# Douglas Connect

# eNanoMapper

Nano Safety Cluster Meeting
Antalya, Turkey
Barry.Hardy@douglasconnect.com
23 April 2014



# Main objectives of eNanoMapper

- Modular infrastructure for data storage, sharing and searching, based on open standards and semantic web technologies, minimum information standards and established security solutions;
- Development of ontologies for the categorisation and characterisation of eNMs in collaboration with other projects
- Creation of new computational models in nanomaterials safety through the implementation of interfaces for toxicity modelling and prediction algorithms which may process all data made available through eNanoMapper (e.g. using algorithms available from the OpenTox FP7 project or statistical/data mining software)
- Meta analysis of nano-bio interactions supporting "safe-by-design" ENMs development by pursuing a Linked Data approach which integrates data and metadata originating from diverse sources within nanoscience, chemistry, biology and toxicology
- Creation of tools for the exchange, quality assurance and reporting of research protocols and data for regulatory purposes
- Creation of a community framework for interdisciplinary collaboration









# Interactions

- We are here to meet you!
- We are here to learn about your projects, needs and initiatives!
- Support of a community framework for interdisciplinary collaboration
- Participation in Working Groups (WG Leaders: Egon Willighagen, Bengt Fadeel)
- Interaction with modelling Group Projects (Harmonisation, Data Standards and Infrastructure, Supporting Analysis, QSAR, Mechanistic Modelling of Pathway Perturbations)
- Interaction with Future Nano Needs on Common Nomenclature
- Interaction with Marina on Templates
- Interaction with Nanosolutions on safety classification
- Interaction with NANoREG regulatory needs, creation of tools for the exchange, quality assurance and reporting of research protocols and data for risk assessment purposes
- Contributions to workshop and training activity (e.g., Milan, Syracuse)

..... and more to define with you through our discussions.



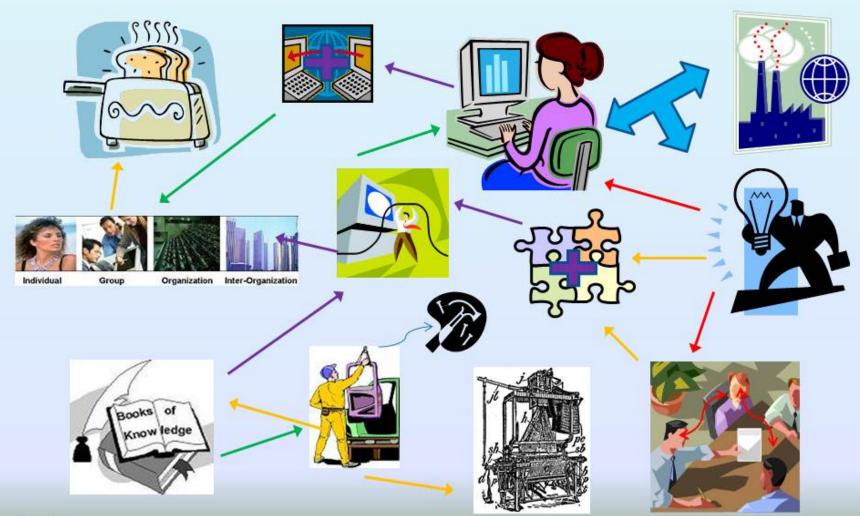
# Islands



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



# **Knowledge Flow**

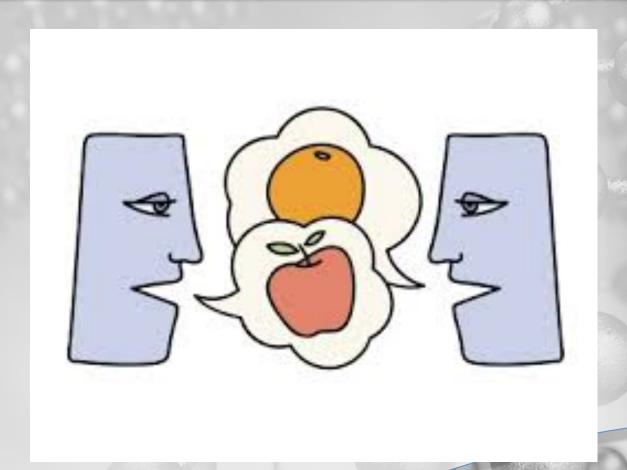




# Interaction



# Common Language



Source: http://sheezaredhead.wordpress.com/2011/01/12/use-common-language-please/



