Ontology-based representation and analysis of conditional vaccine immune responses using Omics data

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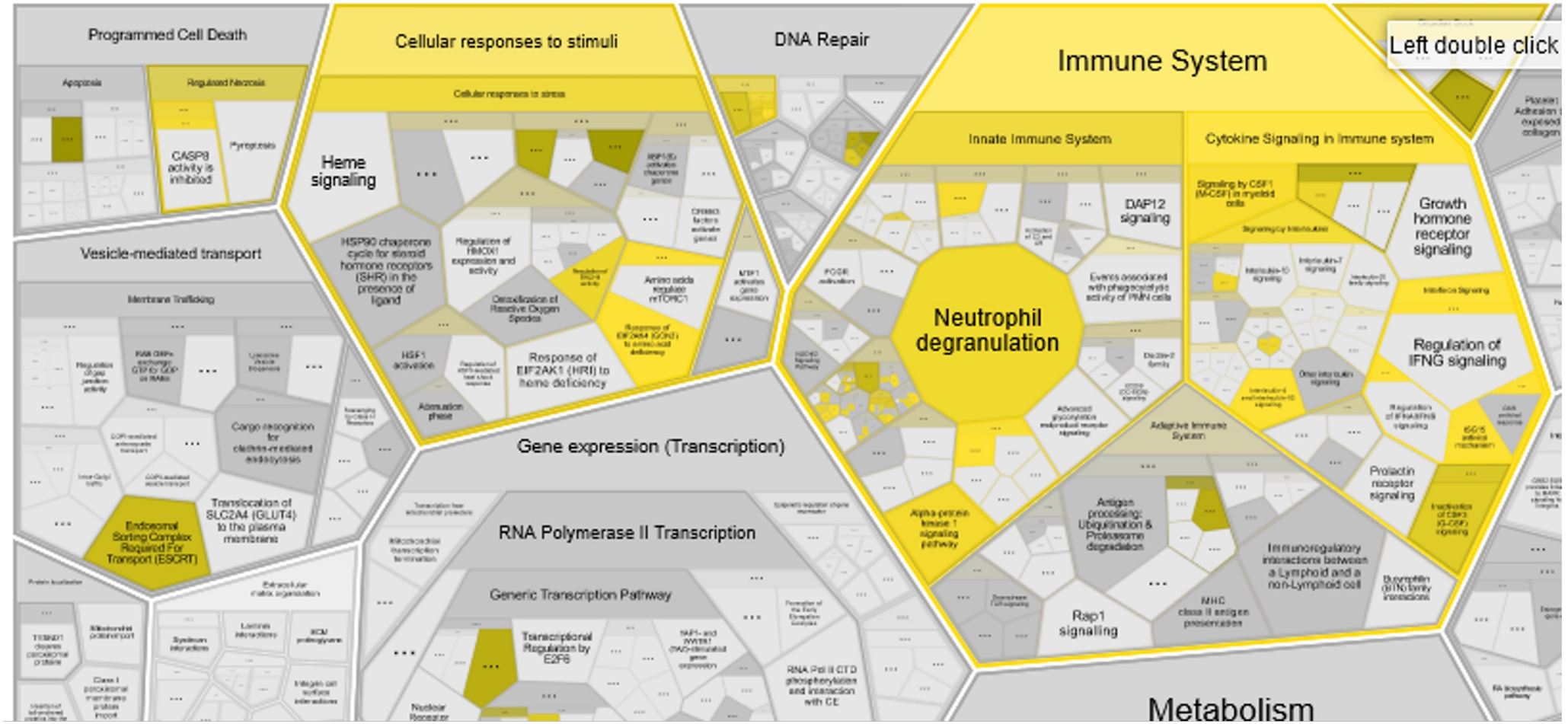
ImmPort database

- ImmPort is NIH-supported Immunology data portal
  - https://www.immport.org/
- Combines data from many sources:
  - Centers of Excellence for Influenza Research and Surveillance (CEIRS)
  - Human Immunology Project Consortium (HIPC)
- Variety of complete clinical and mechanistic studies
  - By assay, and focus
- Datasets are heterogeneous but can be used for pathway analysis

