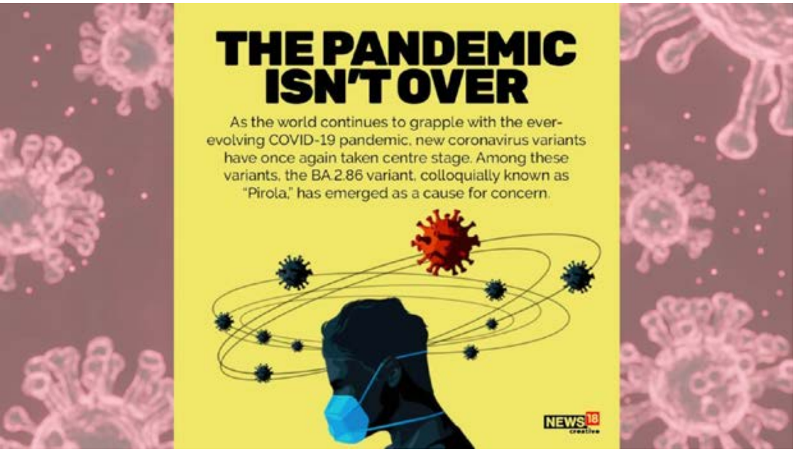
“How to use IEDB in your research”

Examples on SARS-CoV-2

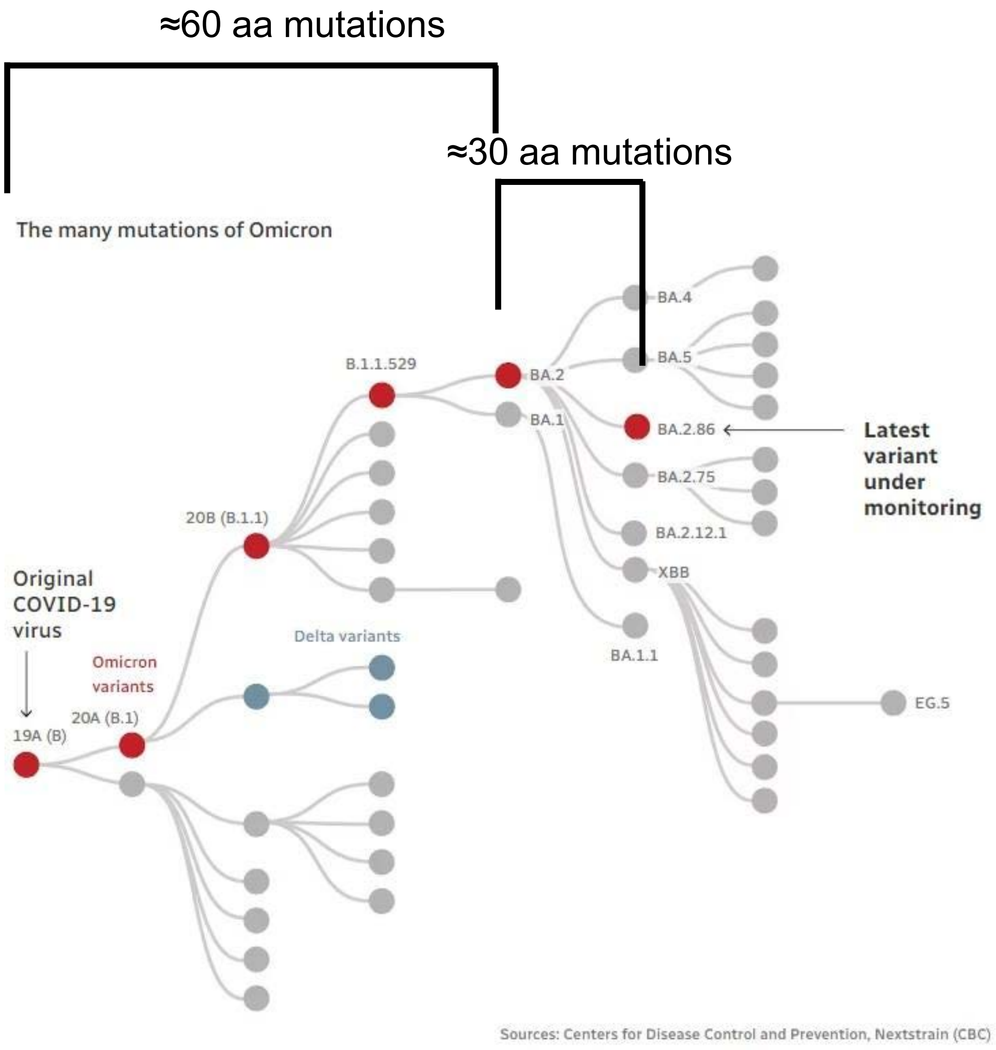
Presented by: Alba Grifoni, Research Assistant Professor

BA.2.86 – Pirola



THE PANDEMIC ISN'T OVER

As the world continues to grapple with the ever-evolving COVID-19 pandemic, new coronavirus variants have once again taken centre stage. Among these variants, the BA.2.86 variant, colloquially known as "Pirola," has emerged as a cause for concern.

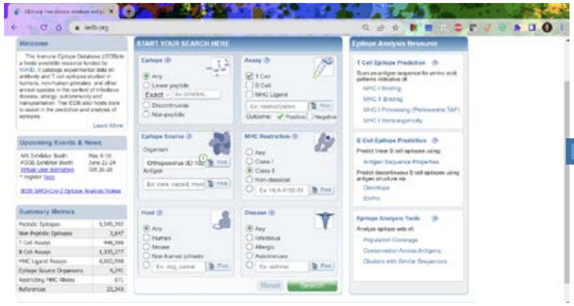


The many mutations of Omicron

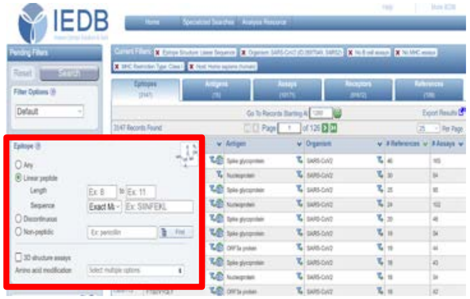
Sources: Centers for Disease Control and Prevention, Nextstrain (CBC)

Can we predict the effect of BA.2.86 on T cells?

