

# TXPO: A toxic process ontology for better understanding of drug-induced liver injury

Yuki Yamagata<sup>a</sup>, Yoshinobu Igarashi<sup>a</sup>, Noriyuki Nakatsu<sup>a</sup>, Hiroshi Yamada<sup>a</sup>

<sup>a</sup> Laboratory of Toxicogenomics Informatics, National Institutes of Biomedical Innovation, Health and Nutrition, Ibaraki, Osaka, Japan

## Abstract

Elucidating the mechanism of toxicity is crucial in drug safety evaluations. We focus on toxic processes and developed a toxic process ontology, designated TXPO. Here, we outline the TXPO, which systematizes toxic processes within the liver in a consistent manner. The TXPO makes processes explicit across granularity using a functional decomposition tree. Concerning the course of toxic processes, we present a framework of causal relationships between processes from latent to toxicity manifestation. In applied work, we introduce a prototype of TOXPILOT, a toxic process interpretable knowledge system. TOXPILOT provides visualization maps of the toxic course, which facilitates capturing the comprehensive picture for understanding toxicity mechanisms. Our ontological approach will help develop new knowledge regarding drug safety evaluations.

## Keywords:

ontology; process; drug-induced liver toxicity

## Introduction

Drug-induced liver injury is a major cause of drug withdrawal from the market and discontinuation of drug development [1]. Therefore, safety assessments during the early stages of drug development are required. Toxicology is a scientific discipline that examines the biological effects (toxic effects) of substances such as chemical compounds, drugs, and drug candidates. We developed a hepatotoxicity prediction informatics system with the aim of developing safety biomarkers during the early stages of drug development. We conduct hepatotoxicity predictions based on computational approaches using toxicogenomics data and machine learning. In order to promote data-driven research and appropriately assess safety, it is necessary to explain computational predicted results in light of the relevant mechanisms. However, the mechanisms of hepatotoxicity are complex, in part because the liver is the site of drug metabolism, the results of which can affect a wide variety of biological structures and functions. For safety management, it is desirable to systematize the necessary knowledge from a consistent viewpoint.

To better clarify toxicity mechanisms, in the present study, we developed a toxic process ontology (TXPO). The TXPO systematizes a wide variety of toxicological terms involving hepatotoxicity processes. We also modeled a representation framework that appropriately describes toxic courses. In applied work, we developed a prototype toxic process interpretable knowledge

system (TOXPILOT). Here, we discuss the current state of our work.

## Methods

### TXPO development

From textbooks [2-6] we researched drug-induced hepatotoxic mechanisms and obtained information about toxic courses and related processes, molecules and their roles, and biological structures. Next, we searched for the latest information from toxic course-related articles using PubMed search terms in Table 1.

Table 1 PubMed search terms for hepatotoxic course

Toxic course	Search terms	Results
ER stress	("endoplasmic reticulum stress"[MeSH Terms] OR "unfolded protein response"[MeSH Terms]) AND "liver"[MeSH Terms]	173
Glutathione depletion	("glutathione"[MeSH Terms] AND "liver"[MeSH Terms]) AND "chemical and drug induced liver injury"[MeSH Terms]	819
Ground glass degeneration	(ground[All Fields] AND ("glass"[All Fields])) AND ("liver"[All fields])	290
Eosinophilic granular degeneration	((("peroxisomes"[MeSH Terms] OR "peroxisomes"[All Fields]) AND proliferation[All Fields]) AND "liver"[MeSH Terms]) OR ("eosin"[All Fields]) AND granular[All Fields]	1224
Phospholipidosis	"phospholipidosis"[All Fields] AND "liver"[MeSH Terms]	165
Lipidosis	"fatty liver"[MeSH Terms] AND "chemical and drug induced liver injury"[MeSH Terms]	772

We used the ontology editing tool Protégé 5.2.0 [7] to develop the TXPO in the Web Ontology Language (OWL) and HermiT reasoner [8] as a Protégé Plug-in.

Figure 1 shows examples of the TXPO development process. First, 1) each toxic course was defined, and related information was annotated using the Annotation Properties. Next, 2) the processes constituting each toxic course were described using a 'has part' relation as Object Property. Then, 3) each process was generalized using an *is-a* hierarchy: processes common to multiple toxic courses, biological processes, and biomedical-independent processes. Furthermore, 4) each process was decomposed into subprocesses (has part relation), and 5) the biological structure in which the process takes place was described (occurs in). In addition, 6) molecules/drugs and their roles in the process were also defined. Finally, 7) causal relationships between process were defined by using a 'has result' relation.