Bubble Summary of ImmPort Studies. Image taken 8/30/2023

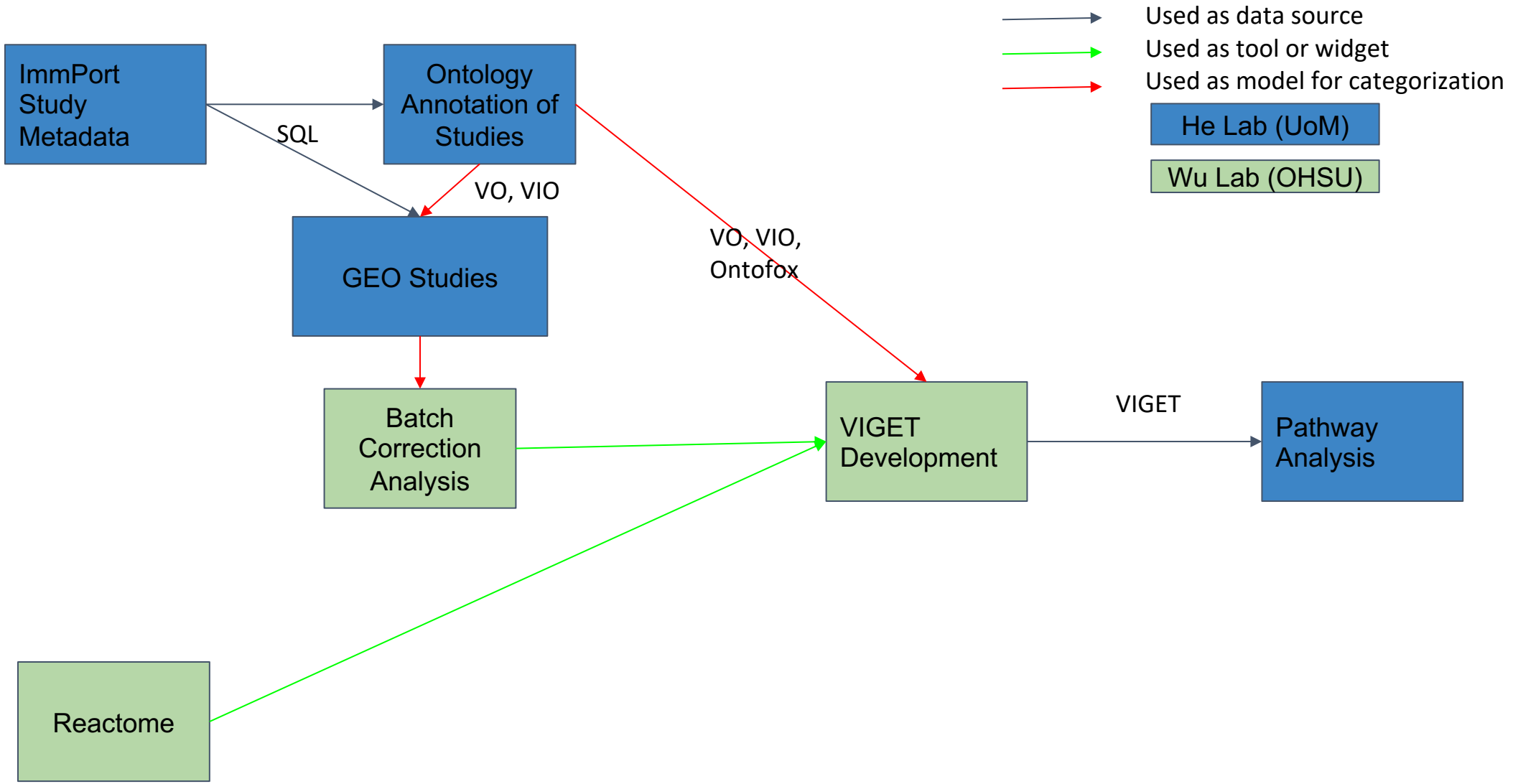
Reactome Pathway Analysis of Female Immune Response to Flu Vaccines



VaximmutorDB and Ontology Standardization

- VaximmutorDB
  - Web-based database focused on vaccine immune effectors (‘vaximmutor’)
  - Vaccines are processed material used to generate immune memory
  - 1700+ experimentally identified vaximmutors
    - E.g. IFN-gamma, IL-2, Il-4, IL-6
  - Pathway analysis focused on 4 yellow fever and influenza vaccines
- Analysis of multiple vaccines hard due to heterogeneity
- Standardization of pathway expression can be done through ontology
  - Vaccine Ontology (VO) for vaccine representation
  - Vaccine Investigation Ontology (VIO) for research of vaccine studies

Study Workflow



Pathway Enrichment Analysis

- Selection of influenza vaccines done via VIGET Web Tool
  - Vaccine Induced Gene Expression analysis Tool
- Expression time points were based on Day 0 to Days 3, 7, 14
  - Day 0 is vaccine administration date
- Gene list determined by following criteria expression:
  - If magnitude change greater than threshold
  - If p-value < 0.05
- Pathway determined significant if adjusted FDR < 0.05

