

NOTOX

Predicting long-term toxic effects using computer models based on systems characterization of organotypic cultures

ToxWiz™ Ontology – categorized lists of terms contributing the capture of long term systemic toxicity

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What is ToxWiz™ Ontology? (Figure 1)

- Controlled vocabularies/terms classified into groups & hierarchies
- Defined relationships between terms and between groups of terms
- Thousands of histopathology ontologies in different levels of granularity

ToxWiz™ Ontology - requirements

- To capture adequately toxicology test results in pre-clinical testing
- To classify and define a spectrum of histopathology findings
- To capture long term toxicity
- To capture all available knowledge from the literature and toxicology reports and deal with human way of interpreting and recording the findings
- To be interoperable with other ontology efforts

ToxWiz™ Ontology – purpose (Figure 2)

- To facilitate prediction of toxic effects – *prospective analysis*
- To help explain causes of toxic effects – *retrospective analysis*
- To elucidate modes of action and create hypothesis for MOA
- To support extraction process of knowledge relevant to toxicology from toxicology reports and literature
- To enable integration and transfer of findings to clinical observations

Ontology of toxic endpoints

Endpoints are organized into categories: Example liver

Category	Example Toxic Endpoint Cluster	Includes	Description
System	Hepatotoxicity	Gall bladder, liver, hepatic system	General observations (e.g. clinical, etc.)
Organ/tissue	Liver toxicities	Liver	Pathology report for any toxicity in liver
Organ/tissue	Liver hypertrophy	Liver	Pathology report of specific toxicity
Cells	Hepatocyte neoplasia	Cells or cell-lines	Result from cell-based assays

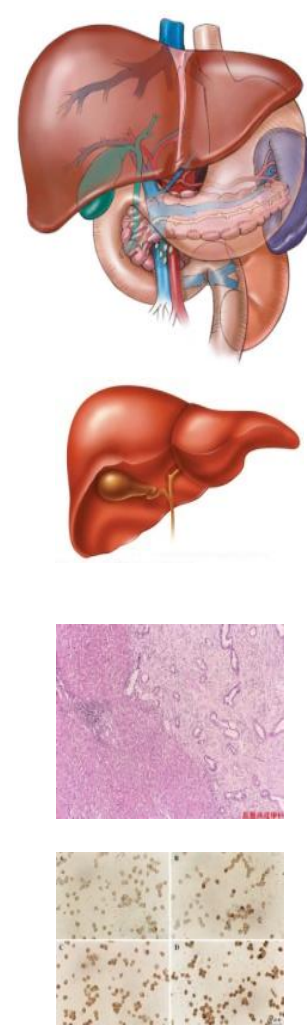
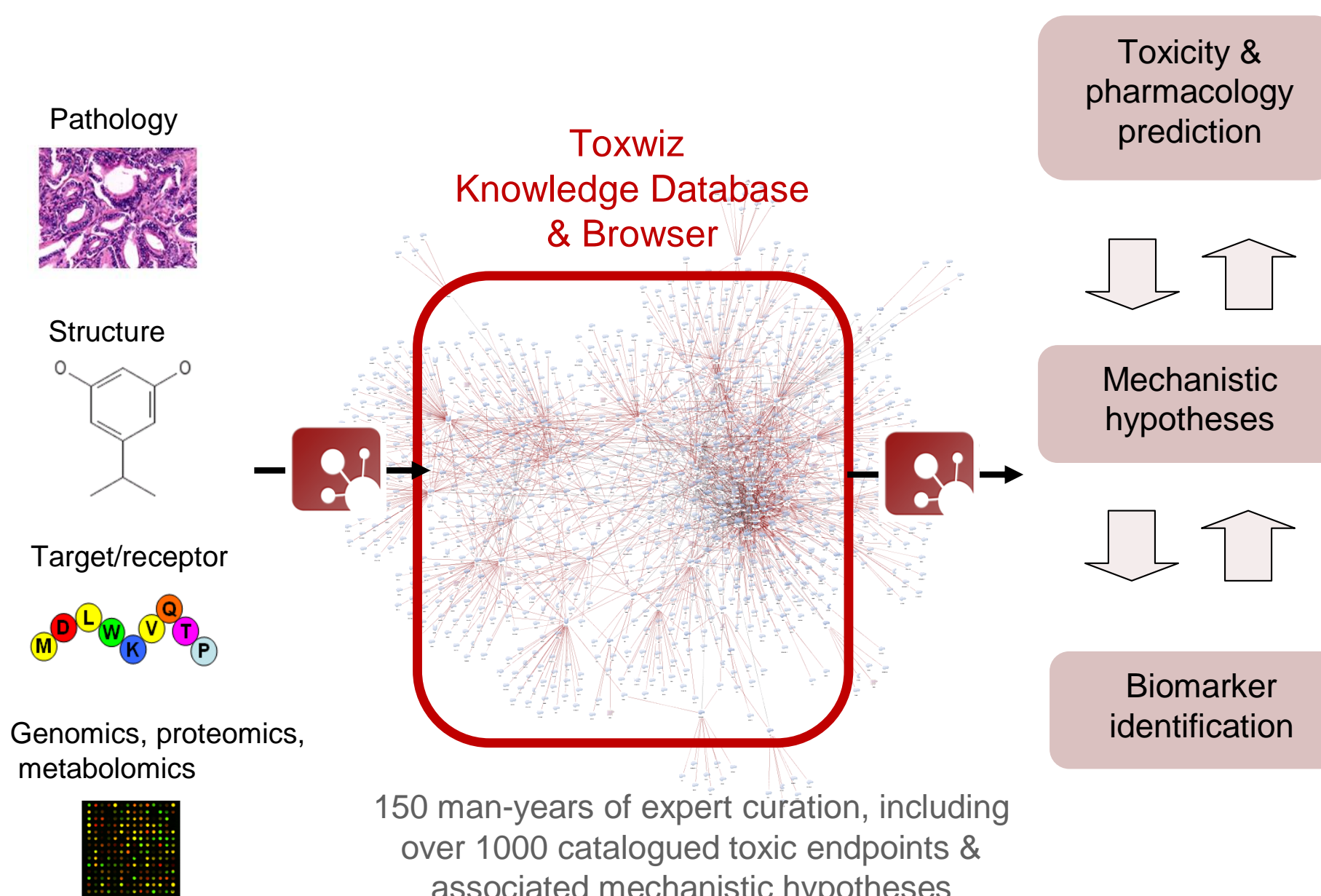