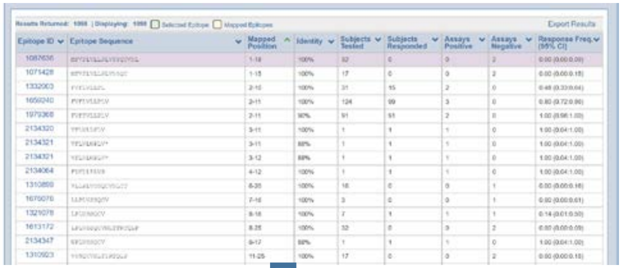
1. Extract SARS-CoV-2 epitopes

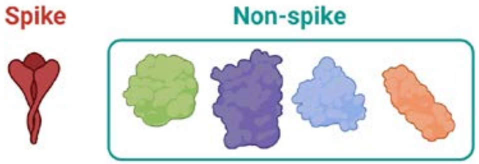


2. Filter for canonical sizes

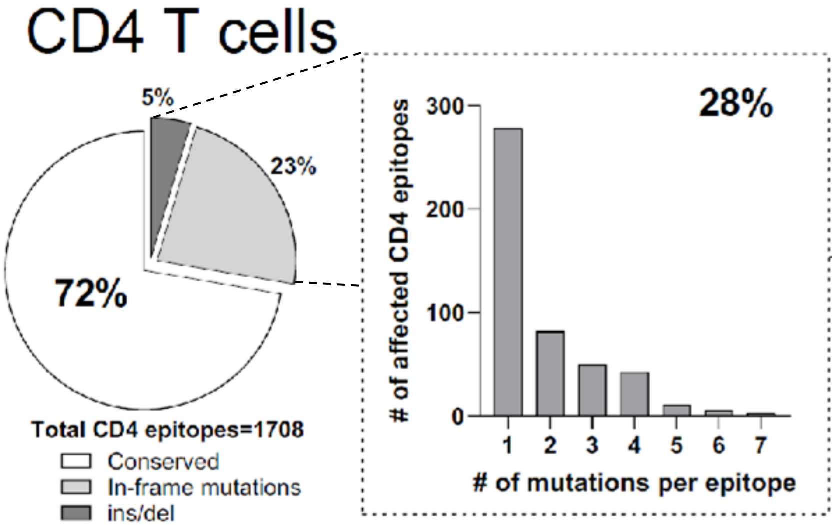


3. Use ImmunomeBrowser to get 100% conserved Ancestral epitopes





4. Evaluate how many epitopes are affected by BA.2.86 amino acid mutations



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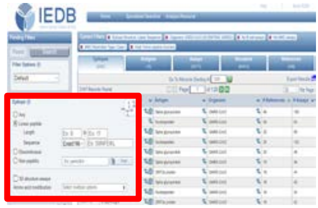
Can we predict the effect of BA.2.86 on T cells?

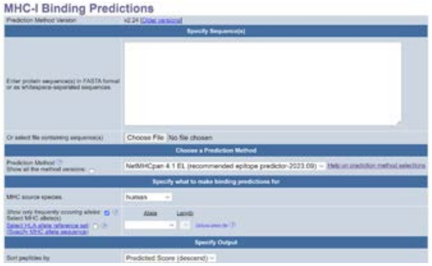
1. Extract SARS-CoV-2 epitopes

2. Filter for canonical sizes



3. Get epitope restrictions

4. Run T cell epitope predictions using ancestral and BA.2.86 mutated epitopes and the HLA restrictions reported in IEDB for that epitope



Prediction Method Version v2.24 [Older versions]

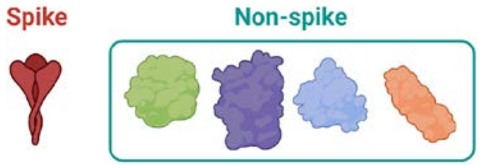
Enter protein sequence(s) in FASTA format or as whitespace-separated sequences.

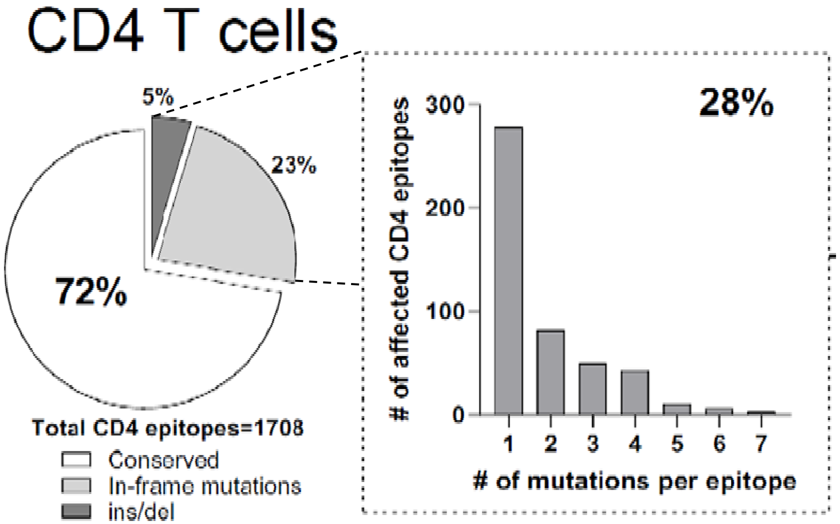
Or select file containing sequence(s) No file chosen

Prediction Method NetMHCpan 4.1 EL (recommended epitope predictor-2023.09) Help on prediction method selections

MHC source species human

Sort peptides by Predicted Score (descend)