# Adverse Outcome Pathway (AOP): Neurotoxicity induced by NMDA receptor over activation

Molecular **Cellular effects Organ effects Organism effects Initiating Event** (MIE) Loss/reduction Intracellular Ca +2 of overload (collapse of calcium cognitive homeostasis) function neurodegenerative Neurodisorders Mitochondrial Overdegeneration Loss/reduction dysfunction/ROS activation of PD, AD, **Autophagy** production of sensory **NMDA** autism, function neuropathic receptor pain Decreased **Apoptosis** ER stress; protein neuronal Loss/reduction aggregation networking of motor function Collapse of ATP/ Secondary **NADH** homeostasis

necrosis

Mitochondrial transition pore





#### **A Semantic Web for Safety Assessment**

**Linked Data** is a term used to describe the exposing, sharing, and connecting of data on the Semantic Web using:

URIs a generic means to identify entities in the world
HTTP a simple yet universal mechanism for retrieving resources
RDF a generic graph-based data model with which to structure and link data

#### Linked Data needs:

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

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



DBpedia = Linked Data approach applied to Wikipedia



#### **Open Standards and Open Source Components**

-New API addition from ToxBank

# Investigation (Study, Assay)

GET POST PUT DELETE

**Feature** 

GET POST

PUT

**DELETE** 

Authorisation & Authentication

GET
POST
PUT
DELETE

#### **Dataset**

GET POST PUT DELETE

#### Compound

GET
POST
PUT
DELETE

#### **AppDomain**

GET POST PUT DELETE

#### Model

GET
POST
PUT
DELETE

#### Algorithm

GET
POST
PUT
DELET

#### Report

GET POST PUT DELETE

#### **Validation**

GET
POST
PUT
DELETE

#### **Ontology**

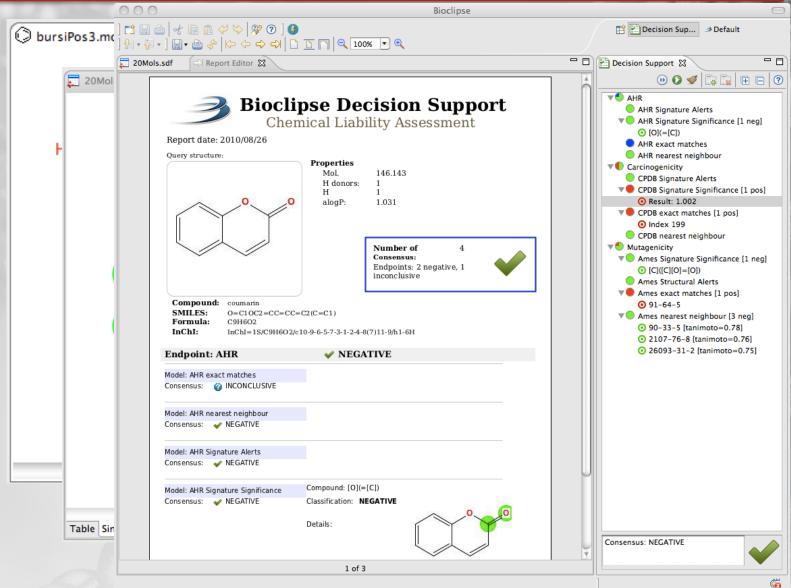
GET
POST
PUT
DELETE





www.opentox.org/dev/apis

#### **Bioclipse – OpenTox Interactive Analysis**



O. Spjuth, L. Carlsson, M. Eklund, E. Ahlberg Helgee, and Scott Boyer. *Integrated decision support for assessing chemical liabilities*. J Chem Inf Model. 2011 Aug 22;51(8):1840-7.



# Requirements Analysis

Contextual Design methodology....