Fig. 1. An example of four different levels of hierarchy and different granularity for describing a biomedical observation for Liver toxic effect. The first three categories from top down are in vivo observations. From up to down in the table it starts with the entire organ system such as hepatotoxicity without specifying if it is liver or gall bladder (these observations mostly come from the clinical observations by medical doctors), the next level are organ specific observation mostly from the clinic, the third level are more specific mostly histopathological findings from in vivo pre-clinical tests, and the fourth is an extra category designed to capture observations from in vitro cell assays that we can try to related to above in vivo observations.

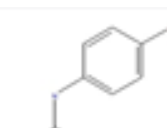
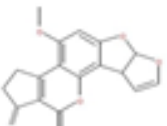
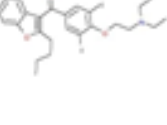
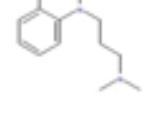

Ontology supported discovery

Fig. 2. The ontology enables getting quick insights (with the background intelligent search engine with an ontology backbone) for a chemical and listing all the reported toxic endpoints and in parallel asking a questions for this chemical what are all reported metabolizing enzymes/nuclear hormone receptor or dysregulated genes for obtaining a quick idea about a possible mechanisms. Furthermore one can ask for a specific chemical and a specific histopathology, what are all reported associated genes and proteins and how they fit into known metabolic and signalling biological pathways



ToxWiz™ Ontology – benefits for SEURAT (Figure 3)

