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)*

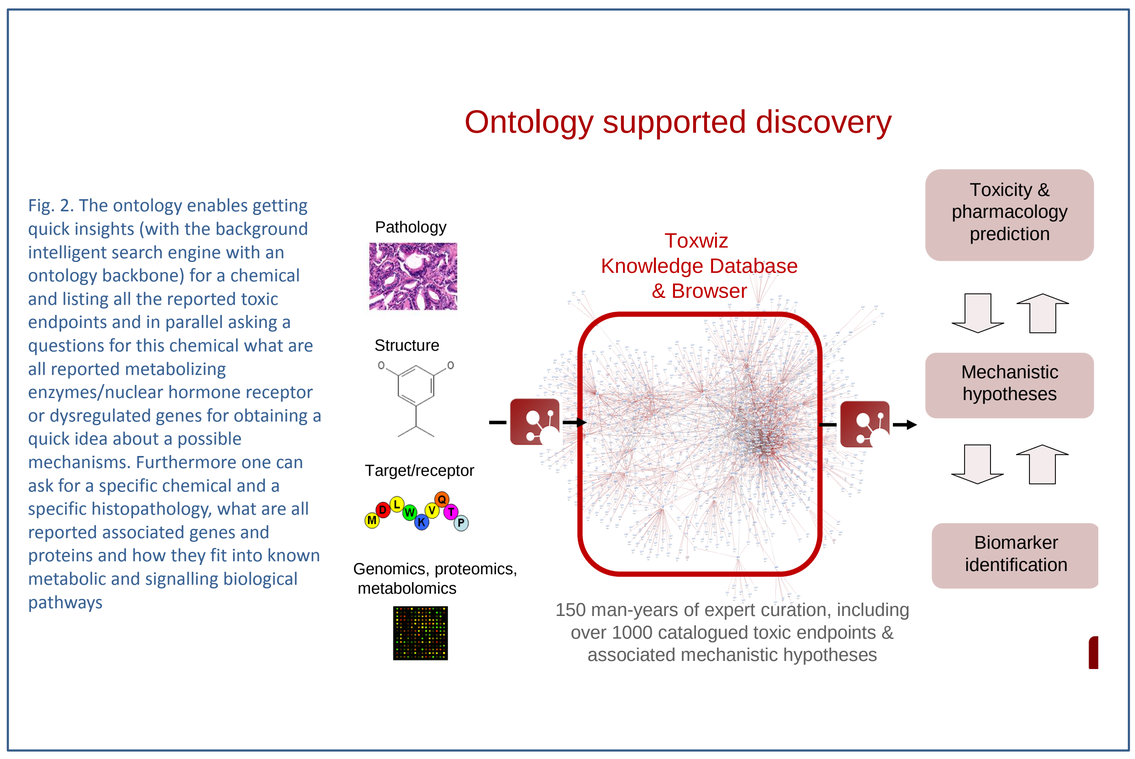
- Controlled vocabularies/terms classified into groups & hierarchies
- Defined relationships between terms and between groups of terms
- Thousands of histopathology ontologies in different levels of granularity

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

ToxWiz toxicology ontology

Endpoints are organized into categories: Example liver

Category	Example Toxic Endpoint Cluster	Includes	Description
System	Hepatotoxicity	Gall blader, 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

