Modeling biomedical experimental processes with OBI

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Abstract

Background

Experimental descriptions are typically stored as free text without using standardized terminology, creating challenges in comparison, reproduction and analysis. These difficulties impose limitations on data exchange and information retrieval.

Results

The Ontology for Biomedical Investigations (OBI), developed as a global, cross-community effort, provides a resource that represents biomedical investigations in an explicit and integrative framework. Here we detail three real-world applications of OBI, provide detailed modeling information and explain how to use OBI.

Conclusion

We demonstrate how OBI can be applied to different biomedical investigations to both facilitate interpretation of the experimental process and increase the computational processing and integration within the semantic web. The logical definitions of the entities involved allow computers to unambiguously understand and integrate different biological experimental processes and their relevant components.

Availability

OBI is available at http://purl.obolibrary.org/obo/obi/2009-11-02/obi.owl

Background

Biomedical investigations use empirical approaches to investigate causal relationships among a large range of variables. The wide range of possible investigations presents a number of challenges when building tools to describe experimental processes. There are varying levels of complexity and granularity and a wide range of material and equipment is used. Furthermore, the use of varying terminology by different communities makes data integration problematic when representing and integrating biomedical investigations across different fields of study. The use of ontologies has been successful in biological data integration and representation [the GO consortium, 2000; Matos *et al*., 2006] and there have been multiple efforts to develop ontologies aimed at providing clearer semantics for data (GO, FuGO, MGED, LABORS, MSI ontology) [Whetzel *et al*., 2006(a); Whetzel *et al*., 2006(b), King *et al*., 2009; Sansone *et al*., 2007]. Work in the transcriptomics, proteomics and metabolomics communities has proceeded in parallel, producing ontologies with overlapping scopes.

Though each focuses on particular types of experimental processes, many terms, such as *investigation* and *assay*, are common to all. Merging common aspects of these formalisms is useful as it provides a mechanism by which terms can be used and understood by all, reducing ambiguity and difficulties associated with post-hoc attempts to integrate data. The practice of consolidating representations is endorsed by organizations such as the OBO Foundry [Smith *et al*., 2007] which requires all member ontologies to define a term only once among them (orthogonality). OBO Foundry members use a common set of relations from the Relations Ontology [Smith *et.al*., 2005], and the upper level Basic Formal Ontology (BFO) [Grenon *et al*, 2004] in order to facilitate cross ontology consistency and to support automated reasoning.

OBO ontologies adhere to common naming conventions [Schober *et al*. 2009] in order to make it easier to learn and understand them.

The Ontology for Biomedical Investigations (OBI) addresses the need for a common, integrated ontology for the description of biological and clinical investigations. OBI is collaboratively developed by representatives from 19 biomedical communities and has been submitted as a candidate for the OBO Foundry. It uses other OBO ontologies wherever possible. OBI defines a set of broadly applicable terms that span biomedical and technological domains, for example, *assay* (the planned process of producing data about something) as well as domain-specific terms relevant to smaller areas of study, for example *T cell epitope recognition assay,* used by the IEDB database to describe experimental data extracted from articles investigating immune epitopes [Peters *et al.*, 2005].

OBI represents experimental processes e.g., *investigation*, *assay*, and the entities involved in preparing for, executing, and interpreting those processes e.g., study design, protocols, instrumentation, biological material, collected data and analyses performed on that data. OBI therefore supports consistent annotation of biomedical experimental processes regardless of the field of study. In this paper, the OBI release of 2009-11-02 is applied to three exemplar use cases, originating from three communities: 1) neuroscience, 2) vaccine protection, and 3) functional genomics. The OBI release of 2009-11-02 is available at http://purl.obolibrary.org/obo/obi/2009-11-02/obi.owl, it also can be accessed via BioPortal (http://bioportal.bioontology.org/) and details of OBI design are described at http://purl.obolibrary.org/obo/obi.