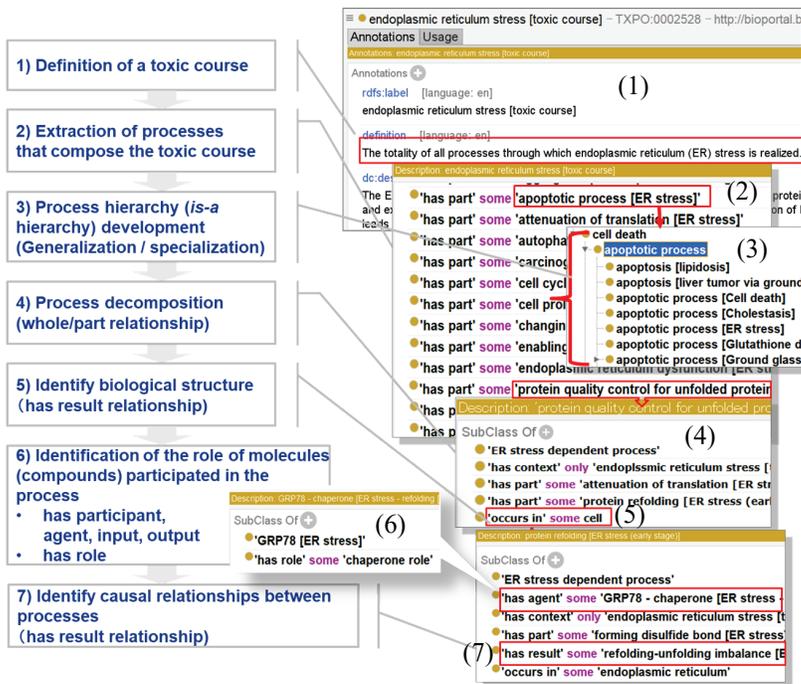


Figure 1 Examples of TXPO development

In generalizing the *is-a* tree construction, we reused existing ontologies. Domain-independent general entities were based on BFO [9], and biomedical entities were imported manually from existing ontologies in NCBO BioPortal [10]. These biomedical ontologies include UBERON [11], Cell Ontology [12], NCBI Taxon [13], ChEBI [14], Gene Ontology [15], PATO [16], INOH [17], and Ontology of Genes and Genomes (OGG) [18].

### TOXPILOT development

TOXPILOT consists of an ontology library, a Resource Description Framework (RDF) database, and a Web application

system. The TXPO file is stored in the ontology library, and the file is converted to RDF format represented by a triple Subject, Predicate, and Object by Protégé. The RDF data are then stored in an RDF triple store using Apache Fuseki [19] to construct the SPARQL endpoint. Regarding the web application system for TOXPILOT, necessary information is dynamically acquired via SPARQL queries. Moreover, TOXPILOT generates graphs using D3.js [20] of the JavaScript library.

## Results

### Development of the TXPO

#### Outline of the TXPO

Figure 2 shows an overview of the TXPO, which is a three-layer model organized in an *is-a* hierarchy of general terms to specialized toxicologic terms. The top layer is domain-independent (domain-neutral) and provides general terms. Most of the entities in the top layer refer to the upper ontology, Basic Formal Ontology (BFO). Upper ontologies support generic categories and relations based on a philosophical orientation. Accordingly, we could construct our ontology with inheritance of the intrinsic nature in a consistent manner. All entities of the TXPO are classified into the basic categories *continuant* or *occurent*. *Continuant* refers to an entity that persists, endures, or continues to exist through time while maintaining its identity and includes *objects*, *roles*, and *qualities*. An *object* is an independent continuant, such as a thing. *Roles* and *qualities* are dependent continuants that can only exist depending on something else. *Occurrent* includes entities that unfold over time, such as *processes*.