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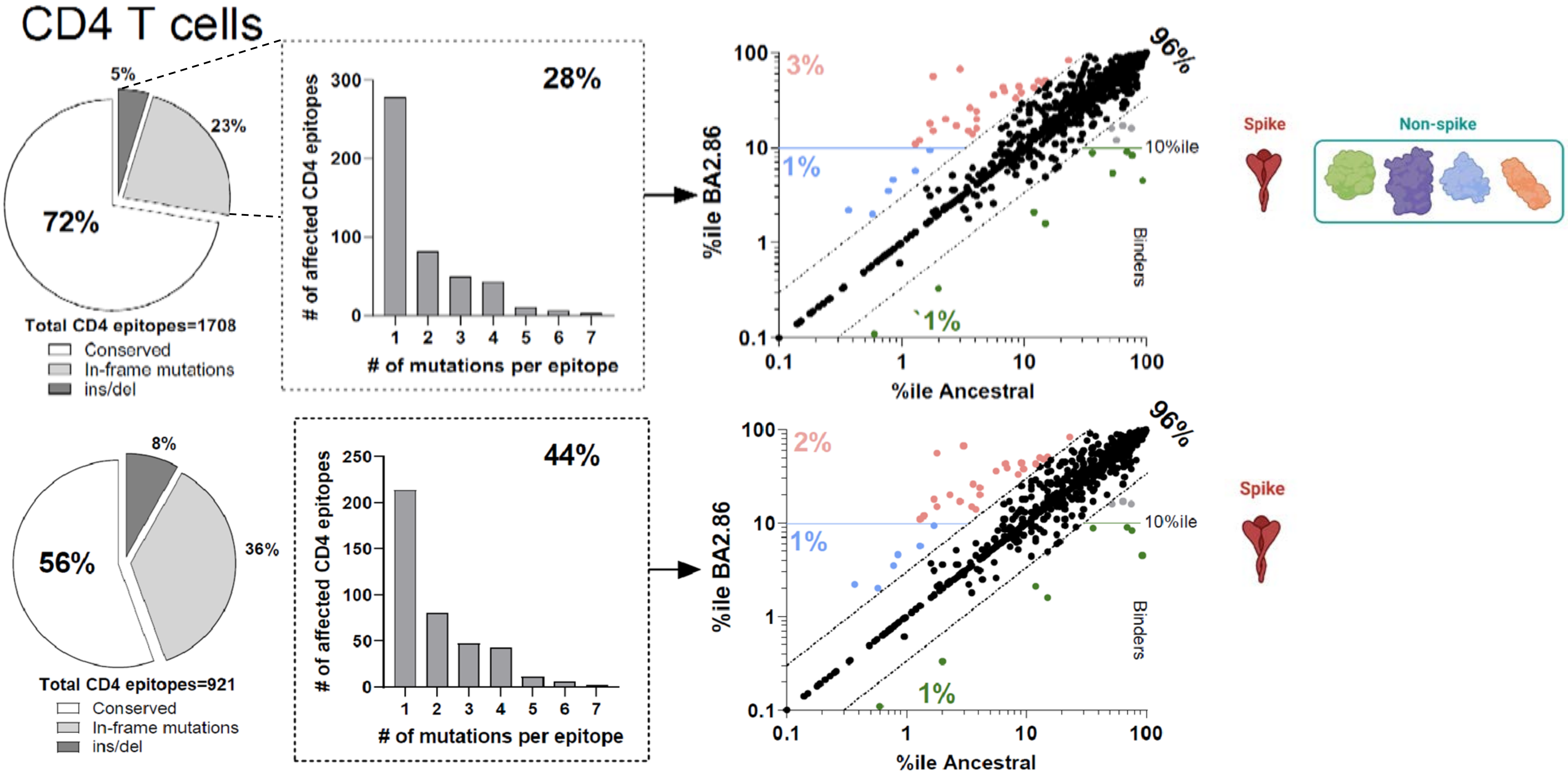
Can we predict the effect of BA.2.86 on T cells?



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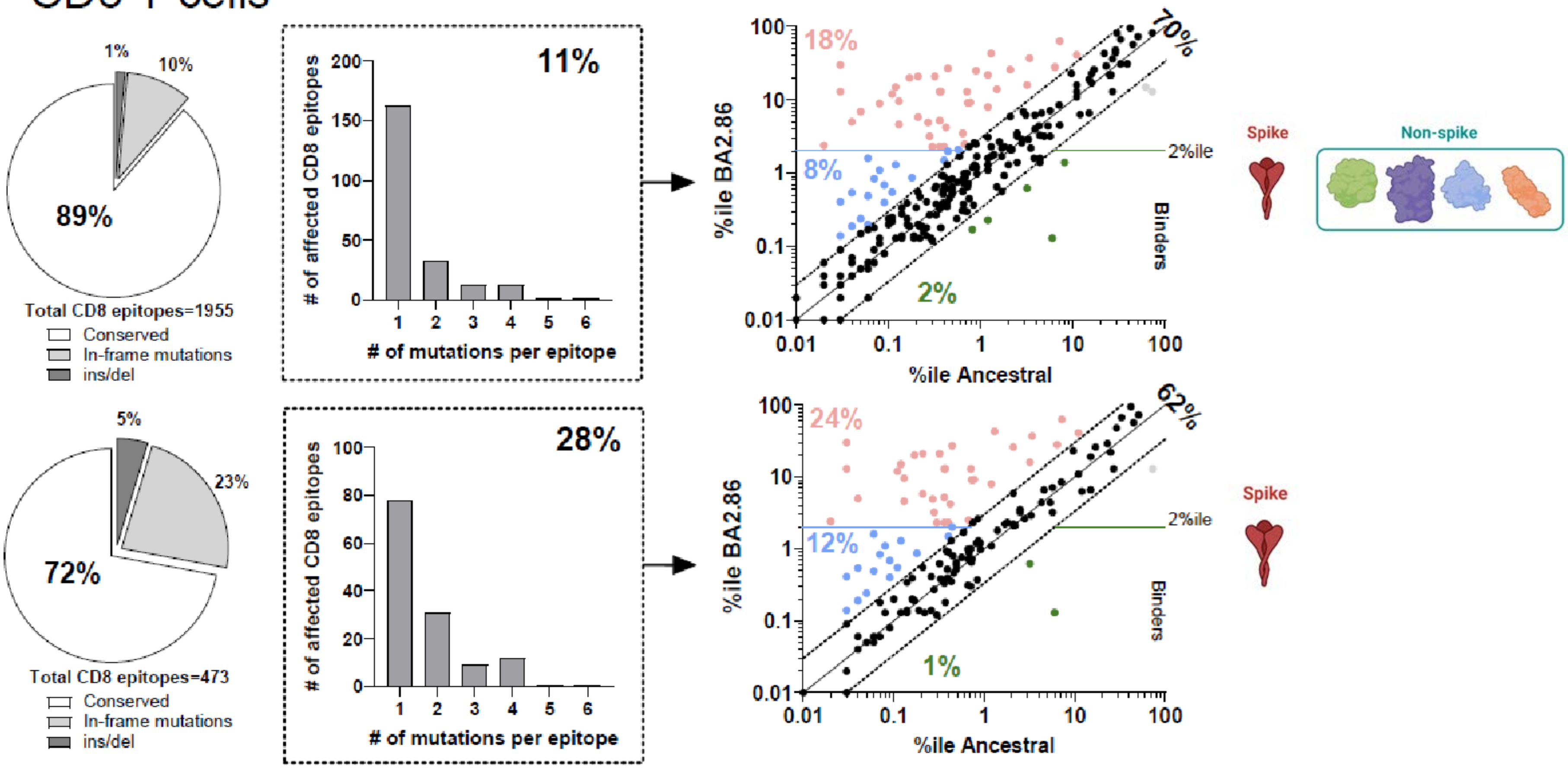
Can we predict the effect of BA.2.86 on T cells?