Results

Biomedical experimental processes involve numerous sub-processes, involving experimental materials such as whole organisms, organ sections and cell cultures. These are represented as subclasses of the BFO class *material entity*. OBI defines an *investigation* as a process with several parts including planning an overall study design, executing the designed study, and documenting the results. An *investigation* typically includes *interpreting data* to draw conclusions. OBI uses BFO's *material entity* as the basis for defining physical things. Material entities are *independent continuants,* entities that are spatially extended, whose identity is independent of that of other entities, and which persist through time, for example *organisms*, *test tubes*, and *centrifuges*. Material entities can bear *roles*, typically socially defined, which are realized in the context of a *process*, e.g. *study subject role*, *host role*, *specimen role*, *patient role*; and *functions,* results of design or evolution that depend on their physical structure e.g. *measure function*, *separation function* and *environment control function.*
To assess the completeness of the OBI release of 2009-11-02 and to demonstrate the use of OBI for annotation, we present three representative use cases. These demonstrate how to model entities and relations between entities involved in experimental processes using OBI. The first use case models a neuroscience experiment described in a journal article [Lauweyrens et al., 2002] and shows how logical definitions are constructed using parts of external ontologies imported into OBI. The second use case details how OBI is used to model vaccine studies; the third describes an investigation run by a Robot Scientist which designs and executes functional genomics experiments.

Use case 1: Neuroscience investigation

This investigation studied the role of the primate caudate nucleus in the expectation of reward following action [Lauweyrens *et al.*, 2002]. It is found that while the caudate nucleus responds preferentially to eye movements in different directions, the response begins prior to eye movement and is dramatically increased when there is expectation of reward for the preferred direction. Here we model a part of the investigation: specifically, a single trial in which the visual target is presented to the animal and the neural response is recorded. This single trial model contains two processes (Figure 1):

1. A *presentation of stimulus* process in which the primate realizes its *study subject role.*
2. A *measuring neural activity* process, modeled as a sub class of *extracellular electrophysiology recording* process which *has specific input* from a neuron*,* which in this study *has location in* the caudate nucleus which is *part of* the monkey.

Thus, the process of measuring the neural activity *unfolds in* the caudate nucleus. The anatomical term *caudate nucleus* is imported from the NIFSTD [Bug *et.al*., 2008] to complete the logical definition of the assay. The function of the microelectrode used to measure the neural activity *is realized as* a *measure function* which inheres in the recording device, and the process *has the specified output* of a spike train datum.

To build logical definitions for this experimental processes required us to ask a series of questions of the domain experts and which are not explicit in the publication. For example, is the location of the micro-electrode extra or intracellular? Are all spike train data generated from the caudate nucleus? How does a spike train relate to the GO process *regulation of action potential* [GO:0001508]?

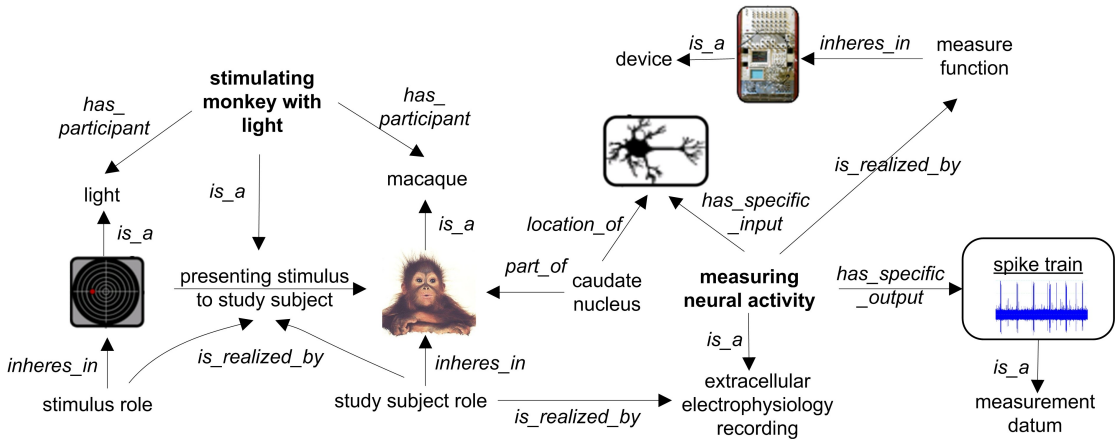

Figure 1. OBI modeling of a single trial in the neuroscience study. Processes in this experimental trial are shown in bold (e.g., **stimulating monkey with light**, **measuring neural activity**), while terms for objects, roles, or processes (e.g., macaque, stimulus role, extracellular electrophysiology recording) are shown in regular font and relationships are in italics (e.g., *is_realized_by*, *has_specific_input*). Diagrams such as those for the light, or the monkey, or the neuron indicate that those are instances of the ontological classes.