The intermediate layer is biomedical domain dependent and

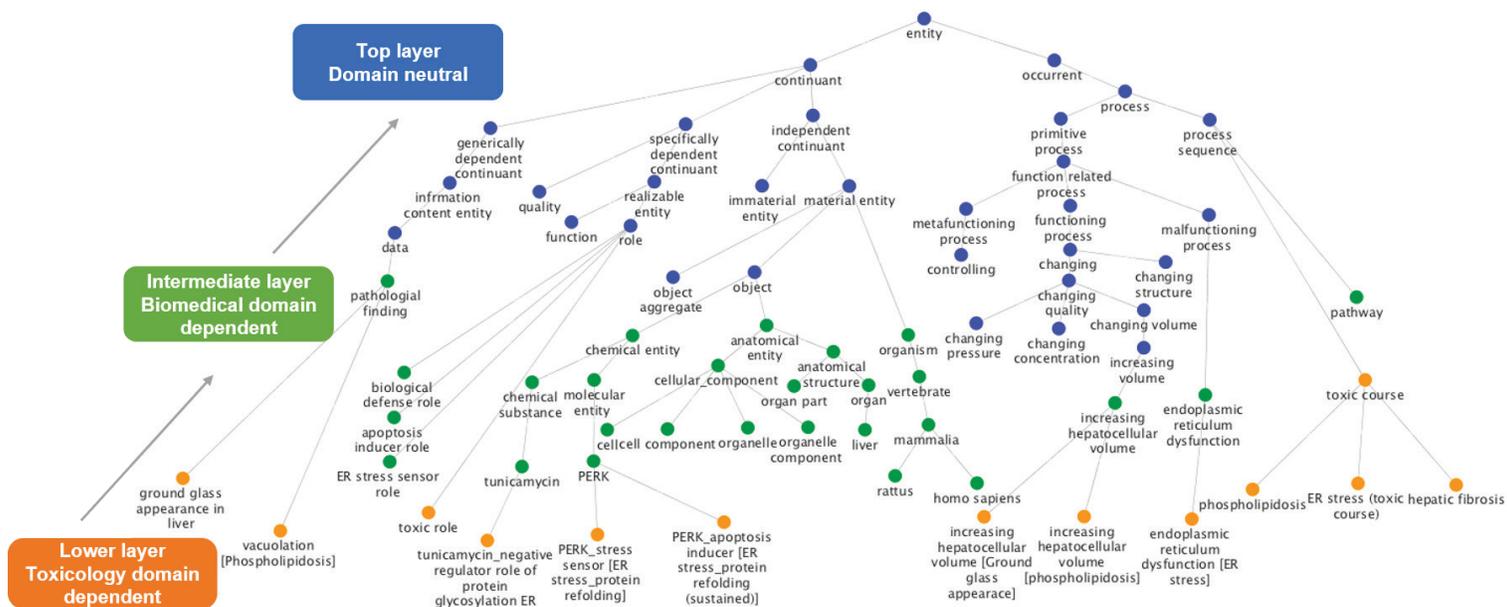


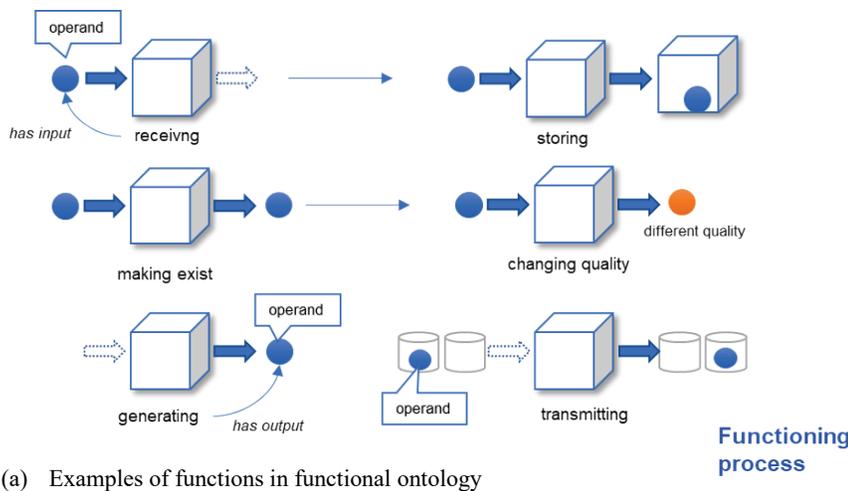
Figure 2. Overview of the Toxic Process Ontology (TXPO). The TXPO contains an *is-a* hierarchy that is organized into three layers: the top layer contains general terms, mostly derived from the Basic Formal Ontology. The intermediate layer contains biomedical terms, and the lower layer contains more granular, toxicology terms.