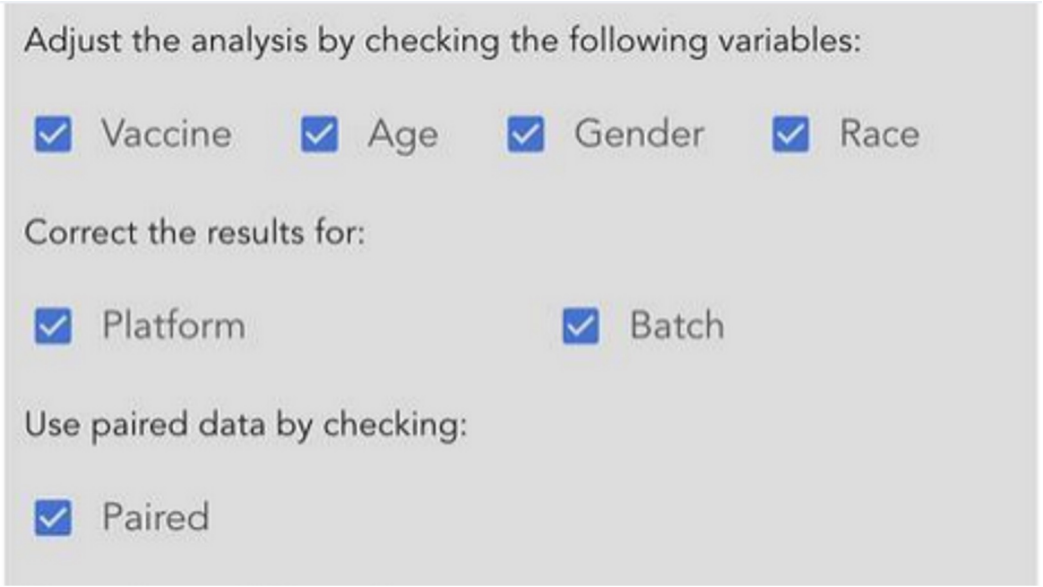
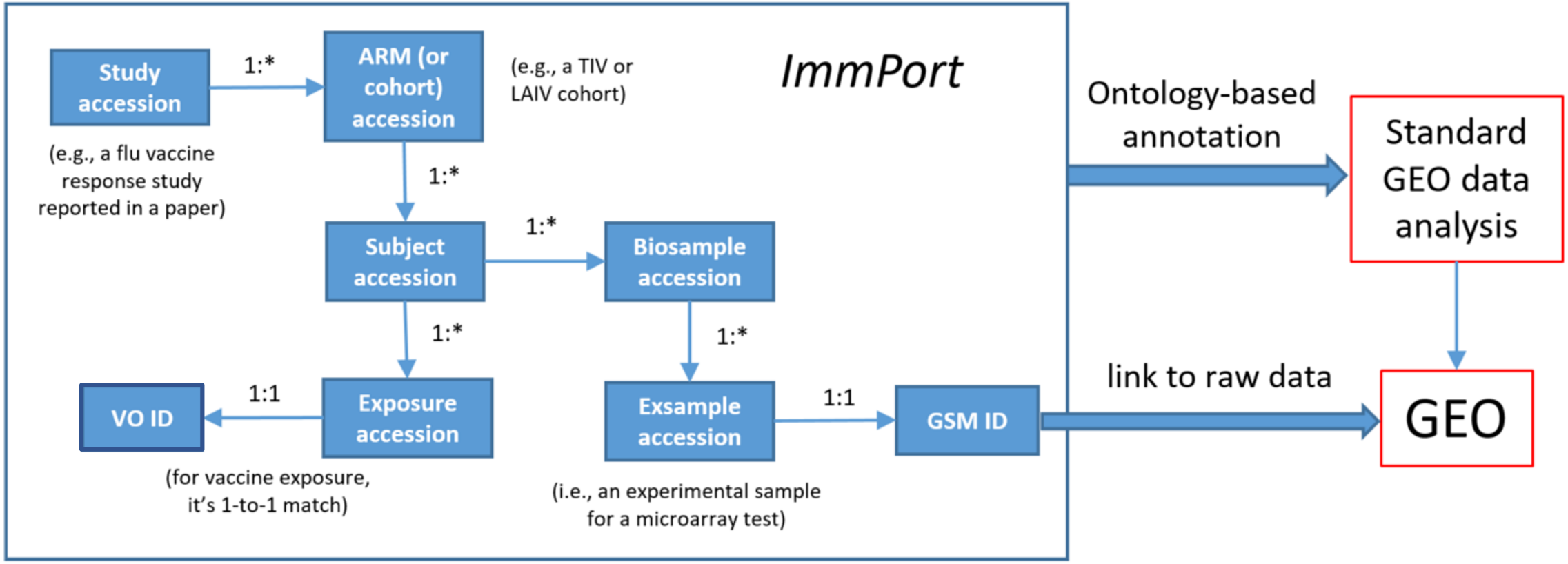


Figure 1 from Bunson et al 2023. Selection of analysis options utilized for VIGET. Analysis utilized the same adjustments.

