

# Integrative representations and analyses of vaccine-induced intended protective immunity and unintended adverse events using ontology-based and theory-guided approaches

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While effective preventive vaccines induce intended protective immunity, they also induce unintended adverse events (AEs). Generally speaking, compared to killed, inactivated vaccines and protein vaccines, live attenuated vaccines induce more protective immune responses. However, live attenuated vaccines are also associated with more AEs and even more serious AEs. For example, while live attenuated smallpox vaccines were critical to the eradication of smallpox, approximately 20–30% of smallpox vaccine recipients also experienced with various AEs that range in prevalence and severity [1]. Inter-individual variations in cytokine and AE response after smallpox vaccinations are in part due to genetic variation. For another example, the attenuated oral poliovirus vaccine (OPV) efficiently induces intestinal immunity and durable humoral immunity. However, OPV has the disadvantage of genetic instability, contributing to rare and sporadic cases of vaccine-associated paralytic poliomyelitis and the emergence of genetically divergent vaccine-derived polioviruses [2]. These AEs are worsened in patients with primary immunodeficiencies. These results suggest that the intended protective immune responses and unintended adverse events are correlated and deserve being studied simultaneously.

A biomedical ontology is a human- and computer-interpretable set of terms and relations that represent entities in a specific biomedical domain and how they relate to each other. Ontologies have emerged to be critical to biomedical data and knowledge representation, exchange, integration, as well as inferring new knowledge. We have initiated and led the development of three vaccine-focused ontologies:

(i) The Vaccine Ontology (VO) is developed to ontologically represent licensed vaccines or experimentally verified vaccine candidates, vaccine components, and host immune responses to vaccines [3,4]. The VO has also represented key vaccine information manually curated from the literature and stored in the VIOLIN vaccine database [5,6]. The hierarchies and logical relations of thousands of terms in VO support computer-assisted automated inferencing. VO has been applied to support various vaccine data integration [7–11] and literature mining [4,12,13].

(ii) The Ontology of Vaccine Adverse Events (OVAE) is an ontology of the AEs known to be associated with the administration of licensed vaccines [14]. By extending VO and the Ontology of Adverse Events (OAE) [15], OVAE effectively imports the information of vaccines and adverse events. With these imported terms, OVAE is able to semantically define vaccine-specific adverse events. Based on the official FDA licensed vaccine package insert documents, age-specific AE occurrence rates in different populations are also represented for specific vaccine-specific adverse events (e.g., influenza vaccine Afluria-

associated pain AE). Currently, OVAE includes all over 1,300 AEs associated with 63 US-licensed human vaccines [14]. OVAE can be easily used to query for important vaccine safety questions such as the most common VAEs observed in humans and the vaccines that have most AEs [14].

(iii) The Vaccination Informed Consent Ontology (VICO) is an ontology targeted to integrate different forms of vaccination informed consent forms with the goal of supporting integrative informed consent form query and result analysis [16]. Although signing a vaccination informed consent is not required at the federal level in the USA and Canada, many pharmacies (e.g., Costco and Walgreens) and state level regulations (e.g., Canada Manitoba government Public Health division) require informed consent before specific vaccinations. The vaccination informed consent forms from these different sources are different, making it difficult to integrate these forms and patients' records for advanced studies. VICO provides an ontological solution to such an issue [16]. In addition, by importing vaccine information from VO to the VICO, it is possible to make advanced inference. For example, based on vaccine contraindication information (from VO) and a user's answer to an allergic question(s) in a vaccination informed consent form, we may infer a possible disqualification of the user for the vaccination due to a contraindication-related safety concern [15].

As described above, VO, OVAE, and VICO focus on the representation and analysis of vaccine formulations, vaccine safety, and vaccination informed consents, respectively. One missing domain of representation is the fundamental causal molecular interactions that eventually result in clinical phenotypes, which can be intended immune protection and unintended adverse events. How to better study the transition from basic molecular mechanisms to clinical phenotypes has remained a huge challenge.

In a recent publication [17], an ontological semantic framework is reported that links biological mechanisms to phenotypes of AEs by combining OAE with MedDRA in clinical FAERS drug case report data analysis. The Medical Dictionary for Regulatory Activities (MedDRA) is the default dictionary for AE reporting in the FDA AE Reporting System (FAERS). In this study, the AEs associated with five Tyrosine Kinase Inhibitors (TKIs) and monoclonal antibodies (mAbs) targeting tyrosine kinases, which induce impaired ventricular function (non-

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QT) cardiotoxicity, were investigated. Statistical analysis of FAERS data identified 1,053 distinct MedDRA terms significantly associated with TKIs/mAbs. These MedDRA terms were mapped to OAE terms that also link to other existing ontologies including the Gene Ontology (GO) [18]. The relations between TKIs/mAbs, cardiotoxicity AEs, and underlying gene products were generated. Such a study demonstrates that the combination of OAE and MedDRA provides a semantic framework to link clinical phenotypes of adverse drug events to biological mechanisms.

Theories provide guidance and hypotheses to practical studies. For understanding vaccine responses, two theories have been recently proposed. First, Dr. Gregory A Poland proposed an “Immune Response Gene Network Theory” [19, 20] which states that the responses to a vaccine are the cumulative results of interactions driven by a host of genes and the interactions among these genes in a choreographed fashion. Important immune response genes, gene polymorphisms, epigenetic modifications, and gene–gene interactions may all change the outcomes of host immune responses to a vaccine [19]. This theory has been used to guide the studies of the associations between immune response gene polymorphisms and various vaccine-induced antibody and cell-mediated immune responses [19] and the development of vaccinomics [21] and adversomics strategies [22].

More recently, Dr. Yongqun He proposed “the OneNet Theory of Life” [23,24]. The OneNet theory treats the whole process of a life of an individual organism as one single complex and dynamic network (abbreviated as OneNet). The OneNet has four characteristics that cover the OneNet Blueprint, OneNet Start, OneNet Dynamics, and OneNet Effectiveness [24]. Compared to the Immune Response Gene Network Theory, the OneNet theory is more focused on the exploration of the root cause of an organism’s phenotypes such as vaccine-induced immune responses and AEs. The OneNet theory targets the systematic representation and analysis of the life of one organism (e.g., a human being), with a special focus on the dynamic interactions among genotype, environments, and phenotypes along the life process. Based on the OneNet theory, it is hypothesized that one human uses one single genotype-rooted mechanism (*i.e.*, OneNet blueprint) to respond to different vaccinations [24]. This hypothesis appears contradictory against obvious experimental observations that human uses different mechanisms against different vaccines. However, experimentally identified mechanisms are hypothesized to be different manifestations of the same OneNet blueprint mechanism under specific conditions [24]. The introduction of the two concepts, OneNet blueprint and OneNet manifestations, establishes a novel framework that integrates genotypes, environments, and phenotypes under a unified, dynamic, and complex network setting.

The theories and ontologies can interact together as semantic frameworks to support integrative vaccinology research. The theories provide the basic structure, the contents and logics of the entities for semantic ontological representation. Meanwhile, without ontology, it is difficult to represent multi-layer, condition-dependent complex network systems covered by the theories. Currently we are developing the Interaction Network Ontology (INO) [13] and Human INO (HINO) [25]. These ontologies will be combined with VO/OAE/OVAE to further support vaccine-specific interaction network representation and analyses. The integration between the ontologies and theories, together with various systems biology approaches, will ensure better integrative representations and analyses of the basic molecular interactions and clinical phenotypes associated with vaccine-induced intended protective/therapeutic immune responses and unintended adverse events.

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