consists of entities commonly used in biomedicine. As lower entities of *continuant*, biological structures such as molecules, compounds, organelles, cells, organs, and species are defined. The open community OBO Foundry [21] seeks to share knowledge and standardize terms among the biological community, and OBO ontologies utilize BFO as an upper ontology. Accordingly, the TXPO imports existing terms and reuses them from biomedical ontologies of OBO foundries. These terms include anatomic structures from UBERON, cells from Cell Ontology, organisms from NCBI Taxon, compounds from ChEBI, biological processes and cellular components from Gene Ontology, qualities from PATO, some molecule families from INOH, and genes from OGG.

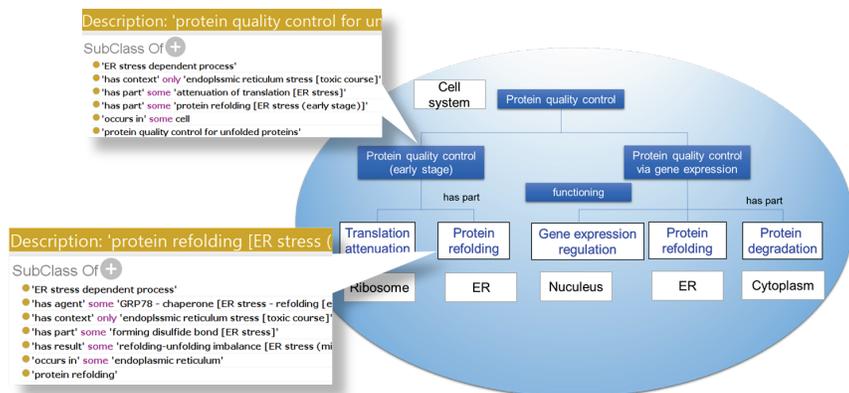
The lower layer encompasses entities specific to toxicology (i.e., entities that are toxicological domain dependent).

### Process in the TXPO

*Process* is a central category in the TXPO. In order to elucidate a toxicity mechanism adequately, we provide two sub-categories, namely, *primitive process* and *process sequence*. The former is defined as a single unit of process, whereas the latter is defined as a series of processes, which includes pathways and toxic courses.



(a) Examples of functions in functional ontology



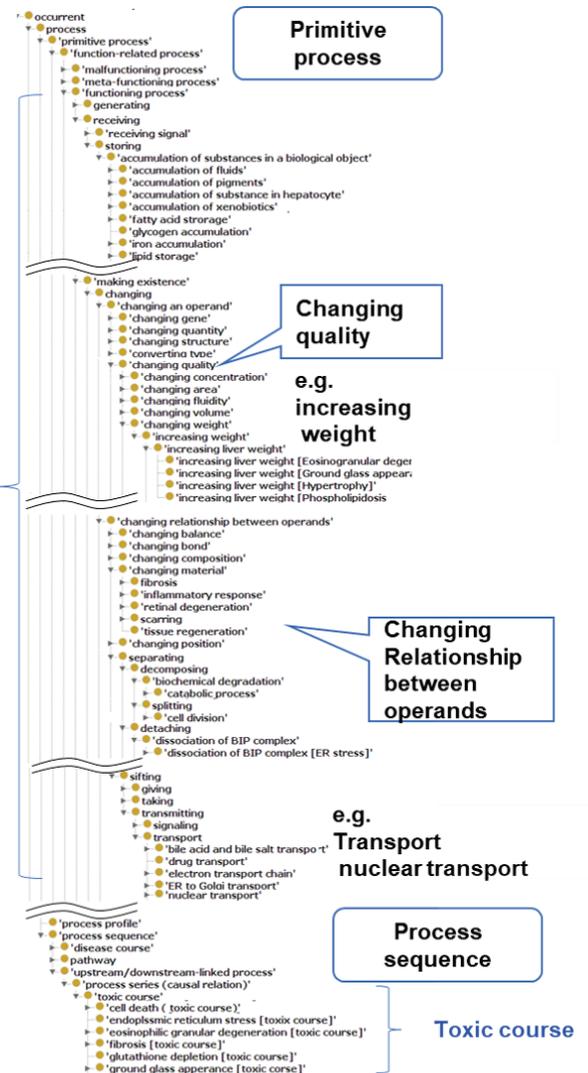
(c) An example of functioning decomposition of protein quality control during ER stress