Vaccine response Omics data analysis using ontology-annotated ImmPort and GEO.



Standardization of ImmPort Exposure Metadata

	A	B	C	D	E	F
1	EXPOSURE_ ACCESSION	ARM_ ACCESSION	EXPOSURE_ MATERIAL_ID	EXPOSURE _MATERIAL _REPORTED	EXPOSURE _PROCESS _REPORTED	SUBJECT _ACCESSION
2	IM48058	ARM5757	VO_0000867	Influvac	vaccination	SUB233686
3	IM48059	ARM5757	VO_0000867	Influvac	vaccination	SUB233687
4	IM48060	ARM5757	VO_0000867	Influvac	vaccination	SUB233688
5	IM48061	ARM5757	VO_0000867	Influvac	vaccination	SUB233689
6	IM48062	ARM5757	VO_0000867	Influvac	vaccination	SUB233690
7	IM48063	ARM5757	VO_0000867	Influvac	vaccination	SUB233691
8	IM48064	ARM5757	VO_0000867	Influvac	vaccination	SUB233692
9	IM48065	ARM5757	VO_0000867	Influvac	vaccination	SUB233693
10	IM48066	ARM5757	VO_0000867	Influvac	vaccination	SUB233694
11	IM48067	ARM5757	VO_0000867	Influvac	vaccination	SUB233695
12	IM22967	ARM5032	VO_0000644	HBV Vaccine	vaccination	SUB209984
13	IM22969	ARM5033	VO_0000644	HBV Vaccine	vaccination	SUB209985
14	IM22971	ARM5032	VO_0000644	HBV Vaccine	vaccination	SUB209986
15	IM22973	ARM5028	VO_0000644	HBV Vaccine	vaccination	SUB209987