- 1. Interview
- 2. Interpretation
- 3. Consolidation
- 4. System design
- 5. Paper prototyping

....provides several opportunities to collaborate in specifying solutions for the Nano Safety cluster













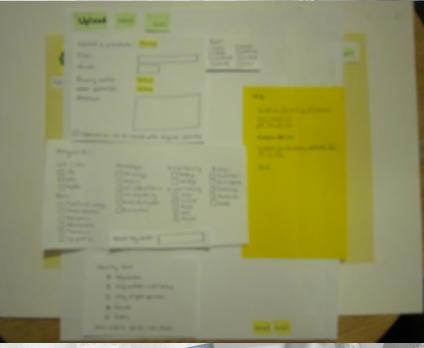




# **Storyboarding** Production ! STREET, SQUARTER SHALL BE MARKET LAN CHARLES THE

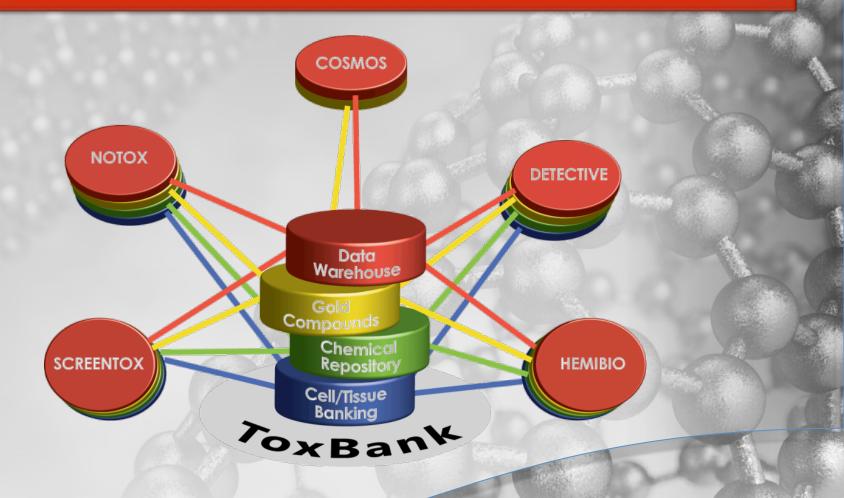
# Paper Prototyping







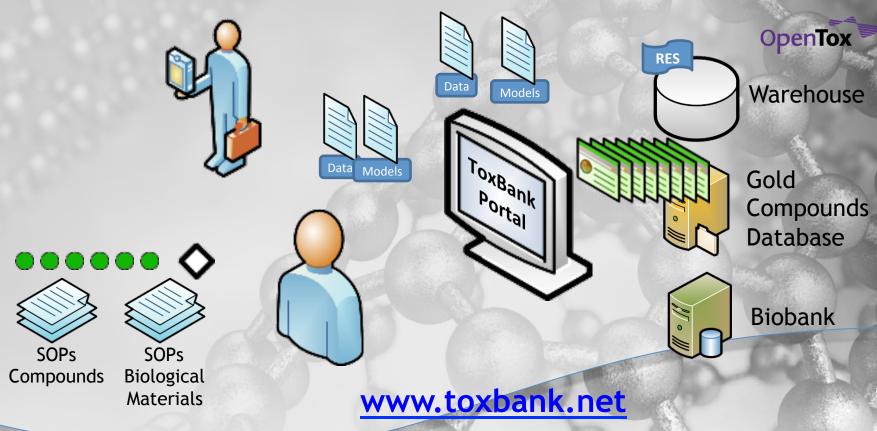
# Collaboration





#### ToxBank Infrastructure System Vision

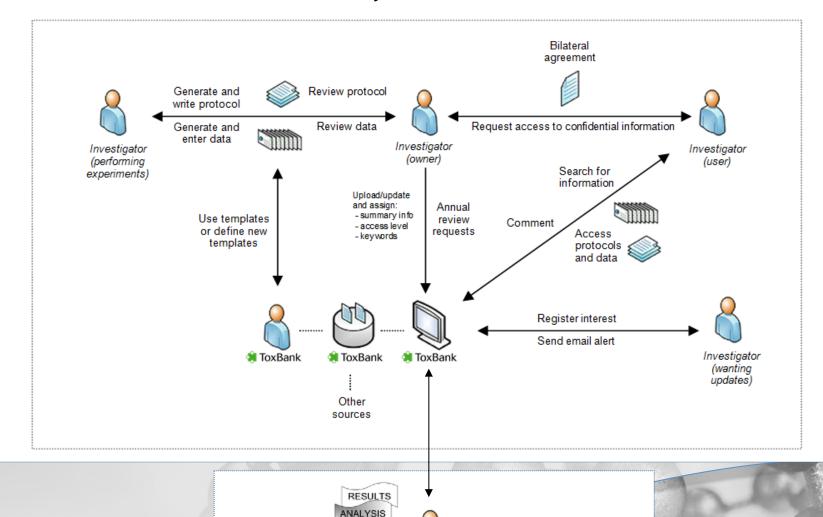
Users access compounds, biological materials, data and models for experimental planning and integrated analysis of experimental results





