Ontological representation, modeling, and analysis of parasite vaccines

By Anthony Huffman, Xumeng Zhang, Meghana Lanka, Jie Zheng, Anna Maria Masci, Yongqun He
8/29/2023

Introduction to Vaccine and Parasite Ontologies

- Vaccine Ontology (VO)
  - OBO ontology focused on representation of vaccines and related terms
- Vaccine Investigation and OnLine Information Network (VIOLIN)
  - Knowledgebase that used primarily for vaccines
  - Aligned with VO
- Ontology of Parasite LifeCycles (OPL)
  - OBO ontology focused on representation of parasite life cycles

Pathogenic parasites

Class: parasite organism

Term IRI: http://purl.obolibrary.org/obo/OPL_0000232

Definition: An organism living in, with, or on another organism in parasitism. Individual members of parasite species, such as Leishmania, Plasmodium, Trypanosoma, etc. are members of this class.

Annotations

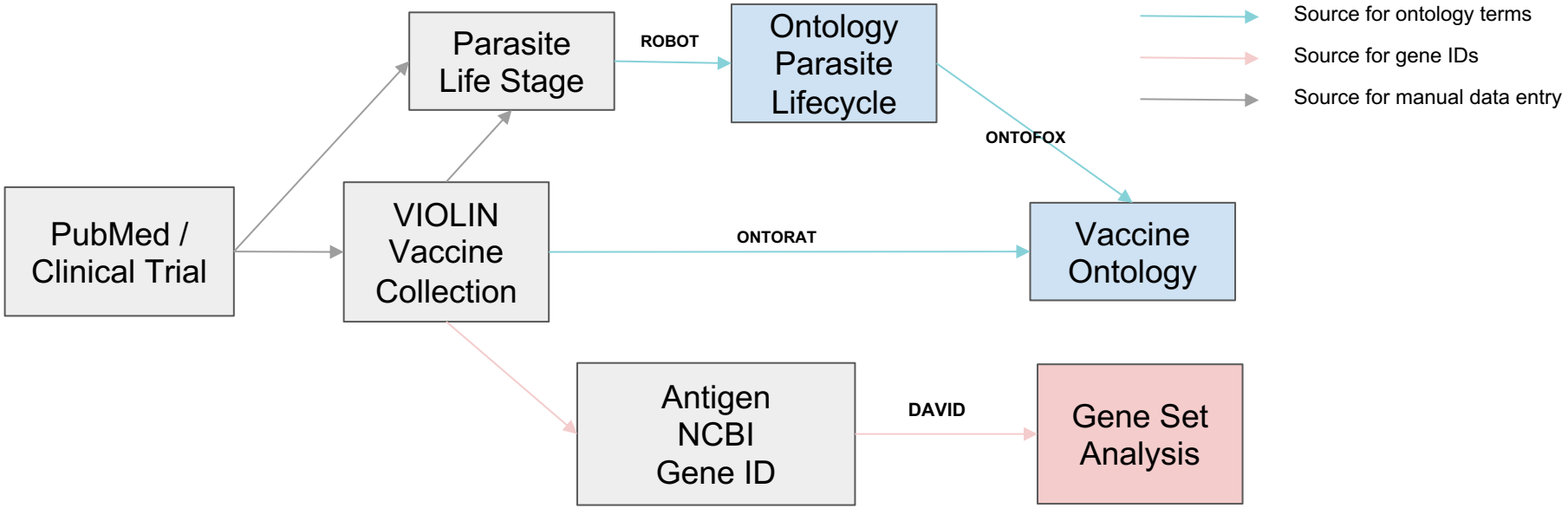
- **definition editor:** Priti Parikh, Jie Zheng
- **definition source:** http://www.merriam-webster.com/dictionary/parasite?show=0&t=1310398415

- Parasites can cause a disease process in host species
  - Malaria (primates), Leishmaniasis (humans), Eimeria (poultry)
- Pathogenic parasites exist as Protozoan, Helminth, and Ectoparasites:
  - Protozoans have vaccines for two specific clades:
    - **Apicomplexa**
    - **Mastigaphora**
- For this paper, protozoan and parasite vaccine are used interchangeably

Motivation and Goals for Study.