- To interpret and explain mechanism of action of drugs/compounds by precisely categorizing terms describing observation/toxicities
- Extracting and mapping information about chemical structures related to
 - Toxicity
 - Disease
 - Hypothesis
- Allows exchange of data between user groups
- Supports –omics interpretations
- Supports in-vitro findings
- Enables use of read across tool

	acetaminophen
	aflatoxin B1
	amiodarone
	chlorpromazine
	chlorzoxazone

Toxic endpoint clusters					Molecules Next To
Rank	Molecular Mechanism	Type	Molecules Inside		
1	Hepatocyte hypertrophy association cluster	Hepatic system	1: AFLATOXIN B1	1: acetaminophen	
2	Hepatocyte degeneration association cluster	Toxic endpoint clusters	1: acetaminophen	1: AFLATOXIN B1	
3	Liver fibrosis association cluster	Hepatic system		4: acetaminophen, chlorpromazine, amiodarone, AFLATOXIN B1	
4	Liver fibrosis marker cluster	Hepatic system		2: acetaminophen, amiodarone	
5	Hepatocyte hepatostasis induction cluster	Hepatic system	1: AFLATOXIN B1	2: amiodarone, acetaminophen	
6	Hepatocyte hepatostasis association cluster	Hepatic system	1: AFLATOXIN B1	2: amiodarone, acetaminophen	
7	Acute liver injury association cluster	Hepatic system	1: AFLATOXIN B1		
8	Acute liver toxicities association cluster	Hepatic system	1: AFLATOXIN B1		
9	Liver neoplasia association cluster	Hepatic system	1: AFLATOXIN B1		
10	Liver hypertrophy cluster	Hepatic system		4: acetaminophen, amiodarone, chlorpromazine, AFLATOXIN B1	
11	Liver fibrosis marker cluster	Hepatic system		1: acetaminophen	
12	Liver fibrosis association cluster	Hepatic system		2: acetaminophen, amiodarone	
13	Liver toxicities association cluster	Toxic endpoint clusters	1: AFLATOXIN B1	1: acetaminophen	
14	Hepatocyte hepatostasis cluster	Hepatic system		4: acetaminophen, chlorpromazine, AFLATOXIN B1, amiodarone	
15	Liver inflammation marker cluster	Hepatic system		1: acetaminophen	
16	Hepatocyte hypertrophy cluster	Hepatic system		4: acetaminophen, AFLATOXIN B1, chlorpromazine, amiodarone	
17	Liver inflammation association cluster	Hepatic system		4: acetaminophen, AFLATOXIN B1, amiodarone, chlorpromazine	
18	Liver atrophy cluster	Hepatic system		3: acetaminophen, chlorpromazine, amiodarone	
19	Liver hypertrophy cluster	Hepatic system		4: acetaminophen, AFLATOXIN B1, chlorpromazine, amiodarone	
20	Liver inflammation association cluster	Toxic endpoint clusters		2: acetaminophen, amiodarone, chlorpromazine	
21	Hepatocyte degeneration induction cluster	Hepatic system	2: AFLATOXIN B1, acetaminophen	4: acetaminophen, amiodarone, chlorpromazine, AFLATOXIN B1	
22	Liver atrophy cluster	Hepatic system		4: acetaminophen, amiodarone, chlorpromazine, AFLATOXIN B1	
23	Hepatocyte apoptosis association cluster	Hepatic system		4: acetaminophen, AFLATOXIN B1, chlorpromazine, amiodarone	
24	Liver neoplasia cluster	Hepatic system		4: acetaminophen, AFLATOXIN B1, chlorpromazine, amiodarone	
25	Hepatocellular toxicities association cluster	Hepatic system	1: AFLATOXIN B1	2: acetaminophen, chlorpromazine	
26	Hepatocyte inflammation inhibition cluster	Hepatic system			
27	Hepatotoxicity association cluster	Toxic endpoint clusters	2: AFLATOXIN B1, acetaminophen		
28	Liver neoplasia induction cluster	Hepatic system	1: acetaminophen		

Fig. 3. List of mechanistic hypothesis of range of liver toxicity, in CCNet's ontological framework, showed here with selected gold hepatotoxic compounds (Acetaminophene, Aflatoxin B1, Amiodarone, Chlorpromazine, Valproate). Categories cover different level of granularity of the observed pathological effects, capturing knowledge from available scientific literature and toxicology reports, including long term toxicity effects.

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