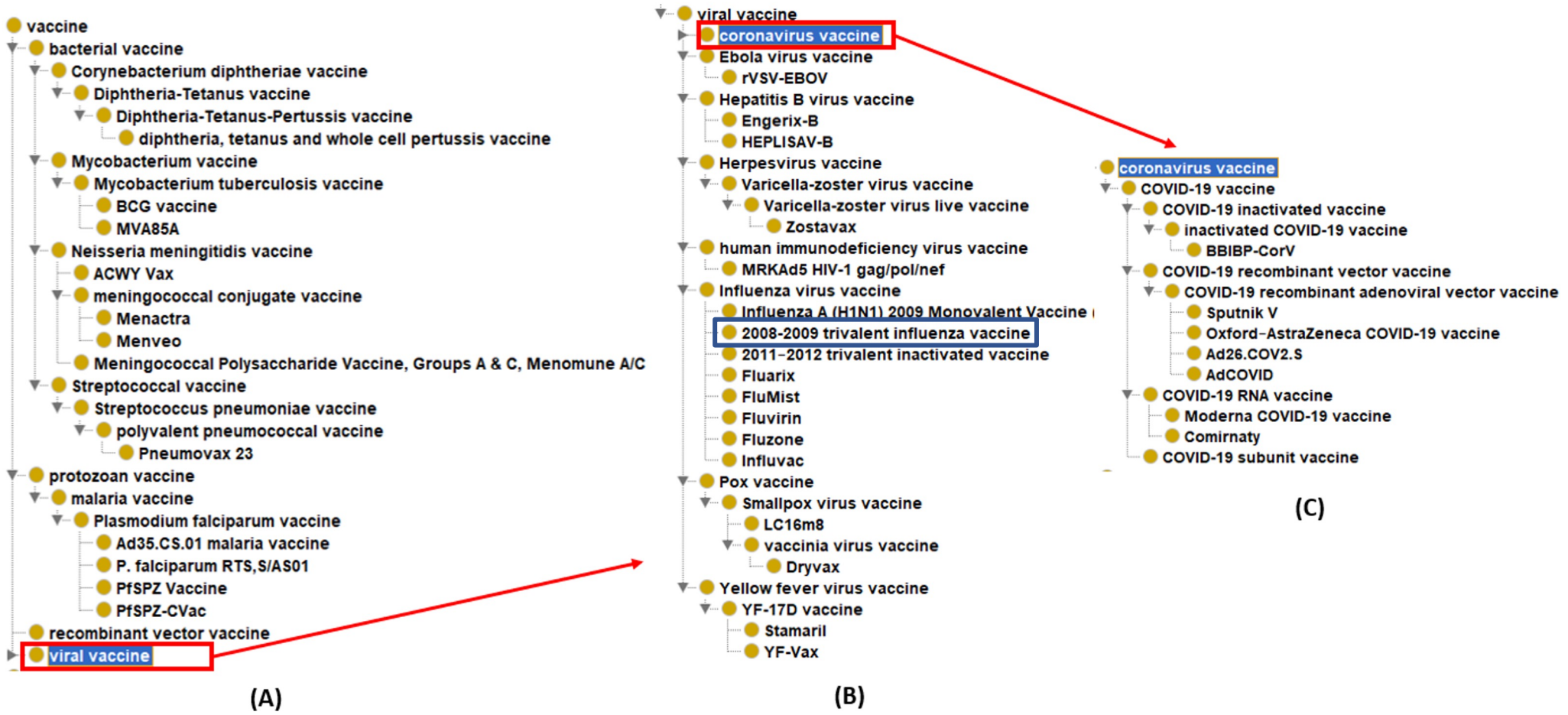
VO IDs

Vaccine names

Statistics of ImmPort Metadata Studies

- Statistics from on February 28, 2023
  - Earlier model used for analysis back in 2020
- 36,140 immune records
- 6,258 vaccine-related immune exposure records
- 4,607 human subjects
- 324 cohorts for each study
- 37 listed vaccines

Ontological representation of 37 vaccines in Immport



Use Case 1: Ontology-based query of vaccines and vaccine investigation data

- VO hierarchy easily identifies differences between vaccine targets
  - Can search by clade or species
  - Can be utilized by SPARQL or DL Queries
- VO axioms can identify additional types of vaccines
  - ‘live attenuated vaccine’ ‘has quality’ some ‘vaccine organism live attenuated’
  - ‘inactivated vaccine’ ‘has quality’ some ‘vaccine organism inactivated’
- VO terms extracted for VIGET to support queries and analysis
  - JSON file contain simplified hierarchy using this format

Use Case 2: Detecting the effect of biological sex on gene expression profiles stimulated by influenza vaccine

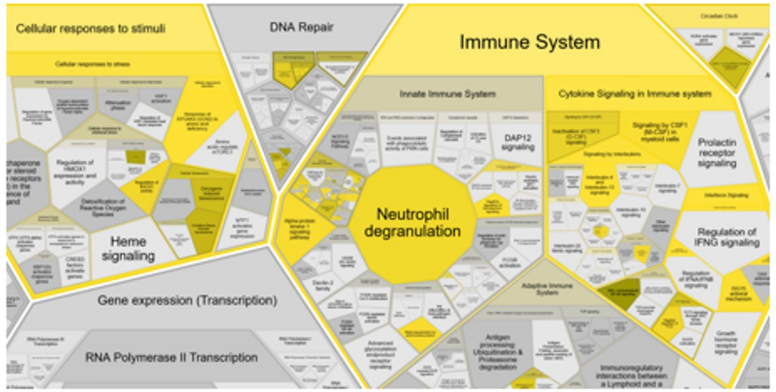
- Males and females have differing immune response
  - Immune response to viruses can affect either harder
- Can VIGET identify these patterns for influenza vaccines
  - Already done in original paper for yellow fever vaccines
- Utilized 16 Studies for 6 influenza vaccines
  - FluMist (VO_000044) - live attenuated
  - Fluarix (VO_000045), Fluzone (VO_000047), Fluvirin (VO_000046), the 2008-2009 trivalent inactivated vaccine (VO_0004808) and the 2011-2012 trivalent inactivated vaccine (VO_0004810) - inactivated
- Analysis covered paired expression data
  - 210 males and 260 females from smallest pairing

Differential gene expression summary

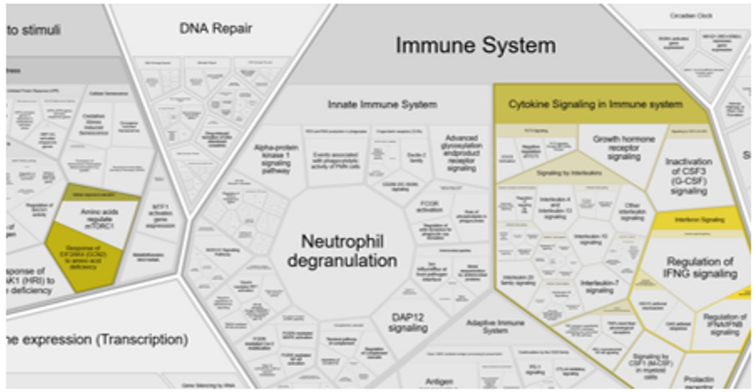
- Day 7 is peak for number of differential genes expressed
- Females have greater differential response for genes than males
- Males lag behind females for significant number of pathways

Time Comparison	Fold Change Threshold (Log_2)	# of Significant Flu M Genes	# of Significant Flu M Pathways	# of Significant Flu F Genes	# of Significant Flu F Pathways
Day 3	0.1	176	17	969	73
	0.2	3	35	56	126
	0.3	0	0	9	126
	0.5	0	0	0	0
Day 7	0.1	1388	0	1427	0
	0.2	1329	0	1052	3
	0.3	1133	0	1048	0
	0.5	1119	0	690	8
	1	626	2	515	10
Day 14	0.1	446	39	969	73
	0.2	44	36	98	70
	0.3	4	68	11	34
	0.5	0	0	0	0