Decisions on the appropriate level of granularity are challenging: in this use case we have not included instances of our classes in the ontology itself, and have specifically added general entities so that these can be re-used for other use cases and communities. We also use some relations from ro_proposed [http://obofoundry.org/cgi-bin/detail.cgi?ro_proposed]. In this case we chose to import *unfolds in* to specify that an *occurrent* (process) happens in a certain location (i.e., the assay of spike trains in the caudate nucleus) rather than *located in* currently in RO which relates only continuants. Finally, we use the NCBI taxonomy [Sayers *et al.*, 2008] to describe the species involved in this experiment. Reusing external

resources fulfill two purposes. First, we rely on domain experts in specific areas to model the information, thus avoiding duplication of efforts. Second, by re using existing resources, we improve future data integration by preventing the need for mapping between several identifiers denoting the same entity.

Use case 2: Vaccine protection investigation

A vaccine protection investigation (also known as a vaccine challenge experiment) measures how efficiently a vaccine or vaccine candidate induces protection against a virulent pathogen infection *in vivo*. Figure 2 demonstrates how to use OBI to represent a typical vaccine protection investigation via the following three sub-processes:

1. *A vaccination* is a kind of *administering substance in vivo* that realizes some *material to be added role* borne by a *vaccine* (e.g., VacX) as well as a *target of material role* borne by an *organism* that also bears a *host role* (e.g., mouse). The term *vaccination* is a term imported from the Vaccine Ontology (VO, http://www.violinet.org/vaccineontology). A *contain function* that inheres in a bottle is realized by the vaccination process. An *injection function* that inheres in a syringe (a processed material or device) is also realized by the vaccination process.
2. *A pathogen challenge* is also a kind of *administering substance in vivo* process. It realizes a number of roles - a *pathogen role* and *material to be added role* borne by the challenge *organism* (e.g., Influenza Virus), and a *target of material role* and *host role* borne by another *organism* (e.g., mouse). An *injection function* that inheres in a syringe is realized by the pathogen challenge process.

3. *A survival assessment* is an *assay* that measures the *survival rate* (occurrence of death events) in one or more *organisms* that are monitored over time. The *survival assessment* is a protection efficiency assay that *has specified input* a number of *organisms* (e.g., mouse) and *has specified output* a *survival rate*, in this case a *measurement datum* that records that 75% of mice survived the *pathogen challenge*.

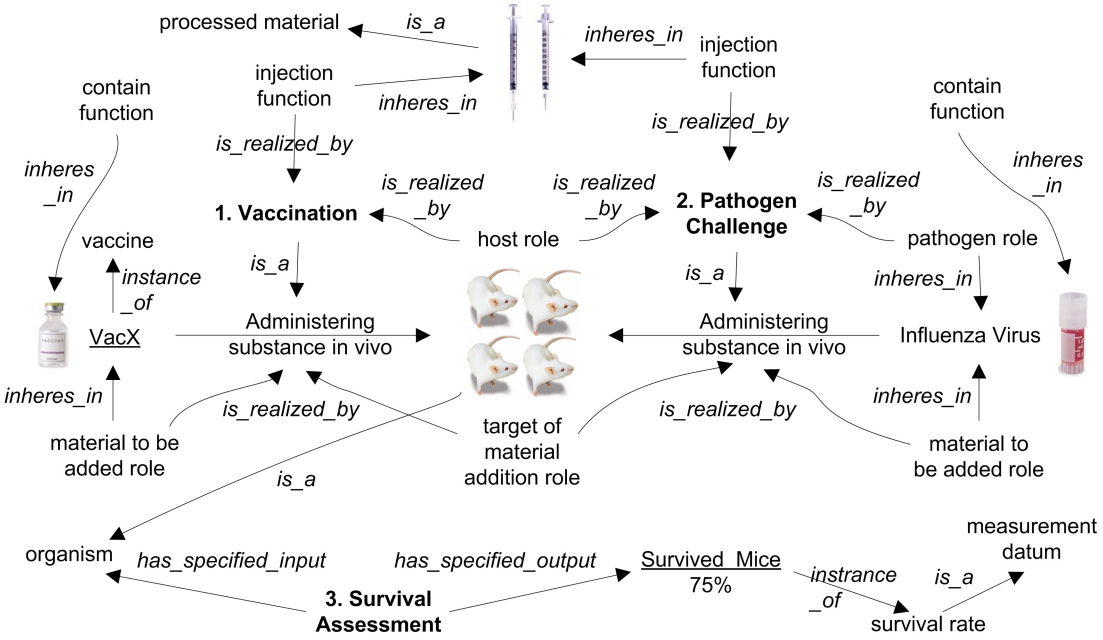

Figure 2. OBI modeling of vaccine protection investigation. The three major processes are highlighted in bold. All italicized terms are properties. Two underlined terms are instances.