Figure 3 functioning process

### (1) Functioning Process

Many biological defense processes function to protect organisms from toxicity-associated injury. Therefore, we focused on functioning processes in the present study. Functioning processes in organisms are diversified in granularity from the molecular level to the organelle, cell, tissue, and organ level. In order to define functioning processes in a consistent fashion, we systematize the functioning tree based on functional ontology [22, 23]. As an ontological engineering approach, functional ontology defines general functions based on changes in the state of the input-output relationship between physical things and models the functional knowledge (Fig. 3 (a)). As a basic idea, a *functioning process* can be categorized into *receiving*, *making existent*, and *generating* groupings based on the number of focused inputs and outputs of the target. The *making existent* category can be further subdivided into *changing an operand* and *changing relationship between operands* classifications. *Changing an operand* includes changing qualities such as concentration, pressure, volume, etc. Examples of subtypes of *changing relationship between operands* are *transmitting* and *separating*. Subtypes of *separating* include *decomposing*, *splitting*, and *detaching*. Based on these terms and by specializing their use, we developed the functioning *is-a* hierarchy in the TXPO (Fig. 3 (b)).

The intermediate layer is biomedical domain dependent. For instance, a lower level of *transmitting* includes biological



(b) The TXPO functioning *is-a* hierarchy

transport processes such as nuclear transport and Golgi vesicle transport. *Decomposing* includes proteolysis and lipid degradation; *splitting* includes cell division; and *detaching* includes complex dissociation. These processes are generally consistent with the GO Biological Process, as some of the GO biological processes can be interpreted as functional processes common to biomedicine.

The lower layer is a toxicology domain dependent. In this study, we define a "toxic process" as a process that constitutes a specific toxic course. For example, by specializing the biomedical process "apoptotic process (GO:0006915)", we define an "apoptotic process [ER stress]" that constitutes a course of ER stress, and an "apoptotic process [Phospholipidosis]" that constitutes a course of Phospholipidosis, and so on.

One of the difficulties of capturing a toxic process is that some toxic effects are protective responses to xenobiotic substances (drugs) [24]; hence, to understand the toxicity mechanisms appropriately, we also regard a process functioning as a biological defense in the specific toxic course as a "toxic process."

Developing a toxicity-dependent process subtree is based on the low-hanging fruit policy. From toxicology-related textbooks and published articles, terms were extracted and manually annotated.

Here, as a function-related process, in addition to the function-execution process, the TXPO defines *meta-functioning processes*. *Meta-functioning processes* are functioning processes specific to other functions and include *controlling*, for example. Subtypes of *controlling* include the regulation of apoptosis and cell cycle control.

## (2) Decomposition of Functioning

The TXPO specifies a functioning process based on a function decomposition framework. As an ontological engineering approach, a device (system) consists of sub-devices (sub-systems). In a function decomposition tree, the whole function of a system is achieved by a sequence of sub-functions of the sub-systems. As biological functions can be considered specializations of systemic functions [25], in the present study, we attempted to clarify the functioning process of biological structures for each granularity based on the whole-part relationship (part of/ has part relationship). At the cell level, we regard a cell as the system and cell components such as organelles as system parts. Figure 3 (c) shows an example describing how the cell system functions from a decomposition perspective. In the toxic course of endoplasmic reticulum (ER) stress, for example, the accumulation of drugs such as tunicamycin in the ER is known to initiate protein unfolding. Therefore, the cell system executes the "protein quality control" function as a biological defense function. Here, we can say that the cell system consists of subparts: the ER, ribosomes, nucleus, and cytoplasm. During the early stages of ER stress, the sub-functioning process "protein refolding" is carried out in the ER. The ER receives input regarding an unfolded protein, and after executing the refolding function, the ER output consists of the refolded protein. In addition, "translation attenuation" is also carried out by the ribosomes to suppress production of new proteins, which supports protein refolding. However, if the refolding process is not sufficient, then, "regulating gene expression" can occur in the nucleus, and in the cytoplasm, "protein degradation" is executed, with the unfolded protein serving as the input and its degradation product as the output. Thus, the cell system achieves protein quality control through specific sub-

functioning processes of the cellular system parts (i.e., organelles).