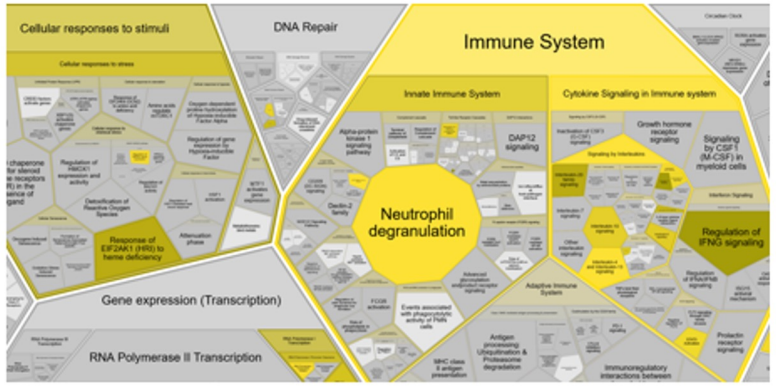
Table 1. Summary of gender differences in number significant genes and pathways in influenza vaccine response. Color indicates that males (M) or females (F) have more significant genes or pathways at each comparison.



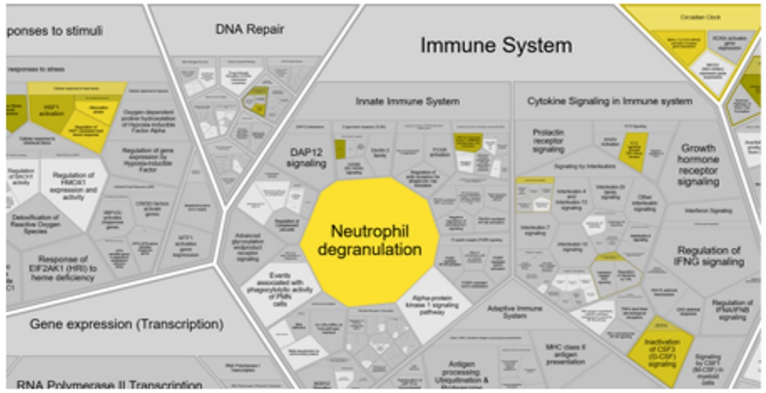
(A) Flu vaccines, Females, Day 3 over Day 0



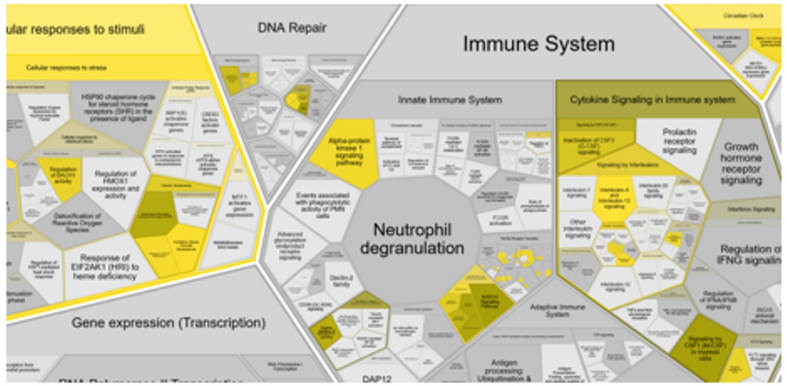
(B) Flu vaccines, Males, Day 3 over Day 0



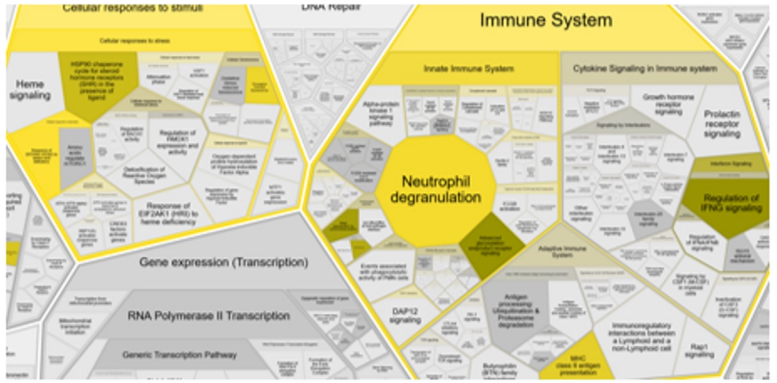
(C) Flu vaccines, Females, Day 7 over Day 0



(D) Flu vaccines, Males, Day 7 over Day 0



(E) Flu vaccines, Females, Day 14 over Day 0



(F) Flu vaccines, Males, Day 14 over Day 0

Figure 4. Comparison of sex-based differences in immune response to influenza vaccines. Pathways expressed for genes.