CD8 T cells



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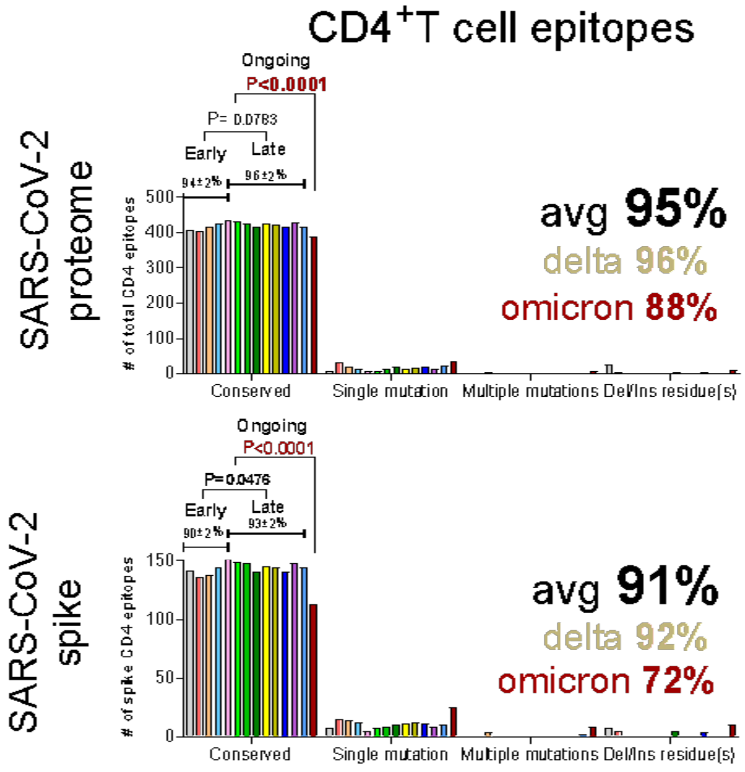
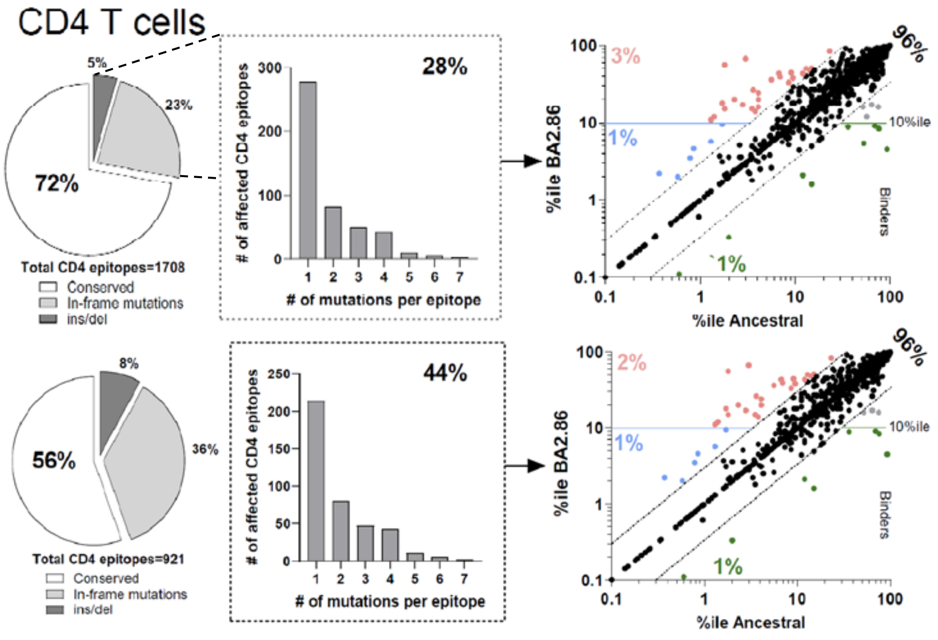
BA.2.86 compared to the original impact observed for Omicron BA.1