- Parasite vaccines are recently being approved
  - Understanding of parasite vaccine antigens needed to aid in R&D
  - Parasite vaccines were neglected compared to yearly updates to VIOLIN for other pathogens
- Parasite vaccines target specific lifecycles
  - VO model assumes a vaccine works regardless of pathogen age or stage
  - ‘Vaccine’ ‘protects against microbe’ some ‘pathogen’
- **Do parasite vaccines affect all life stages for pathogens?**
- **Do parasite vaccine antigens share common features?**

Workflow Design for VO Parasite Organism Design



Vaccine Collection and Annotation

- 260 parasite vaccines within VIOLIN
  - 77 previously existed in VIOLIN
  - 20 parasites
  - 198 parasite antigens
  - 12 non-human vaccines

Table 1: A list of parasites with at least 10 vaccines curated in VIOLIN. VIOLIN combines *Plasmodium* and *Eimeria* species into single categories due to each genus is listed as causing the same disease. Table takes statistics from July 2023.

Pathogen Name	Disease	Number of Vaccines	Number of Licensed Vaccines	Number of Vaccine Antigens
Plasmodium spp.	Malaria	67	0	54
Toxoplasma gondii	Toxoplasmosis	58	1	26
Typanosoma cruzi	Chagas disease	34	1	27
Leishmania donovani	Visceral leishmaniasis	17	0	16
Leishmania major	Cutaneous leishmaniasis	13	0	15
Eimeria spp.	Coccidiosis	11	8	1
Neospora caninum	Neosporosis	11	2	10
Schistosoma japonicum	Schistosomiasis	10	0	8