Day 7 Immune Pathway Highlights

- Males had 2 significant immune pathways
  - ‘neutrophil degranulation’ (FDR = 6.48 e-7)
  - ‘innate immune system’ (FDR = 1.02e-2)
- Females had 10 significant pathways
  - ‘neutrophil degranulation’ (FDR = 5.06 e-11)
  - ‘IL-4 and IL-13 signaling’ (FDR = 2.31e-5)
  - ‘IL-10 signaling’ (FDR = 4.01e-2)
  - ‘CLEC7A/inflammasome pathway’ (FDR = 4.77e-2)
- Females also found ‘cell response to stress’ (FDR = 3.19e-4)
  - All genes were found to be up-expressed

Sex and vaccine role cross-section analysis

- Analysis of immune response for four combinations:
  - Male live attenuated flu vaccine
  - Female live attenuated flu vaccine
  - Male inactivated influenza vaccine
  - Female inactivated influenza vaccine
- Live attenuated vaccine comparison restricted due to small data size
  - Could not run Day 0 to 3 female live attenuated influenza vaccine analysis
- Inactivated vaccines show differences in pathways at Day 14.
  - Both had reduced power due to smaller data size
  - Females: ‘innate immunity’ (FDR = 4.0e-2), ‘programmed cellular death’ (FDR = 2.13e-3)
  - Males: ‘immune system’ (FDR = 2.0e-2), ‘interferon alpha/beta signaling’ (FDR = 3.2e-2)

Applications of Ontologies to ImmPort Studies

- Ontology successfully used to guide analysis of ImmPort
  - VIGET for sex differences for influenza and yellow fever vaccines
- Process for mapping ImmPort had initial difficulties
  - Day 0 Definition Inconsistency: Of study or vaccination
  - Many tables for data not well-explained, but well annotated.
- Can be applied to other ImmPort studies
  - Analyze studies for differences in procedures or patient phenotypes
  - Age hard to analyze as it is stored by cohort and not individual

Effect of Biological Sex on Vaccine Immune Response for ImmPort Influenza Vaccines

- Males have delayed differential gene expression vaccines
- Female immune response shows stronger cellular response to stress
  - Females also had earlier pattern of neutrophil degranulation
    - Exocytosis of secretory granules for proteases and inflammatory mediators
  - Neutrophil degranulation linked to inflammatory disorders
  - Apoptosis linked to cellular stress
- Uncertain if innate effect for females or issue with safety or formulation

Acknowledgements

- Funding:
  - NIH grant 1UH2AI132931
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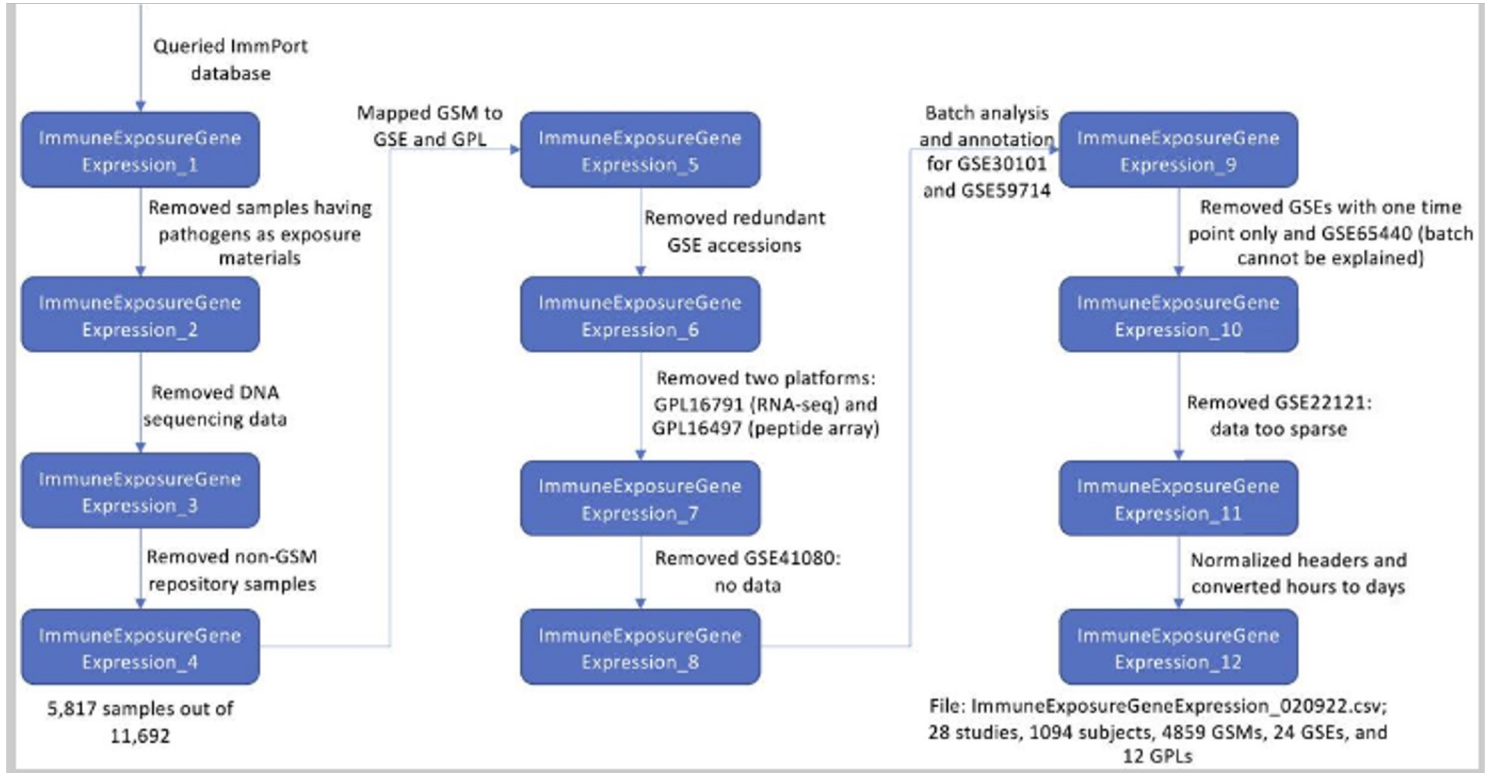
Thank you!