*Tarke…. Crotty, **Grifoni**, Sette Cell 2022*



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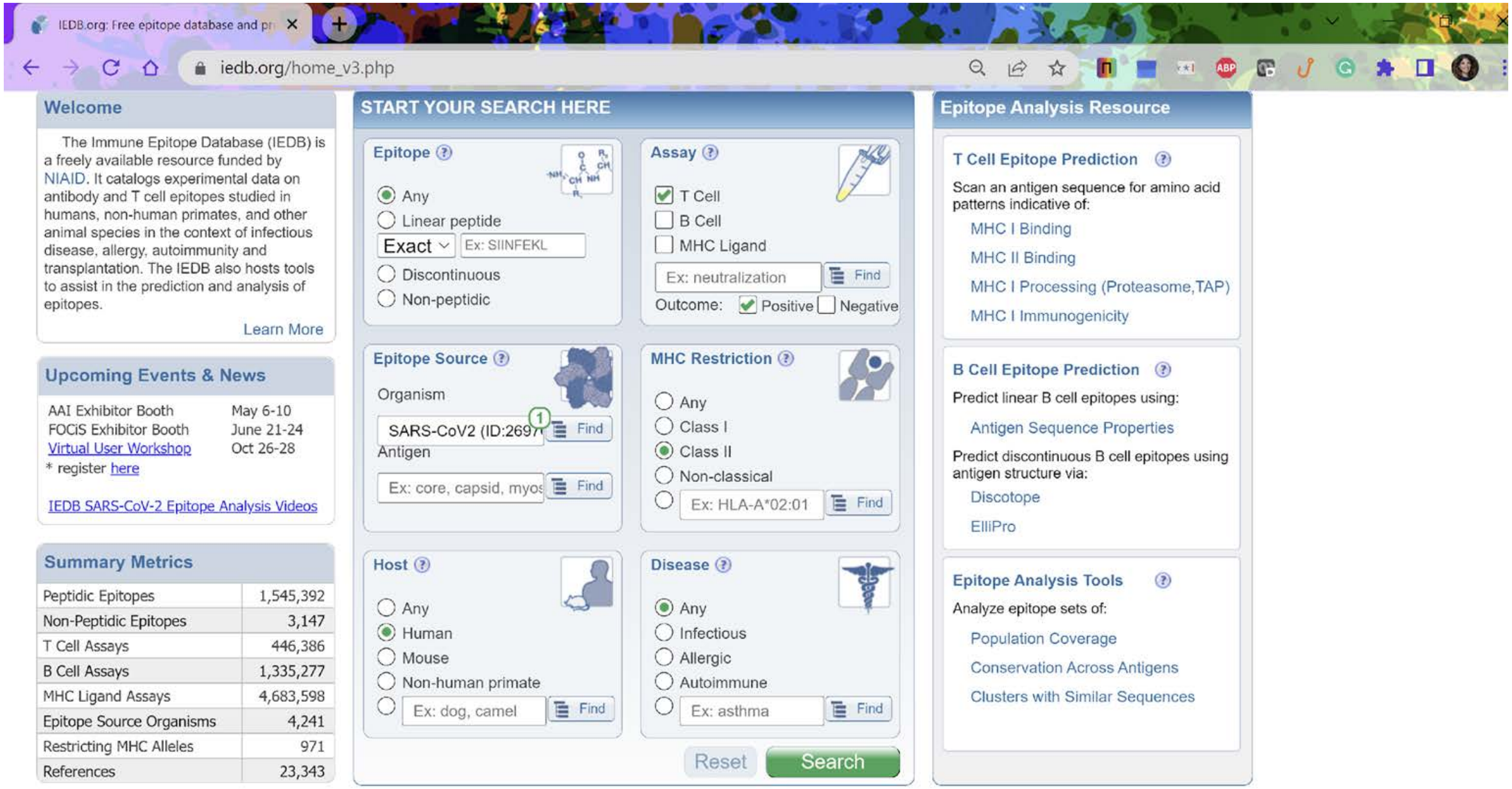
How to use ImmunomeBrowser to define spike T cell immunodominant regions

IEDB
Immune Epitope Database & Tools

CD4 epitope query



iedb.org/home_v3.php

Welcome

The Immune Epitope Database (IEDB) is a freely available resource funded by NIAID. It catalogs experimental data on antibody and T cell epitopes studied in humans, non-human primates, and other animal species in the context of infectious disease, allergy, autoimmunity and transplantation. The IEDB also hosts tools to assist in the prediction and analysis of epitopes.

Learn More

Upcoming Events & News

AAI Exhibitor Booth	May 6-10
FOCiS Exhibitor Booth	June 21-24
Virtual User Workshop	Oct 26-28

* register here

IEDB SARS-CoV-2 Epitope Analysis Videos

Summary Metrics

Peptidic Epitopes	1,545,392
Non-Peptidic Epitopes	3,147
T Cell Assays	446,386
B Cell Assays	1,335,277
MHC Ligand Assays	4,683,598
Epitope Source Organisms	4,241
Restricting MHC Alleles	971
References	23,343

START YOUR SEARCH HERE

Epitope
- ● Any
- ○ Linear peptide
  - Exact — Ex: SIINFEKL
- ○ Discontinuous
- ○ Non-peptidic

Assay
- ☑ T Cell
- ☐ B Cell
- ☐ MHC Ligand
- Ex: neutralization — Find
- Outcome: ☑ Positive ☐ Negative

Epitope Source
- Organism: SARS-CoV2 (ID:2697 — Find
- Antigen: Ex: core, capsid, myos — Find

MHC Restriction
- ○ Any
- ○ Class I
- ● Class II
- ○ Non-classical
- ○ Ex: HLA-A*02:01 — Find

Host
- ○ Any
- ● Human
- ○ Mouse
- ○ Non-human primate
- ○ Ex: dog, camel — Find

Disease
- ● Any
- ○ Infectious
- ○ Allergic
- ○ Autoimmune
- ○ Ex: asthma — Find

Epitope Analysis Resource

T Cell Epitope Prediction

Scan an antigen sequence for amino acid patterns indicative of:
- MHC I Binding
- MHC II Binding
- MHC I Processing (Proteasome,TAP)
- MHC I Immunogenicity

B Cell Epitope Prediction

Predict linear B cell epitopes using:
- Antigen Sequence Properties

Predict discontinuous B cell epitopes using antigen structure via:
- Discotope
- ElliPro

Epitope Analysis Tools

Analyze epitope sets of:
- Population Coverage
- Conservation Across Antigens
- Clusters with Similar Sequences