#### Outline of the ToxBank Data Warehouse

Phase 1: Unified data access



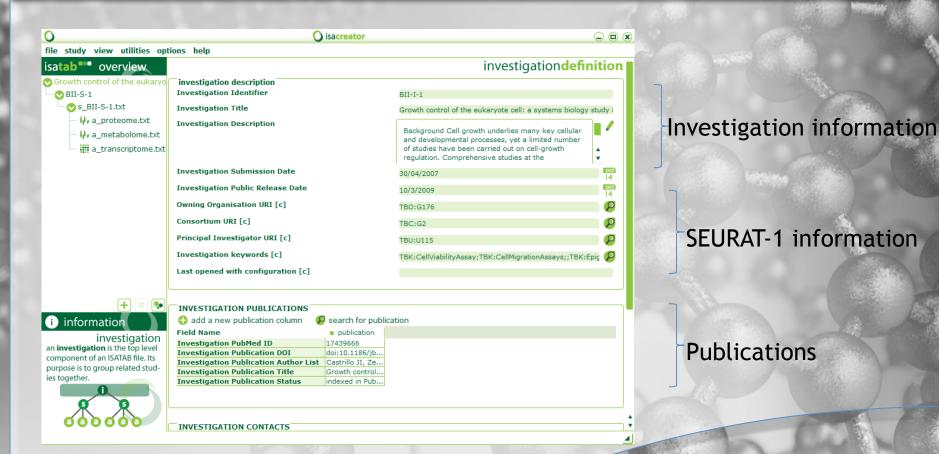




Investigator

MODEL

#### **Use of SEURAT-configured ISAcreator to prepare datasets**



Templates are used to describe different experiments in a standardised way



#### Use of SEURAT-configured ISAcreator to prepare datasets

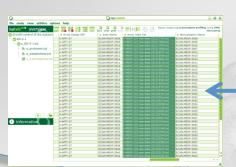


Investigation information SEURAT-1 information

**Publications** 



Templates for different assays

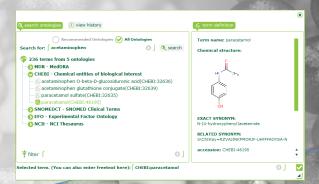


Specify experimental factors

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



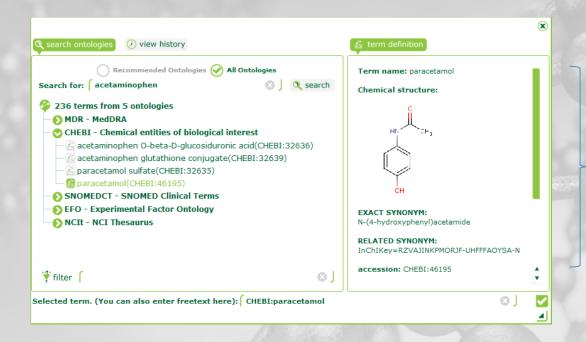
# Each step linked to a SEURAT-1 protocol