Use case 3: An automated functional genomics investigation

Robot Scientist "Adam" is designed to perform high-throughput growth curves measurements (phenotypes) of selected microbial strains (genotypes) in a defined media (environment) [King *et al.*, 2009]. The robot requires a complete and precise description of all experimental actions, and this use case demonstrates how OBI can be used to provide elements of such a description. Here we have represented an *investigation* in which Adam tests hypotheses about which metabolites can restore a function of the removed yeast gene (Figure 3).

1. Adam's *planning* yields a *plan specification* that has, as part, an *objective specification* to test an inferred statements which are modeled as *hypothesis textual entity*. Each statement *is about* whether metabolite will affect yeast strain growth. Adam's plan specifies an *assay* to test these hypotheses: to grow yeast with and without addition of the metabolite.
2. The planned process *automated investigation of the enzyme EC.6.1.39* is an *instance of* the class *hypothesis driven investigation* with the objective to test the hypothesis specified in the *planning* process (we represent a single *hypothesis textual entity* which serves as a design pattern). The *specified output* of the *investigation* is the *study result* – whether the metabolite affected the growth of the yeast strain (see Figure 3, panel: process 3). The upper growth curve shows the growth rate with the addition of the metabolite, and the lower curve shows the rate with no metabolite. The results interpretation is modeled as *conclusion textual entity* that states that the statement inferred by Adam has been confirmed and the robot can update its background knowledge.
3. The *investigation* process *has part* several *assays* that provide data used to test the hypotheses. The assay *has specified inputs* the metabolite and the yeast

strain specified in the hypothesis, and *specified output* is a *data set* consisting of several optical density measurement data. The yeast bears the *evaluant role*, and the metabolite the *nutrient role.*

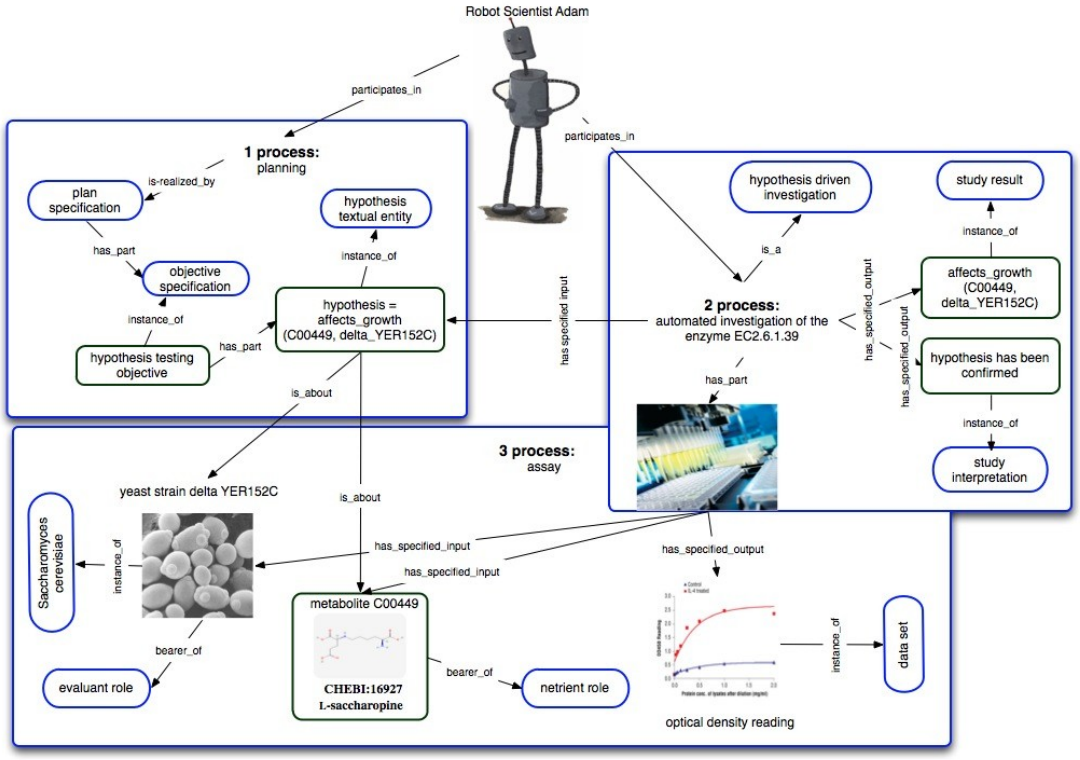

Figure 3. OBI modeling of the Robot Scientist automated investigation (a fragment). The three major processes are highlighted in bold, instances are in green boxes and classes are in blue boxes.