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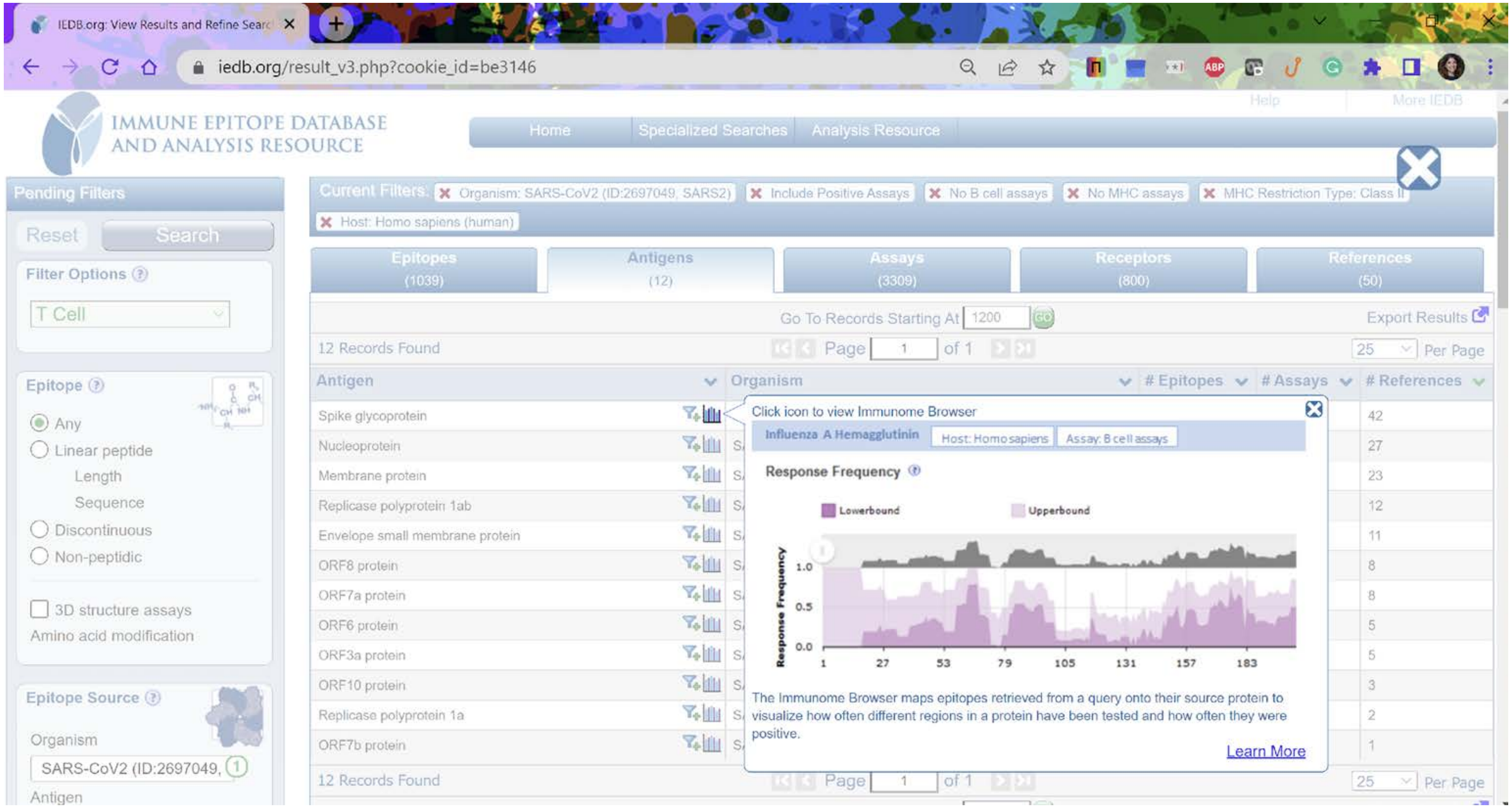
CD4 epitope results: Antigen



Current Filters: ☒ Organism: SARS-CoV2 (ID:2697049, SARS2) ☒ Include Positive Assays ☒ No B cell assays ☒ No MHC assays ☒ MHC Restriction Type: Class II ☒ Host: Homo sapiens (human)

Go To Records Starting At 1200

12 Records Found — Page 1 of 1 — 25 Per Page

Antigen	Organism	# Epitopes	# Assays	# References
Spike glycoprotein				42
Nucleoprotein				27
Membrane protein				23
Replicase polyprotein 1ab				12
Envelope small membrane protein				11
ORF8 protein				8
ORF7a protein				8
ORF6 protein				5
ORF3a protein				5
ORF10 protein				3
Replicase polyprotein 1a				2
ORF7b protein				1

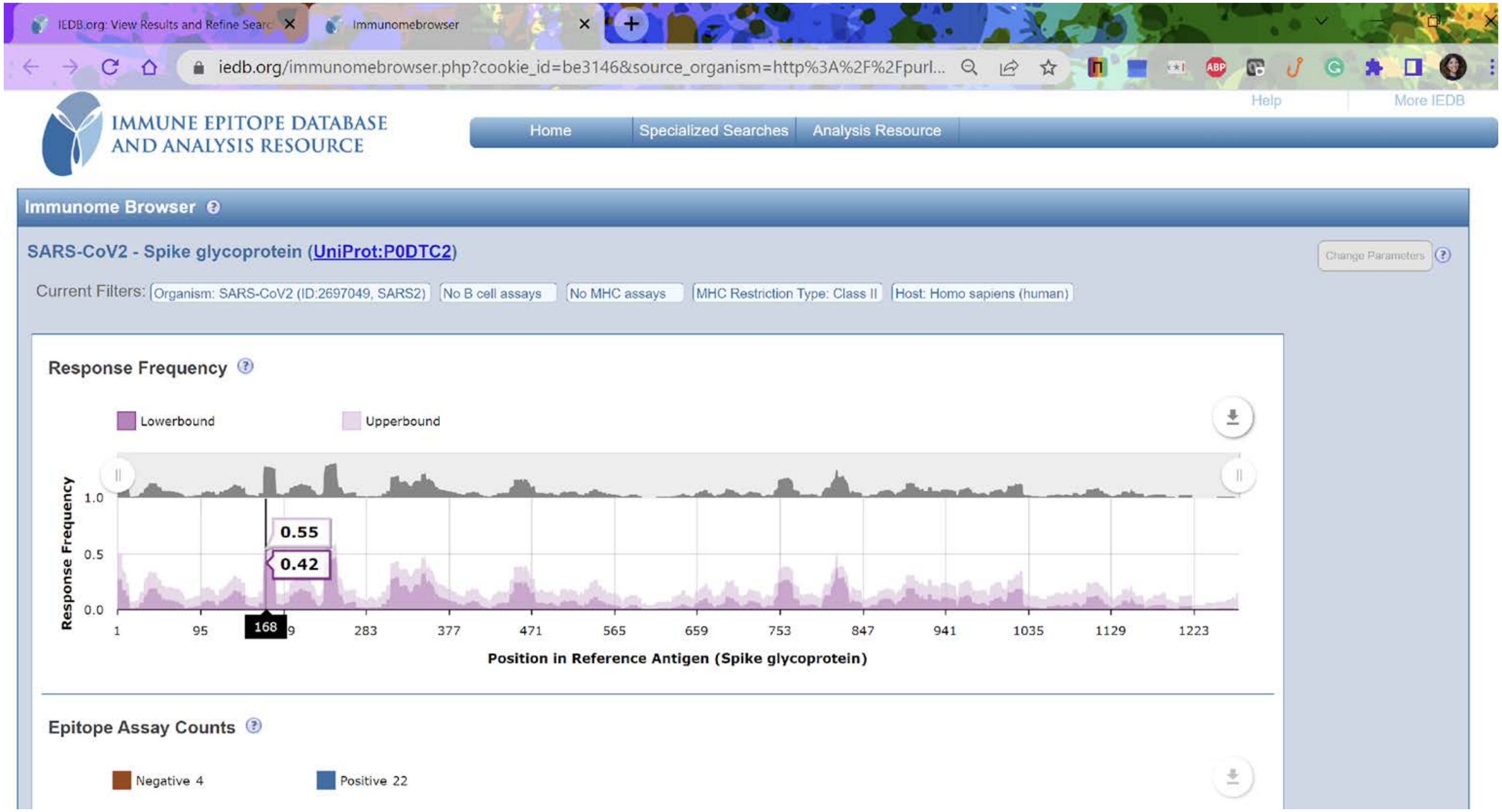
Click icon to view Immunome Browser

Influenza A Hemagglutinin — Host: Homo sapiens — Assay: B cell assays

The Immunome Browser maps epitopes retrieved from a query onto their source protein to visualize how often different regions in a protein have been tested and how often they were positive.