Terms mapped to ontologies



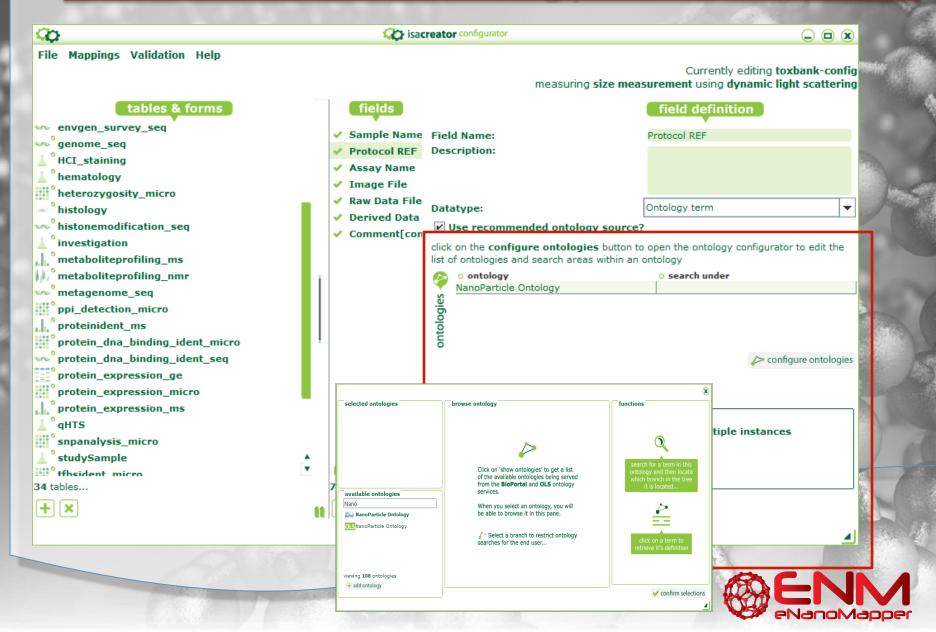
#### **Use of SEURAT-configured ISAcreator to prepare datasets**



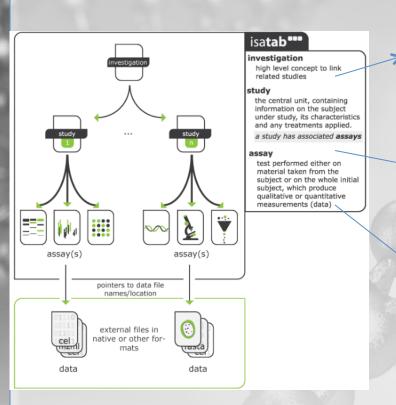
Mapped to terms in ontologies



# Define Ontology source

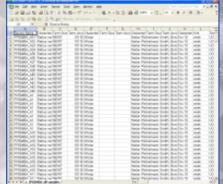


#### ISATab archives are created for each investigation



| Section | Sec

Overall investigation design and information (i... files)



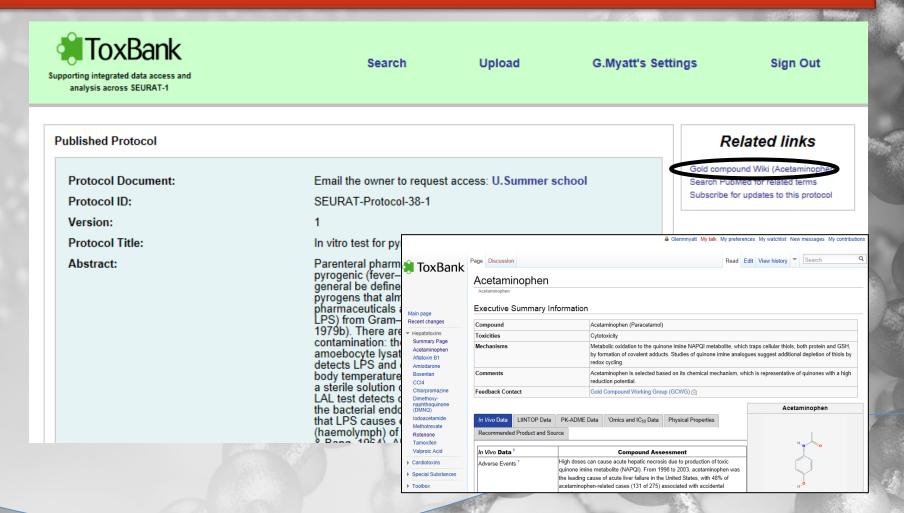
Study description (s... files)

| The state of the

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

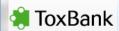


# New data may be combined with reviewed community data on reference compounds





#### ToxBank Wiki Reference Information Resource



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

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

[edit]

Q

[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

Recent News

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]

[edit]