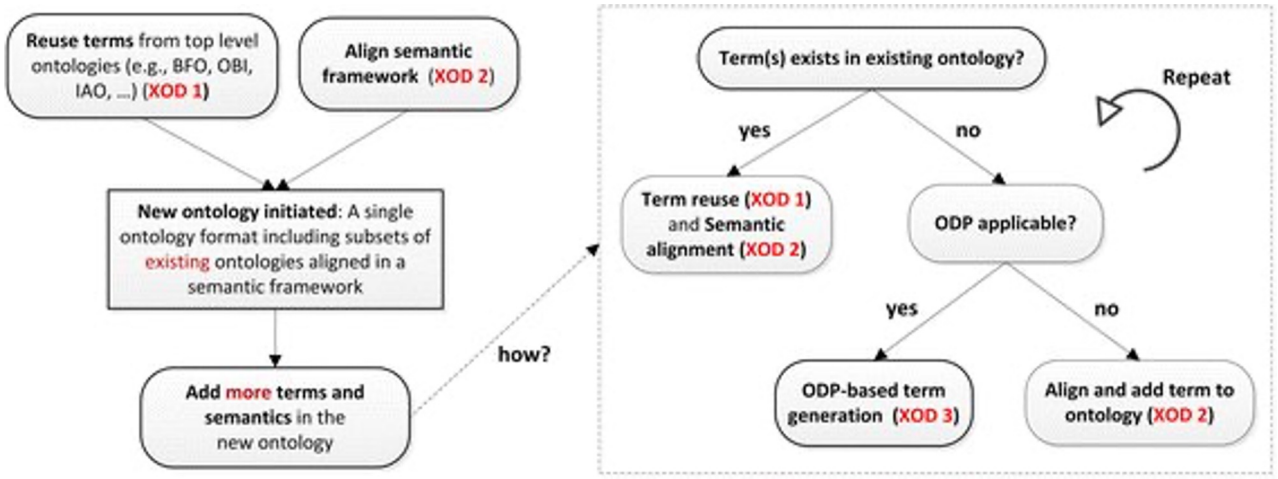
Bonus Slides

Flowchart of the workflow on collecting vaccination metadata from ImmPort and manual checking and annotation.



The eXtensible ontology development (XOD)

- 4 XOD principles:
  - XOD 1: Ontology Term Reuse
  - XOD 2: Ontology Semantic Alignment
  - XOD 3: Ontology Design Pattern (ODP) for Term Generation & Editing
  - XOD 4: Community Extensibility
- XOD supports interoperability



- Aim: **Use XOD to update CIDO** by incorporating new host-coronavirus interaction knowledge from COVID-19 publications available in ImmPort

Ref: He Y, Xiang Z, Zheng J, Lin Y, Overton JA, Ong E. The eXtensible ontology development (XOD) principles and tool implementation to support ontology interoperability. *J Biomed Semantics*. 2018 Jan 12;9(1):3.