Discussion

OBI was built to provide a comprehensive and versatile representation of biomedical investigations. Our three biological use cases are represented by statements in terms defined in OBI. Individual experimental steps - the two processes in the neuroscience use case, the three processes in the vaccine protection case, and the three processes in the functional genomics case - all fall under *planned process* in OBI. The processes *vaccination* and *pathogen challenge* are disjoint subclasses of *administering*

substance in vivo. *Survival assessment* is a type of *assay* (Table 1). We found that all these required processes, as well as all other entities described in the use cases could be represented using OBI idioms. Syringe is a *device* that participates in different processes. Entities such as vaccine are types of *material entity. Host role*, *pathogen role*, and *material to be added* are types of *role.*

These entities are used to represent disparate experimental processes in a standard way in order to be suitable for computer-assisted reasoning. These use cases are examples at a high level of representation across a disparate set of domains; each of the examples can be modeled more completely, to include, for example the process delivering the reward in the neuroscience example, or specific details of the influenza virus development process in the vaccine example. The distinction between extracellular *in vivo* electrophysiological recording that unfolds in the caudate nucleus or other regions of the brain can be represented within this framework, as can different details of similar experiments.

That OBI can be used to represent experimental processes for different applications and domains is appealing because it suggests that we can better leverage the work we each do. Approximately 400 vaccines have been manually curated and stored in the VIOLIN vaccine database system [Xiang *et al.,* 2008]. Currently, the vaccine protection experimental data in VIOLIN is stored in plain text and can be difficult to interpret. The lack of a common ontology to aid in representing this data has prevented optimal use of the VIOLIN vaccine data. We plan to apply the representation described in this paper to that data in order to enable advanced querying both within the data as well as across data from other biomedical communities that represent their data using OBI. As an example, consider that a vaccine candidate against Alzheimer disease may induce specific changes on the

brains of transgenic mice or human patients (http://www.ncbi.nlm.nih.gov/pubmed/12379846). Therefore enabling query across the domains of vaccinology and neuroscience would be of utility in conducting such research.

The representations of the investigations run by Adam were stored as instances of the defined classes in a relational database [Soldatova *et al.*, 2006]. Accurate and complete recording of all experimental processes involved in the investigations allows efficient re-use of produced data and results for different investigations with different objectives.

OBI's approach to representation for automation suggests new possibilities for automated investigations, desirable because such methods offer high throughput mechanisms not only for data generation, but also for hypotheses generation and the results analysis. As using terminology from a wide range of biology is a central part of OBI's methodology, we can easily imagine that it is reasonable to extend the reach of such an approach. For example, DNA microarray experiments may also be performed using Robot Scientists in order to generate and test hypotheses regarding the transcript expression level in brain or other tissues, and knowledge encapsulated the Gene Ontology or other ontologies could be applied to interpreting the results of such experiments.

Conclusions

Here we provide three real world use cases as examples of how to represent experimental processes with OBI. Experience such as this helps validate OBI's current design choices as well show how to extend it in domain specific ways. It also generates competency questions that allow us to identify parts of OBI that are insufficiently expressive and to identify external resources that can be used to extend

OBI's coverage. We found that a major technical challenge is the requirement to import terms from other ontologies to construct logical definitions: due to its broad scope OBI spans multiple existing ontological resources. There is a significant cost preventing those large imports, as reasoning becomes slower and the ontology is harder to navigate. To solve this problem the OBI consortium developed the MIREOT mechanism [Courtot *et al.*, 2008], which preserves namespaces of imported terms and allows their direct use into OBI. We also hope that technologies such as views [Detwiler & Brinkley, 2008] and modules [Parsia *et al.*, 2009] as well as improvements to existing reasoners will address these issues. OBI will be further developed to expand the coverage and depth of biomedical investigations and the use cases presented here helped us in testing the forthcoming release candidate 1.0 version of the ontology.