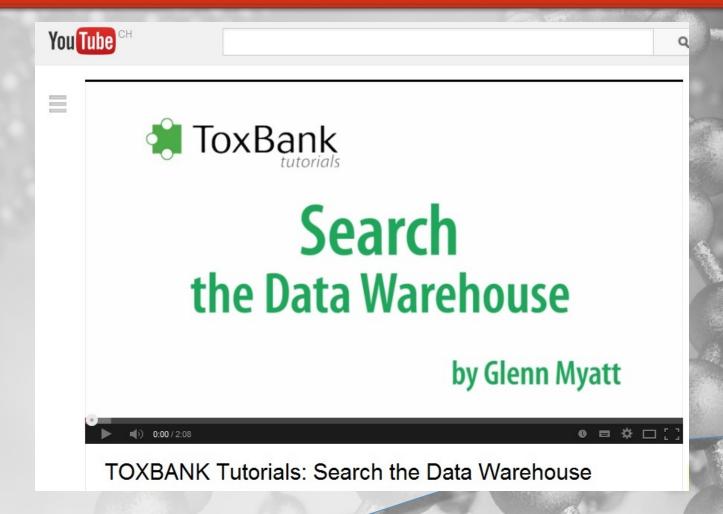
This wiki contains information on cells and reagents relevant to the SEURAT-1 cluster. The following document provides guidance for the banking and supply of human embryonic stem cells:

Questions, inquiries, comments and feedback regarding the scientific content on these pages may be directed to the Luam Kidane (2) at the UK Stem Cell Bank.

A report detailing the compound selection strategy was produced as a result of the numerous insightful meetings held at the Seurat-1 2<sup>nd</sup> Annual Meeting @ and may be downloaded here.

Read Edit View history

#### Data Warehouse Search Demo and Tutorial



Play Tutorial at <a href="https://www.youtube.com/watch?v=mE54EnY8uB4">www.youtube.com/watch?v=mE54EnY8uB4</a>



#### 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, [a] Nina Jeliazkova, [f] Vedrin Jeliazkova, [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

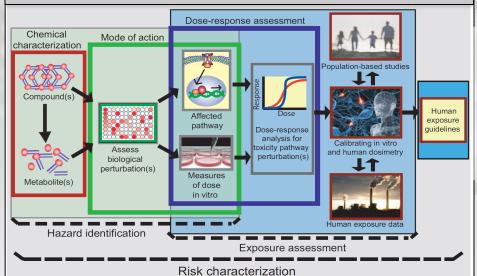
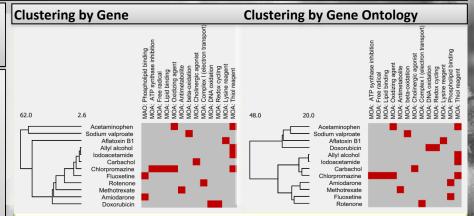
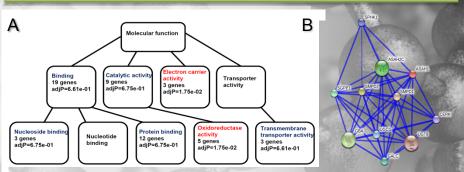


Figure 1. Multiple tools will be, step by step, implemented into an innovative toxicity testing strategy based on mode-of-action.

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.



**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 <u>databases and data management solutions</u> to aid in systems toxicology-based risk assessment



ToxBank





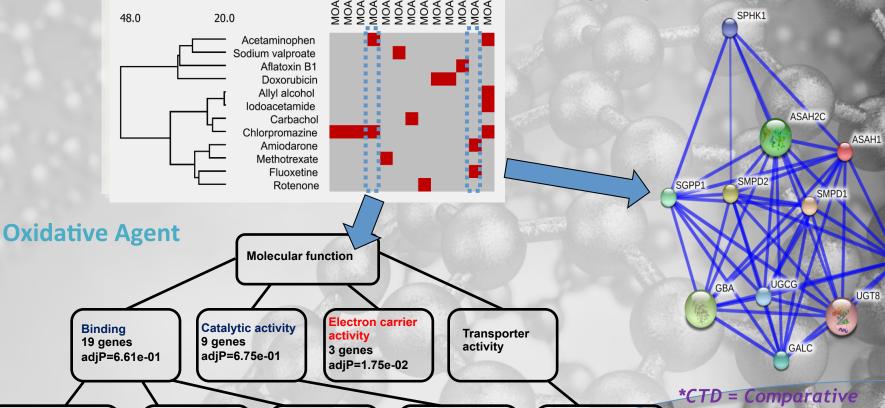


# Clustering by Gene Ontology associations from CTD\*

MOA: ATP synthase inhibition
MOA: Free radical
MOA: Lipid binding
MOA: Oxidizing agent
MOA: Oxidizing agent
MOA: Antimetabolite
MOA: Complex I (electron trans)
MOA: Complex I (electron trans)
MOA: DNA oxidation
MOA: Redox cycling
MOA: Phospholipid binding