Annotation of vaccines in the Protozoan parasite life cycle

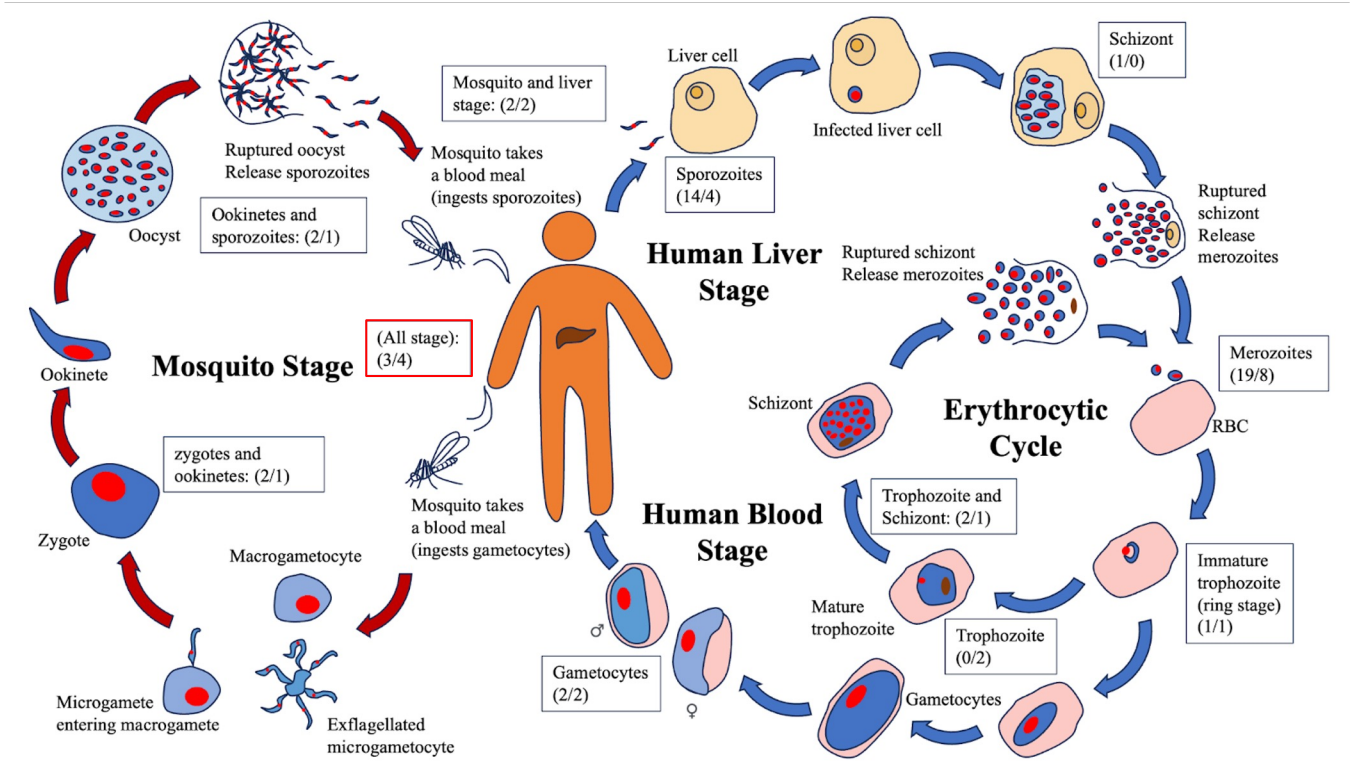


Fig. 1. *Plasmodium falciparum* life cycle and vaccines at different stages. Boxes indicate total number of vaccines/antigens for each life stage. Figure and life cycle adapted from NIH.gov

Annotation of vaccines in the Protozoan parasite life cycle

- Pathogen parasites have multiple life cycle stages
  - Each life cycle stage is phenotypically unique
- Vaccine antigens work only if antigen is expressed
- Many parasite antigens are ineffective
- Therefore new pattern needed for parasite vaccines

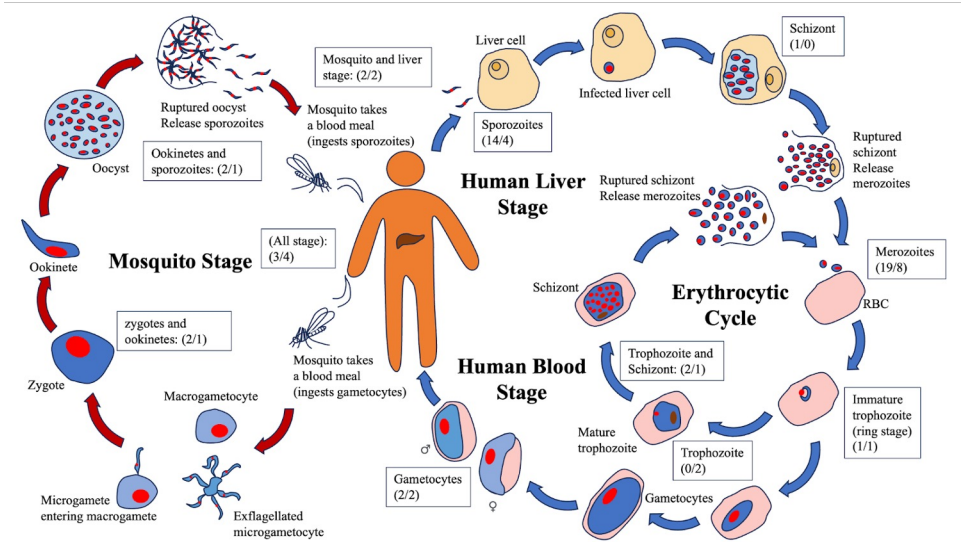
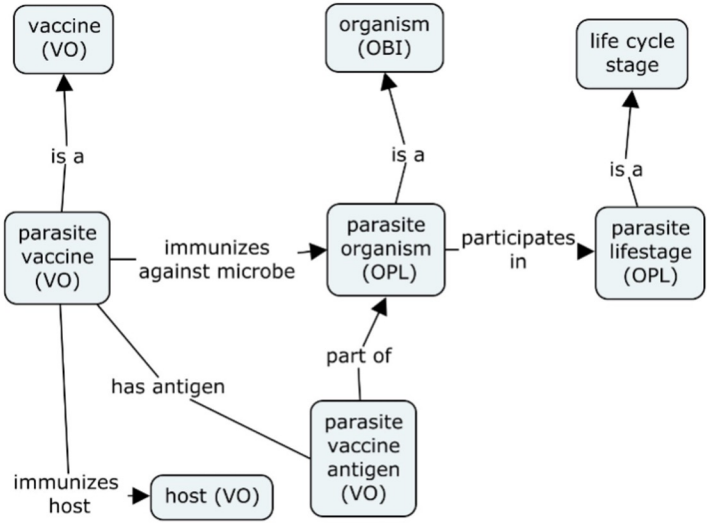


