New Compound Add Result

Results 1 to 100 of 197

Compound ID	Phase	VS	Dock	Dock 2	Binding Prediction Stoplight	QSAR ADME	QSPR ADME	ADME Prediction Stoplight	Binding + ADME Prediction Stoplight	Logic Based Tox	Limited Free Energy Tox	Toxicology Prediction Stoplight	Binding + ADME + Tox Prediction Stoplight	Saturation Binding Assay	Protein-DNA Binding Assay	Binding Assay Stoplight	In Vitro Toxicology Assay	In Vivo Toxicology Assay	Toxicology Assay Stoplight	Binding + Tox Assay Stoplight	Final Stoplight
UC0000353		0	0					0.0	-6.0999999												
UC0000862		1	1					-10.47	-10.8												
UC0000864		1	1					-10.2	-10.9												
UC0000884		1	1					-9.1400003	-10.6												
UC0000885		1	1					-9.1400003	-10.5												
UC0000886		1	1					-9.41	-10.6												
UC0000921		1	1					-10.91	-9.1000004												
UC0001349		1	1					-9.9799995	-11.2												
UC0001350		1	1					-9.96	-11.2												
UC0001500		1	1					-9.3299999	-9.3999996												
UC0001501		1	1					-9.5699997	-9.6000004												
UC0001623		1	1					-9.4899998	-9.1000004												
UC0001624		1	1					-9.4899998	-9.1000004												
UC0001699		1	1					-12.2	-10.9												
UC0001700		1	1					-9.9899998	-9.8000002												
UC0001702		1	1					-13.37	-9.6000004												
UC0001703		1	1					-10.61	-10.7												
UC0001743		1	1					-9.29	-9.1000004												
UC0001775		1	1					-9.7700005	-9.1000004												
UC0001875		1	1					-9.84	-9.2												
UC0001987		1	1					-9.7700005	-9.1999998												
UC0002838		1	1					-9.1999998	-9.8999996												
UC0002854		1	1					-10.09	-10.0												
UC0003266		1	1					-9.4799995	-9.8000002												
UC0003454		1	1					-9.1899996	-10.0												
UC0003835		1	1					-9.1000004	-9.8000002												
UC0003867		1	1					-10.25	-9.3999996												
UC0003923		1	1					-9.7200003	-9.8000002												
UC0003941		1	1					-10.52	-9.3000002												
UC0003973		1	1					-9.3100004	-9.1999998												

Previous Next Results per page: 100

Aggregate Resource

Project Subject Compound Set Compound

Title: Project-1001

Status ?

Edit Status: Versionable

Owner: jspitzner

My Role: Notebook Creator

Closed: No

Checked Out: No

Visibility: Shared

Id: 26203 (Federation: 43214, Server: 801)

Metadata ?

Title: Project-1001

Submission/Modification

Resource Type: Drug Design Project

Creation Date: Oct 21, 2010 2:57:10 PM

Last Update: Oct 21, 2010 2:57:10 PM

Contributor: Jeff Spitzner

Relations and Annotations ?

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2013 Jul;18(13-14):681-6.

ToxBank Acknowledgements

DouglasConnect

in silico toxicology



*UK Stem Cell Bank,
NIBSC-HPA*

Ideaconsult Ltd