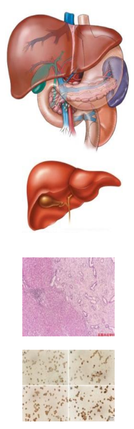
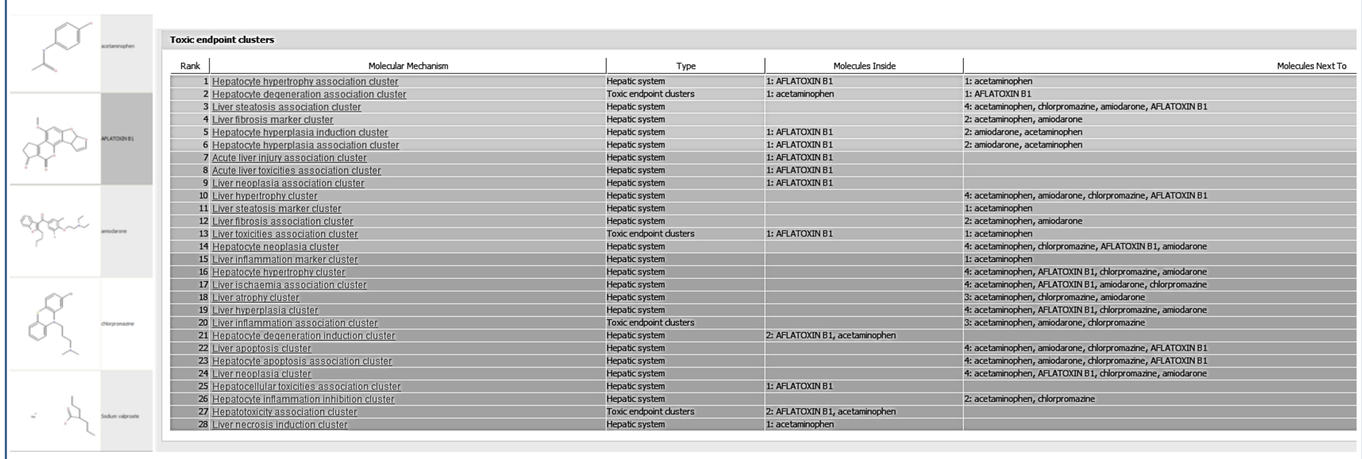


Fig. 1. An example of four different levels of hierarchy and different granularity for describing a biomedical observation for Liver toxic effect. The first three categories from top down are in vivo observations. From up to down in the table it starts with the entire organ system such as hepatotoxicity 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.

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



Toxic endpoint clusters

Rank	Molecular Mechanism	Type	Molecules Inside	Molecules Next To
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 steatosis association cluster	Hepatic system		4: acetaminophen, chlorpromazine, amiodarone, AFLATOXIN B1
4	Liver fibrosis marker cluster	Hepatic system		2: acetaminophen, amiodarone
5	Hepatocyte hyperplasia induction cluster	Hepatic system	1: AFLATOXIN B1	2: amiodarone, acetaminophen
6	Hepatocyte hyperplasia 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 steatosis 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 neoplasia 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 ischaemia association cluster	Hepatic system		4: acetaminophen, AFLATOXIN B1, amiodarone, chlorpromazine
18	Liver atrophy cluster	Hepatic system		3: acetaminophen, chlorpromazine, amiodarone
19	Liver hyperplasia cluster	Hepatic system		4: acetaminophen, AFLATOXIN B1, chlorpromazine, amiodarone
20	Liver inflammation association cluster	Toxic endpoint clusters		3: acetaminophen, amiodarone, chlorpromazine
21	Hepatocyte degeneration induction cluster	Hepatic system	2: AFLATOXIN B1, acetaminophen	
22	Liver apoptosis cluster	Hepatic system		4: acetaminophen, amiodarone, chlorpromazine, AFLATOXIN B1
23	Hepatocyte apoptosis association cluster	Hepatic system		4: acetaminophen, amiodarone, chlorpromazine, AFLATOXIN B1
24	Liver neoplasia cluster	Hepatic system		4: acetaminophen, AFLATOXIN B1, chlorpromazine, amiodarone
25	Hepatocellular toxicities association cluster	Hepatic system	1: AFLATOXIN B1	
26	Hepatocyte inflammation inhibition cluster	Hepatic system		2: acetaminophen, chlorpromazine
27	Hepatotoxicity association cluster	Toxic endpoint clusters	2: AFLATOXIN B1, acetaminophen	
28	Liver necrosis 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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SEVENTH FRAMEWORK PROGRAMME