## (3) Toxic course

In toxicology research, elucidating the mechanism of toxicity is crucial for safety management. Toxicity mechanisms are generally explained in terms of multiple processes, such as toxicant delivery, biological defense processes, cellular dysfunction/dysregulation, and cell death. Therefore, in the present study, we focused on toxic courses. As a subtype of the *process sequence*, the TXPO defines a toxic course as a series of processes in an organism from latency to the manifestation of toxicity, which is not part of the normal life of the organism. Subtypes of the toxic course include specific themes, such as ER stress, glutathione depletion, phospholipidosis, lipidosis/fatty liver, ground glass appearance of hepatocytes, and eosinophilic granular degeneration.

In the present study, we developed a framework called the "toxic course map" to represent toxic courses uniformly. The map represents a toxic course as causal relationships between processes (Fig. 4). With regard to development of toxicity, we applied the imbalance theory [26]. In the present study, supply indicates the functioning processes associated with biological defense and maintaining homeostasis, and demand refers to toxic activity. As illustrated in Figure 4, in the imbalance model, the basic units are as follows:

- 1) a functioning process (supply) for biological defense and maintaining homeostasis;
- 2) a functional demand process (demand) as toxic activity;
- 3) balance/imbalance between toxic activity and defense processes; and
- 4) outcome from organelles, cells, or tissues to the organ exhibiting toxicity manifestations

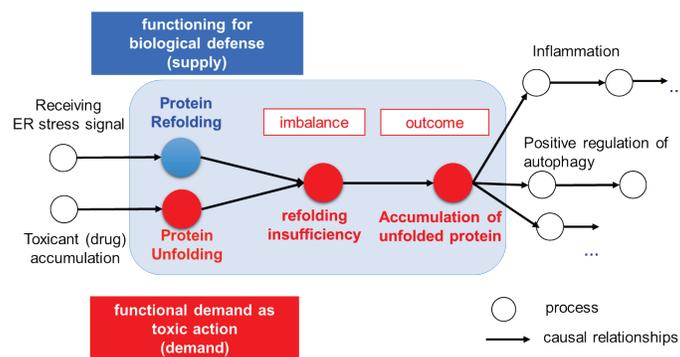


Figure 4 Representation framework of a toxic course

The degree of functioning performance can change according to changes in demand; however, if demand exceeds the performance of functioning, an imbalance occurs and results in an outcome that is no longer latent and manifests toxicity. Table 2 shows examples describing the imbalance framework in ER stress.

Table 2. Examples of imbalance in ER stress

Granularity	Toxic action (Demand)	Imbalance	Functioning (Supply)	Outcome
ER	Unfolding	>	Refolding	Accumulation of unfolded protein
Cytoplasm	Producing unfolded protein	>	Degrading unfolded protein	Protein aggregate formation
Cell (hepatocyte)	Increasing protein aggregates	>	Autophagy (removing protein aggregates)	Abnormal ER formation
Tissue	Increasing abnormal cells	>	Apoptosis (removing abnormal cells)	Accumulation of abnormal cells
Organ (liver)	Cell death (increasing apoptosis, necrosis)	>>	Cell survival	Liver failure
Organ (liver)	Cell death (increasing apoptosis, necrosis)	<<	Cell proliferation	Liver carcinogenesis

(4) Role

In general, a molecule plays multiple roles in the body. Therefore, in the present research, we tried to explicate the roles of molecules participating in specific processes in the toxic course. For example, in ER stress, GRP78 participates in the protein refolding process and can play the role of a "chaperone" that assists protein refolding (Fig. 5). GRP78 also plays the role of "autophagy inducer" in the positive regulation of autophagy process during ER stress. As viewed relative to the role of a molecule, the TXPO contributes to identifying biomarkers that participate in the turning points of processes that cause cell injury during the course of toxicity manifestation. As for drugs, TXPO makes explicit the role of drugs in a specific toxic process. For example, tunicamycin plays a 'protein glycosylation inhibitor' role and participates in the negative regulation of glycosylation process. Tunicamycin also plays an 'apoptosis inducer' role in the positive regulation of apoptosis in the liver (Fig. 5).

(5) Relationship between entities

As of February 1, 2018, the TXPO defined approximately 6000 entities, and Figure 5 shows the major relationships between terms defined in the TXPO.