Fig. 1. *Plasmodium falciparum* life cycle and vaccines at different stages. Boxes indicate total number of vaccines/antigens for each life stage. Figure and life cycle adapted from NIH.gov.

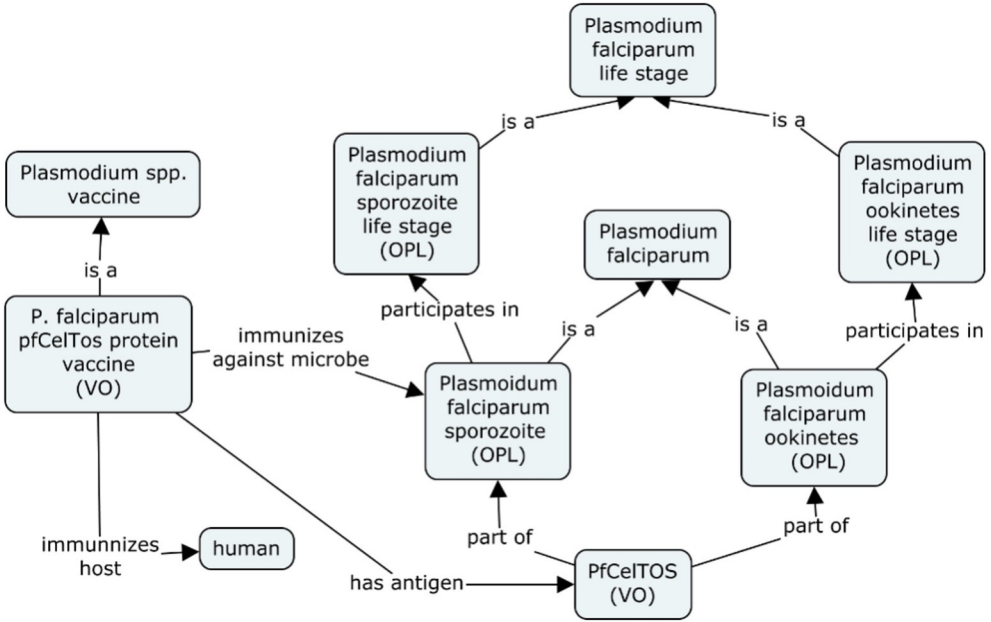
ODP for Parasite Vaccines

- Primary change to parasite vaccines relates to parasite life stages.
- Parasite vaccines ‘immunizes against microbe’ some parasite organism
- Parasite antigens mapped to parasite organism in life stage