How to use ImmunomeBrowser to define spike T cell immunodominant regions

CD4 ImmunomeBrowser: Spike



SARS-CoV2 - Spike glycoprotein (UniProt:P0DTC2)

Current Filters: Organism: SARS-CoV2 (ID:2697049, SARS2) | No B cell assays | No MHC assays | MHC Restriction Type: Class II | Host: Homo sapiens (human)

How to use ImmunomeBrowser to define spike T cell immunodominant regions

IEDB
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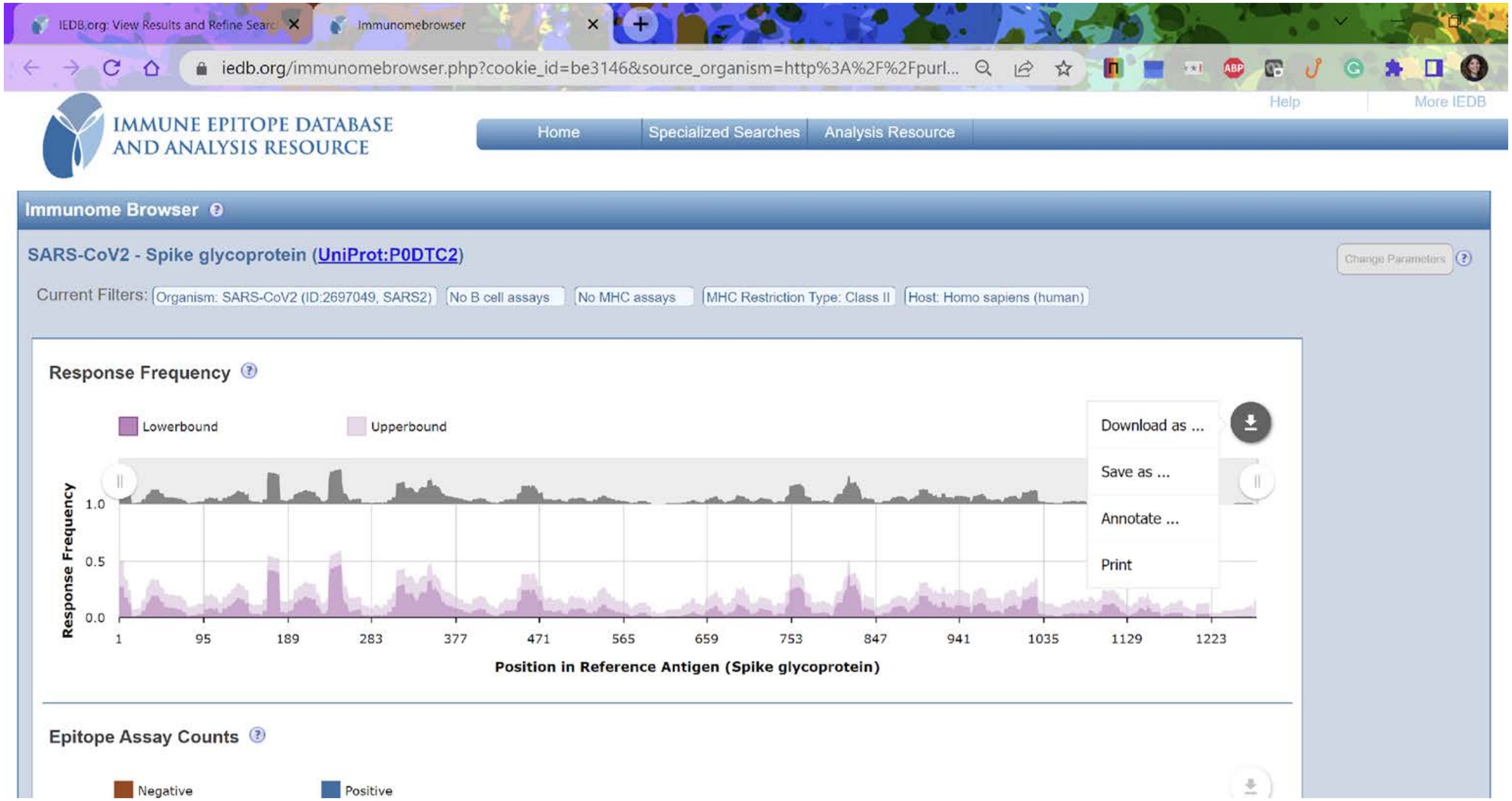
CD4 ImmunomeBrowser: Spike