Applications

We developed a prototype toxic process interpretable support knowledge system, known as TOXPILOT. The TOXPILOT provides varied useful information based on the TXPO (Fig. 6). The TOXPILOT visualizes toxic course maps (Fig. 6 (a)), as described in the previous section. Since our map can visualize molecules that participate in toxic processes, we can apply the map to facilitate explanation of biomarkers for toxicity prediction by machine learning. Our preliminary data show that by using maps, *in vivo* and *in vitro* data of predicted marker genes of liver toxicity can be comparatively analyzed. As a result, we can identify genes predicted to participate in common processes in ER stress based on rat *in vivo* and human *in vitro* analyses. Thus, this toxic course map facilitates evaluation and extrapolation to humans for translational research.

The TXPO also provides process maps (Fig. 6 (b)), in which sub-processes can be displayed according to the whole-part relationship of systemic functioning across granularities. These maps also enable visualization of pathologic findings associated with a process.

The TXPO also provides a general course map that visualizes general toxic courses common to multiple specific toxic courses (Fig. 6 (c)). In safety evaluation, toxicologists sometimes want to know whether one phenomenon that occurs in a particular toxic course could occur in other toxic courses. For instance, in the course of lipidosis, "lipid accumulation" can cause "increasing hepatocyte volume." The TXPO system extracts information from the RDF database by SPARQL and automatically generates a general course map. In the general course map, common processes are represented as large nodes. As a result, users can obtain information indicating that "increasing hepatocyte volume" is common to other toxic courses, such as cholestasis. Moreover, users can obtain information regarding different causes associated with other courses. Each toxic course is colored, so users can see easily that, for example, "bile acid accumulation" occurs specifically in the course of cholestasis.

Our system also provides a function for searching routes from specific processes (Fig. 6 (d)). When users want to conduct retrospective analyses, TOXPILOT provides an illustration of 'upstream' of the focused process in the toxic course, which can help identify critical causes during the early stages of toxicity. In the same way, if users wish to know how a process unfolds with the progress of the toxicity development, our system provides a 'downstream' illustration that supports severe manifestation risk management.