## Public Data Analysis

#### **Phospholipid Binding**



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 adiP=6.61e-01 \*CFD = Comparativ Toxicogenomics Database (www.ctd.org)



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



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## molecular informatics models — molecules — systems

#### Full Paper

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

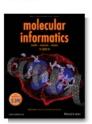
Pekka Kohonen<sup>1</sup>, Emilio Benfenati<sup>2</sup>, David Bower<sup>3</sup>, Rebecca Ceder<sup>1</sup>, Michael Crump<sup>3</sup> , Kevin Cross3, Roland C. Grafström1, Lyn Healy4, Christoph Helma5, Nina Jeliazkova6 . Vedrin Jeliazkov<sup>6</sup>. Silvia Maggioni<sup>2</sup>. Scott Miller<sup>3</sup>, Glenn Myatt<sup>3</sup>, Michael Rautenberg<sup>5</sup> , Glyn Stacey<sup>4</sup>, Egon Willighagen<sup>1</sup>, Jeff Wiseman7, Barry Hardy8,\*

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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)

How to Cite | Author Information | Publication History | Funding Information

Abstract

Article

References

Supporting Information

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### SEURAT-1 - Tox21 Collaboration

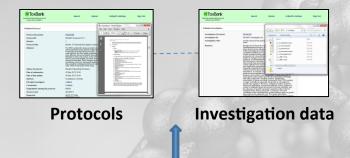




### **ToxBank – Integrated Data Analysis**

### Integrate experimental data across consortia





Integrate with public data (clinical, Tox21, ...)



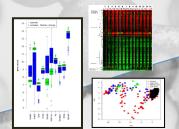
# DASHBOARD Integrate/organize





Pathway integration across projects, omics platforms, and experiments





**Analysis and visualization** 



Links to other resources

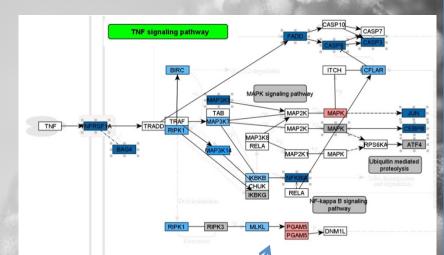


#### **Differential Expression**

Ensembl	Entrez	Symbol	Log-average expression	FC'HC8hr'	FC'MC8hr'	FC'LC8hr'
ENSG00000000003	7105	TSPAN6	10.52	0.021	-0.112	0.005
ENSG00000000005	64102	TNMD	4.04	0.21	0.066	0.214
ENSG00000000419	8813	DPM1	12.31	0.168	0.316	0.184
ENSG00000000457	57147	SCYL3	7.19	-1.049	-0.206	0.101
ENSG00000000460	55732	C1orf112	5.26	-0.402	-0.497	-0.143
ENSG00000000938	2268	FGR	5.77	0.157	0.299	-0.026
ENSG00000000971	3075	CFH	10.1	0.571	0.232	0.035
ENSG0000001036	2519	FUCA2	10.46	0.036	-0.05	-0.041
ENSG00000001084	2729	GCLC	9.22	-0.377	-0.153	0.105
ENSG00000001167	4800	NFYA	6.88	-1.052	-0.966	-0.214
ENSG0000001460	90529	STPG1	6.42	0.046	0.025	0.005
ENSG00000001461	57185	NIPAL3	6.88	-0.048	0.223	0.056
ENSG0000001497	81887	LAS1L	8.9	0.303	0.129	-0.012
ENSG00000001561	22875	ENPP4	7.24	-0.059	-0.391	0.008
FNICCO0000001617	CADE	CENANDE	6 55	0.120	0.207	0.111