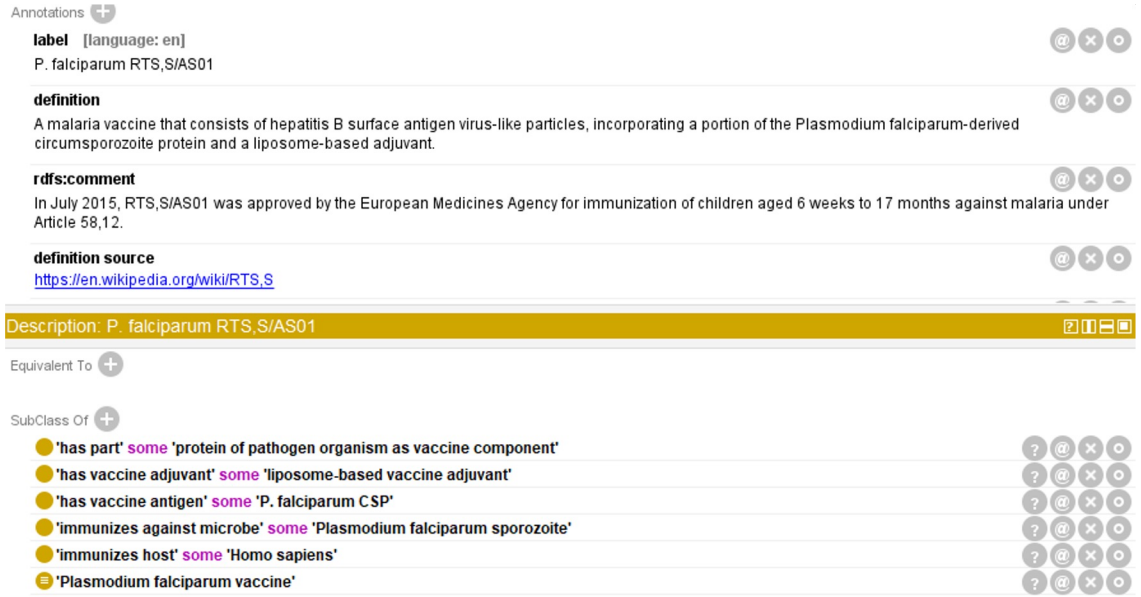
Representation of for Parasite Vaccines

- New ODP can be used to link vaccines to multiple lifestages
- *‘P. falciparum pfCelTos vaccine’*
  - Utilizes antigen found in ookinetes and sporozoite
  - Experiments done only against sporozoite
  - Possible inference that PfCelTOS will work for multiple stages