List of abbreviations

GO: Gene Ontology

IAO: Information Artifact Ontology

LABORS: LABoratory Ontology for Robot Scientist

MGED: Microarray Gene Expression Society

MIREOT: Minimum Information to Reference an External Ontology Term

MSI: Metabolomics Standards Initiative

NCBI: National Center for Biotechnology Information

NCBI_Taxon: NCBI Taxonomy

NIFSTD: Neuroscience Information Framework standardized

OBI: Ontology for Biomedical Investigations

OBO: Open Biomedical Ontologies

VO: Vaccine Ontology

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

The three use cases were primarily provided by DD/JT, YH, and LNS. All authors contributed to the development of OBI.

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Table 1. Ontology terms used in the three use cases (note: instances are not included):

Ontology terms	Sources and term IDs	Parent class	Use cases
Classes			
administering substance in vivo	OBI: OBI_0600007	material combination	2
assay	OBI: OBI_0000070	planned process	3
caudate nucleus	NeuroLex: birnlex_1373	anatomical entity	1
centrifuge	OBI: OBI_0400106	processed material	
conclusion textual entity (alternative term: conclusion)	IAO: IAO_0000144	textual entity	3
contain function	OBI: OBI_0000370	function	2
data set	IAO: IAO_0000100	data item	3
environment control function	OBI: OBI_0000401	function	
evaluant role	OBI: OBI_0000067	role	3
extracellular electrophysiology recording	OBI: OBI_0000454	assay	1
function	snap#Function	realizable_entity	
host role	OBI: OBI_0000725	role	2
hypothesis driven investigation	OBI: OBI_0000355	planned process	3
hypothesis textual entity (alternative term: hypothesis)	IAO:TMPIAO_0000005	textual entity	3
independent_continuant	snap#IndependentContinuant	continuant	
injection function	OBI:OBI_0005246	function	2
interpreting data	OBI: OBI_0000338	process	
investigation	OBI: OBI_0000066	planned process	
light source	OBI: OBI_0400065	processed material	1
Macaca fuscata	NCBI_Taxon: NCBITaxon_9542	organism	1
material combination	OBI: OBI_0000652	planned process	
material to be added role	OBI: OBI_0000319	role	2
material_entity	snap#MaterialEntity	IndependentContinuant	
measure function	OBI: OBI_0000453	function	1
measurement datum	IAO: IAO_0000109	data item	1,2
measuring neural activity in the caudate nucleus	OBI: OBI_0000812	extracellular electrophysiology recording	1
micro electrode	OBI: OBI_0000816	processed material	1
neuron	FMA: FMA:54527	anatomical entity	1
objective specification	IAO: IAO_0000005	directive information entity	3
organism	OBI: OBI_0100026	material_entity	2
pathogen challenge	OBI: OBI_0000712	administering substance in vivo	2
pathogen role	OBI: OBI_0000718	role	2
patient role	OBI: OBI_0000093	role	
plan specification	IAO: IAO_0000104	directive information entity	3
planning	OBI: OBI_0000339	planned process	3
presentation of stimulus	OBI: OBI_0000807	process	1
process	span#Process	processual_entity	
processed material	OBI: OBI_0000047	material_entity	1,2,3
role	snap#Role	realizable_entity	
Saccharomyces cerevisiae	NCBI_Taxon: NCBITaxon_4932	organism	3
separation function	OBI: OBI_0000372	function	
specimen role	OBI: OBI_0000112	role	
spike train datum	OBI: OBI_0000801	measurement datum	1
study result	OBI: OBI_0000682	information content entity	3
study subject role	OBI: OBI_0000097	role	1

survival assessment	OBI: OBI_0000699	assay	2
survival rate	OBI: OBI_0000789	measurement datum	2
syringe	OBI: OBI_0000422	processed material	2
T cell epitope recognition assay	OBI: OBI_1110037	assay	
target of material addition role	OBI: OBI_0000444	role	2
test tube	OBI: OBI_0000836	processed material	
vaccination	VO: VO_0000002	administering substance in vivo	2
vaccine	VO: VO_0000001	material_entity	2
Property terms			
bearer_of	RO: OBO_REL#bearer_of		1,3
has_part	ro.owl#has_part		3
has_participant	ro.owl#has_participant		1
has_specified_input	OBI: OBI_0000293		1,2
has_specified_output	OBI: OBI_0000299		1,2
inheres_in	RO: OBO_REL#inheres_in		1,2
is about	IAO: IAO_0000136		3
Is_a	RO: OBO_REL:is_a		1,2,3
is_realized_by	IAO: IAO_0000122		1, 2, 3
location_of	ro.owl#location_of		1
part_of	ro.owl#part_of		1
participates_in	ro.owl#participates_in		3
unfolds_in	RO: OBO_REL#unfolds_in		1