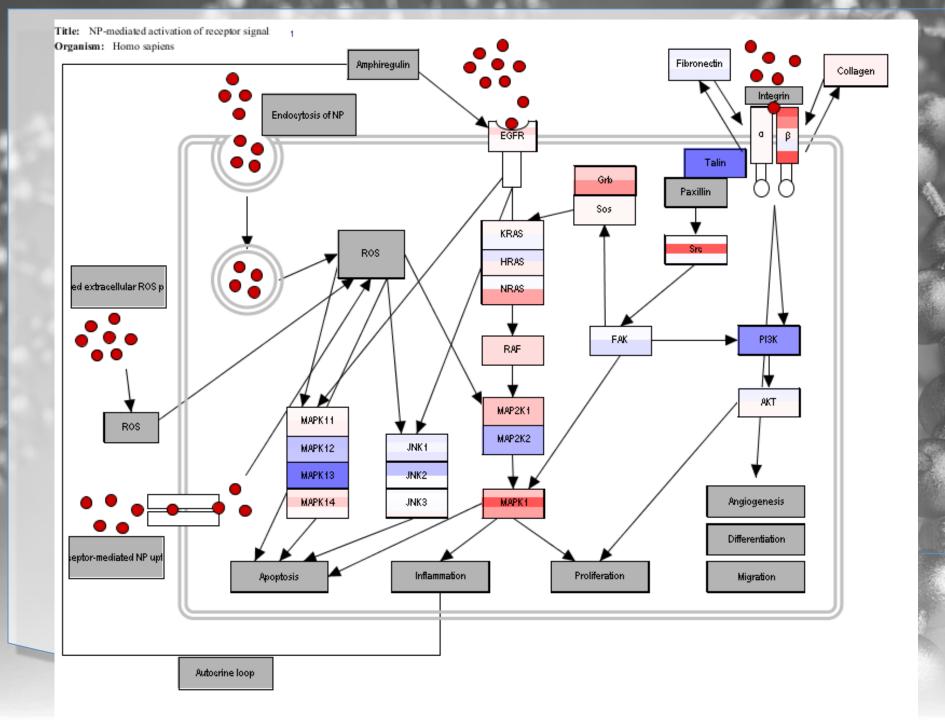
\*InCroMAP software (http://www.ra.cs.unituebingen.de/software/InCroMAP)

Pathway enrichment\*



Pathway class	Pathways	FC'LOShr'	FC'MO8hr'	FC'HO8hr'	FC'ML8hr'	FC'HL8hr'	FC'HMBhr'	FC'LC24hr'	FC'MC24hr'	FC'HC24hr'	FC'ML24hr'	FC'HL24hr	FC'HM24hr'	FC'LOShr24hr'	FC'MO8hr24hr'	FC'HO8hr24hr'	FC'HL8hr24hr'	FC'ML8hr24hr'	FC'HMBhr24hr	FC'CGhr24hr'
Cellular Processes; Cell growth and death	Cell cycle	*						*	*	*				*	*					
Cellular Processes; Cell growth and death	p53 signaling pathway								*											
Cellular Processes; Cell growth and death	Oocyte meiosis							*						*						
Environmental Information Processing; Signal transduction	TNF signaling pathway									*										
Genetic Information Processing; Replication and repair	DNA replication							*	*					*	*					
Genetic Information Processing; Replication and repair	Mismatch repair								*											
Genetic Information Processing; Replication and repair	Fanconi anemia pathway							*	*											
Human Diseases; Cancers	Viral carcinogenesis							*												
Human Diseases; Immune diseases	Rheumatoid arthritis									*										*
Human Diseases; Infectious diseases	Influenza A									*		*								
Human Diseases; Infectious diseases	Chagas disease (American trypanosomiasis)									*		*								
Human Diseases; Infectious diseases	Hepatitis B									*		*	*							
Human Diseases; Infectious diseases	Herpes simplex infection									*										
Metabolism; Nucleotide metabolism	Pyrimidine metabolism							*	*						*					
Organismal Systems; Endocrine system	Progesterone-mediated oocyte maturation													*						
Organismal Systems; Immune system	Toll-like receptor signaling pathway									*		*								





# Douglas Connect

# eNanoMapper

Nano Safety Cluster Meeting Antalya, Turkey Barry. Hardy@douglasconnect.com 23 April 2014