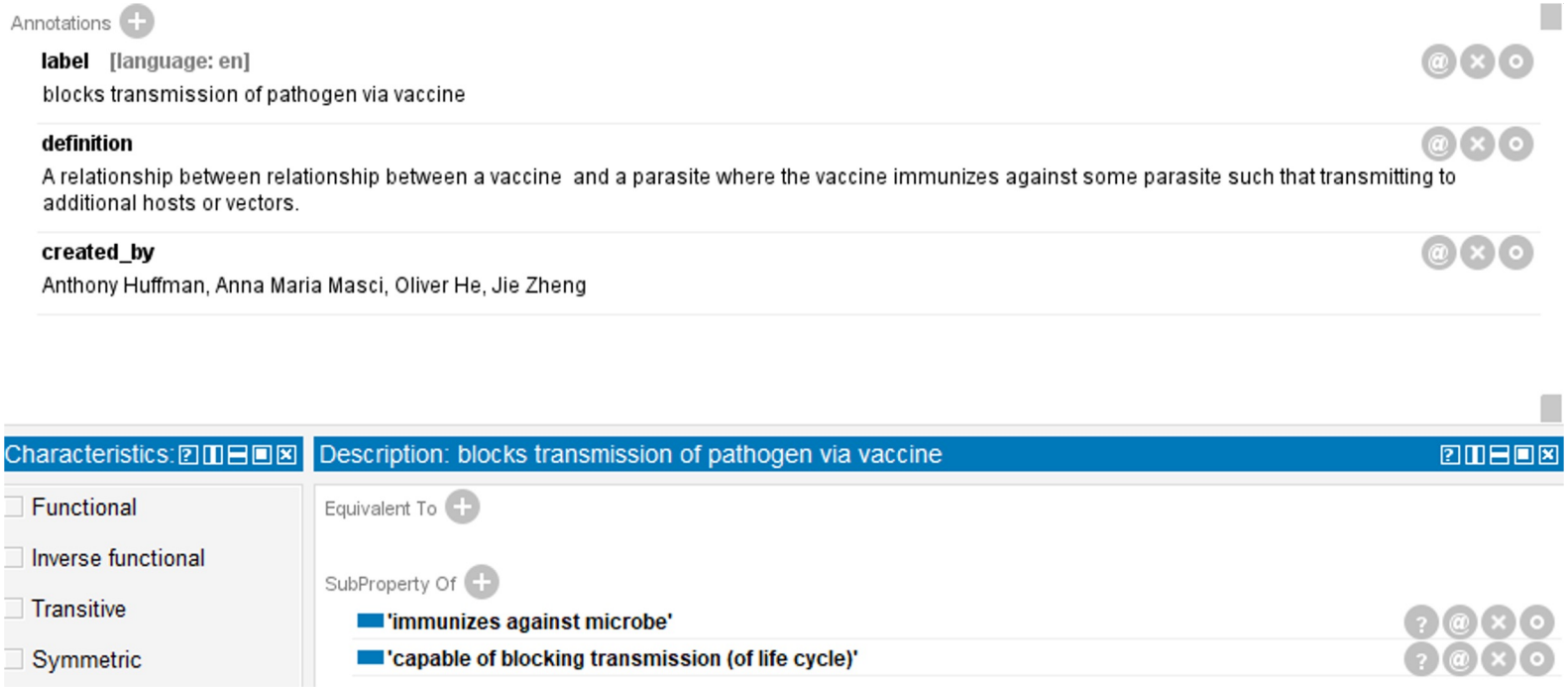


Mosquirix Representation in Vaccine Ontology

- Mosquirix is first licensed malaria vaccines.
- New representation clarifies life stage that the vaccine immunizes against

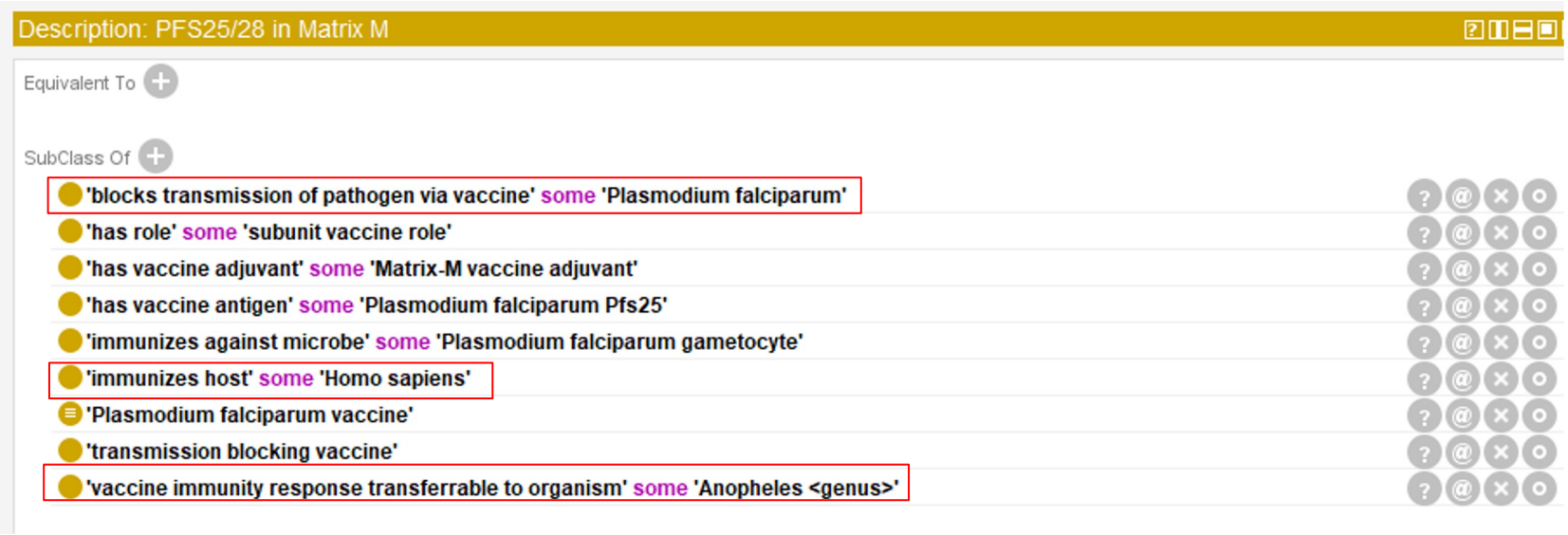


Transmission Blocking Vaccine



PFS25/28: A transmission blocking vaccine

- Has three key axioms.
  - ‘Blocks transmission of pathogen via vaccine’ – target pathogen
  - ‘Immunizes host’ – host that will generate source of vaccine immune response
  - ‘vaccine immunity response transfer to organism’ shows’ – host/vector receive immune response