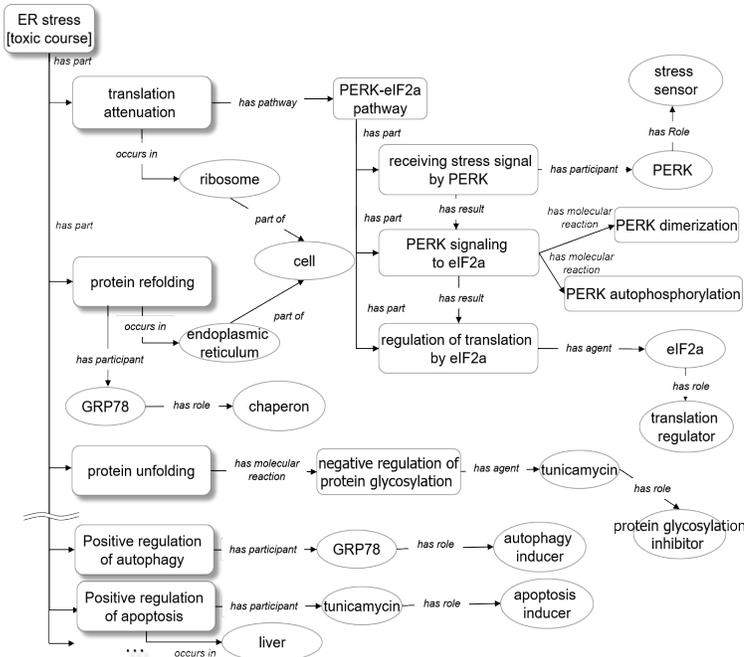


Figure 5 Examples of TXPO relationships



## Discussion

There are many biomedical pathway databases, including KEGG [27], WikiPathways [28], and Reactome [29]. Since these databases deal with a large number of pathways, one might conclude that they also explain toxic mechanisms. However, most of these databases are based on molecular-molecular interactions. Such molecular-centered approaches do not cover cell- or organ-level granularity. The AOP covers key events leading to adverse effects with varying granularities [30]. However, the AOP focuses primarily on measurable changes. Furthermore, as an essential point, the AOP is not an ontology, and the terms described in its pathways lack consistency and in some cases are redundant. Ontology can provide richer information flexibly by generalization, specialization, and other relationships in a consistent manner. The TXPO is an ontology and systematizes toxic processes according to an *is-a* hierarchy with inheritances from general to specific terms based on a philosophical view that makes the intrinsic nature explicit. Moreover, by employing systemic functional decomposition, the TXPO covers various processes across granularities in a consistent manner. We confirmed that we can describe both pathway- and molecular-level processes in a unified manner with regard to ER stress. However, we found that the number of molecular processes is so large that it can be difficult to grasp the overall picture of the mechanism. Therefore, the TXPO deals primarily with process-process interactions with grain sizes from the organelle level. With regard to the molecular level, we describe molecules as participants in toxic course processes. Furthermore, we explain the role of each molecule in a given specific process.

Understanding toxicity mechanisms is a hard task. Among the many issues involved, one aspect is the complexity of various interactions in the toxic course. We demonstrated that our imbalance model can make the context clearer and distinguish toxic actions from body defense functions in each granularity, thus facilitating interpretations of toxic mechanisms. Interestingly, we found that sometimes one functioning process plays both a biological defense role and toxic role. For example, as shown in Table 2, during the course of ER stress, apoptosis plays a defensive role in removing abnormal cells accumulating unfolded proteins, whereas increasing apoptosis has a toxic effect at the organ level that can lead to liver failure. Furthermore, our imbalance model is possible to explain that an imbalance also occurs when defensive functioning becomes excessive. For instance, when the cell proliferation function becomes excessive, liver carcinogenesis can develop at the organ level. We are currently trying to introduce the imbalance model for other toxic courses and clarify the relationships between functioning demand and the defense function.

The identification of biomarkers for toxicity prediction using machine learning techniques is a frequent objective of computational toxicology research. However, such machine learning approaches often lack accountability. By annotating markers based on the ontology of TXPO, associating markers with the toxicity process as a progression of toxicity development, and by visualizing them, it is possible to provide accountability for marker genes. Therefore, the TXPO and TOXPILOT will contribute to the enhancement of safety evaluations. Moreover, the general course map in TOXPILOT provides an indication of causal relationships across various mechanisms of toxicity. Therefore, it could be used to discover previously unknown relationships and contribute to the identification of new risks.

Using TOXPILOT, researchers can obtain an overall picture of the mechanism of toxicity in the liver and explore the systemic effects of biological functions. Moreover, from a fragmented knowledge perspective, our maps facilitate the discovery of new knowledge through commonality. Also, our system supports both retrospective and forward analyses. In this way, TOXPILOT enables the generation of knowledge cycles based on the TXPO (Fig. 6).

## Conclusions

In the present work, we developed a TXPO to organize toxic process knowledge. As an application, we developed the TOXPILOT as a prototype system for supporting the interpretation of toxicity mechanisms. We are currently annotating more toxic courses and enhancing the level of sophistication of the terms in the TXPO. In the future, we plan to cover toxic courses in other organs, such as the kidney. We are also planning to reuse various ontologies, such as the Disease Ontology (<http://disease-ontology.org/>), and the Monarch Disease Ontology (Mondo, <https://github.com/cmungall/tbd-disease-ontology>.) Bridging domains on toxicity knowledge from basic to clinical medicine could help elucidate multiple mechanisms of toxicity.

In furthering the applications of the TOXPILOT, we are striving to enhance its functions. The first version of the TXPO is available via the NCBO BioPortal, and the prototype TOXPILOT is open at the following site: <https://toxipilot.nibiohn.go.jp>. New term requests and reporting of issues can be made via a GitHub tracker (<https://github.com/txpo-ontology/TXPO/issues>.) We plan to submit TXPO to the OBO foundry for collaboration and knowledge sharing among not only toxicologists but also other biomedical communities.

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## Address for correspondence

Yuki Yamagata [y-yamagata@nibiohn.go.jp](mailto:y-yamagata@nibiohn.go.jp)  
Hiroshi Yamada [h-yamada@nibiohn.go.jp](mailto:h-yamada@nibiohn.go.jp)  
Laboratory of Toxicogenomics Informatics, National Institutes of Biomedical Innovation, Health and Nutrition  
7-6-8 Asagi, Saito, Ibaraki City, Osaka  
567-0085, Japan  
Phone: +81-72-641-9826

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