VO ID Expansions

- We have added 417 new terms added to VO*
  - 165 new parasite vaccines; for 240 parasite vaccines
  - 125 new parasite antigens; for 250 parasite antigens
  - 15 new parasite vaccine categories
  - 5 new vaccine relationships
  - 107 new OPL parasite organism and life stages

*Number listed in paper, has since been updated

Use Case: Identify common features of parasite antigens

- Mapping of Gene IDs
  - Protective antigens include genes not listed in NCBI database
  - GeneID for protective antigens required for Gene Set Enrichment Analysis
  - 198 protective antigens to 140 Gene IDs
- Perform Gene Set Enrichment Analysis using DAVID
  - Database for Annotation, Visualization and Integrated Discovery (DAVID)
  - Identifies common ontology annotations for a given gene list
    - Gene Ontology, UniProt, KEGG pathway
  - Same method can be used to identify transcriptome data for different life stages
  - Initial analysis is focused purely on vaccine antigens

Gene Set Enrichment Analysis Results

- Three species had multiple significant terms for vaccine antigens.
  - Poor results due to small gene list size
  - Highest term for cluster shown in Table 2
- Blue boxes represents disease or signal
- Red boxes represent localization/function
- Uncertain if pattern is species or clade-specific

Table 2. Most significant GSA clusters of Apicomplexans & Mastigophorans. Full list is in Supplemental Table with a threshold of FDR < 0.5 for significance.

GO / Uniprot Enrichment Term	# of antigens	Percentage	p-values	FDR
Toxoplasma gondii (Toxoplasmosis, Apicomplexa)				
Signal	19	18.1	1.7E-07	9.9E-07
Toxoplasmosis	7	6.7	6.3E-07	7.5E-06
DOMAIN:Protein kinase	7	6.7	3.2E-05	8.4E-04
Plasmodium falciparum (Malaria, Apicomplexa)				
plasma membrane	13	12.4	2.9E-14	9.7E-13
Signal	15	14.3	2.1E-07	1.3E-06
entry into host	8	7.6	3.4E-07	8.2E-06
Anchored component of plasma membrane	4	3.8	4.5E-05	2.9E-04
Malaria	9	8.6	5.5E-04	5.5E-03
Trypanosoma cruzi (Trypanosomiasis, Mastigophora)				
motile cilium	2	6.5	2.0E-02	4.0E-02

Future Directions

- Expand annotation for other categories of vaccine design
  - Analyze commonalities with vaccine efficacy with specific life stages in species
  - Consider expansion of sub-categories to other vaccine designs
    - Viral vaccines incorporate strain differences (E.g. COVID-19)
- Continue with GESA analysis for RV Analysis
  - Incorporate life stages as predictive features for parasite antigen design
  - Follow up on patterns found in Apicomplexan v. Mastigophora parasites
- Search for additional parasite vaccines for new species
  - Protozoan: Ciliophora and Sarcodina
  - Helminth: Intestinal worms
  - Ectoparasites: Fleas

Thank you!

Pathogenic parasites

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- Parasites can cause a disease process in another host species
  - Malaria (primates), Leishmaniasis (humans), Eimeria (poultry)
- Pathogenic parasites exist in three major categories:
  - Protozoan. Single cell organisms
    - **Apicomplexa,** Ciliophora**, Mastigaphora**, Sarcodina
- Protozoan parasite have multiple distinct life stages.
- Do parasite vaccines effects all life stages for pathogens?

Vaccine Ontology Update

- Added 435* new terms into Vaccine Ontology
  - 165 new parasite vaccines
  - 125 new parasite vaccine antigens
  - 15 new vaccine categories
  - 5 new vaccine relationships
  - 107 new terms from OPL