Immunome Browser

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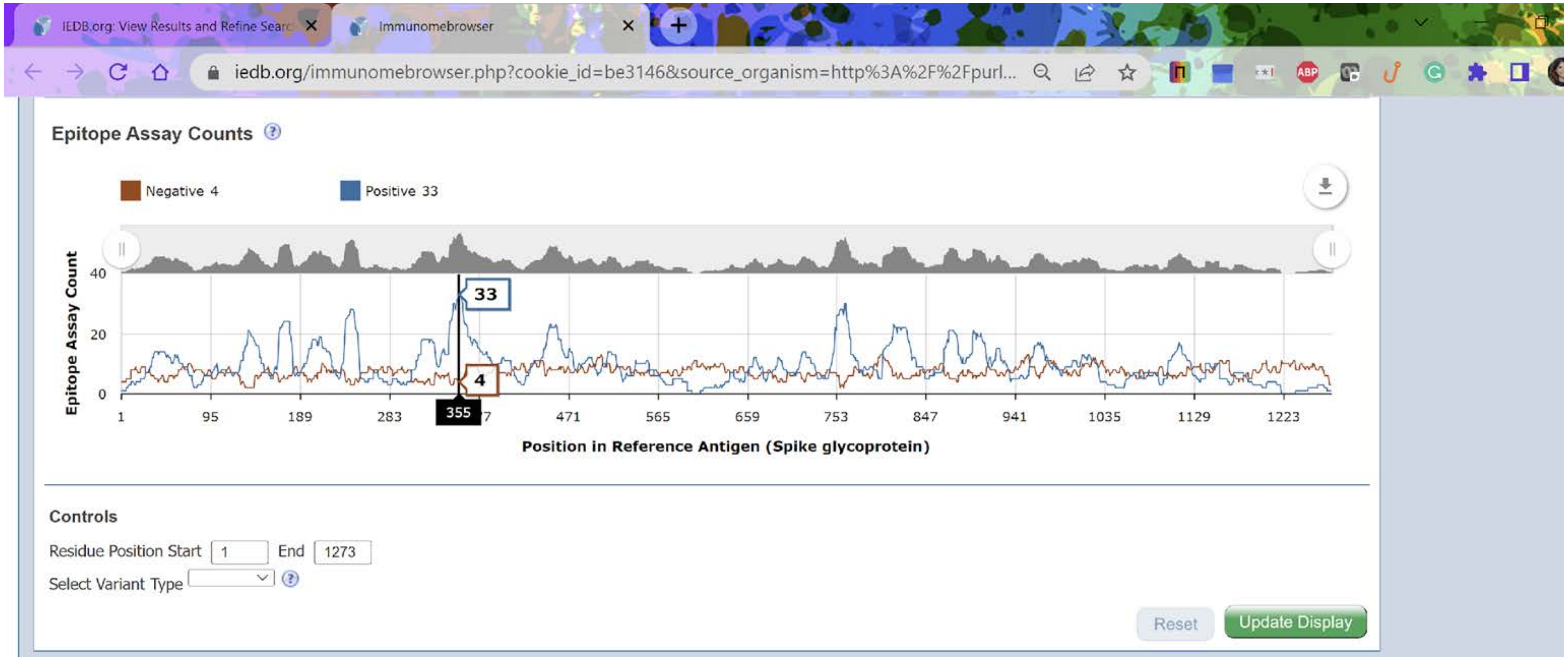
IEDB
Immune Epitope Database & Tools

CD4 ImmunomeBrowser: Spike



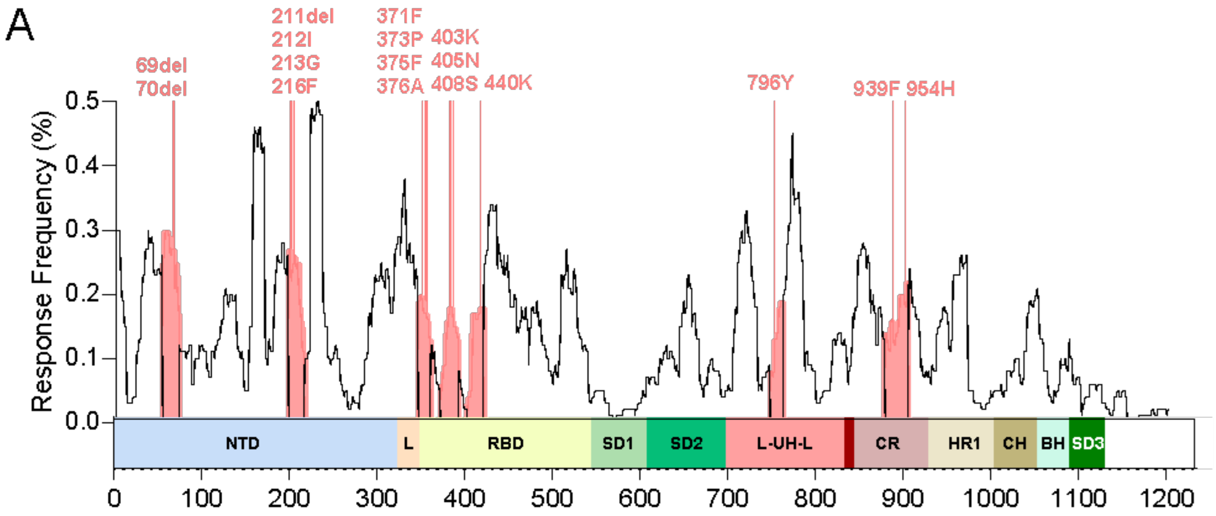
iedb.org/immunomebrowser.php?cookie_id=be3146&source_organism=http%3A%2F%2Fpurl...

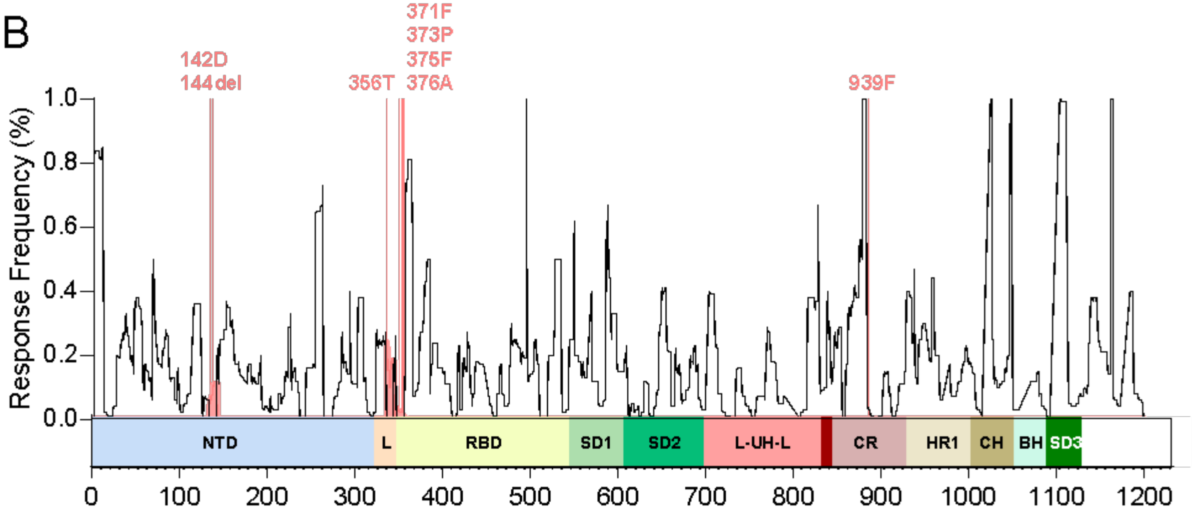
Controls

Residue Position Start 1 End 1273

Select Variant Type

Mapping effect of BA2.86 amino acid mutations on immunodominance





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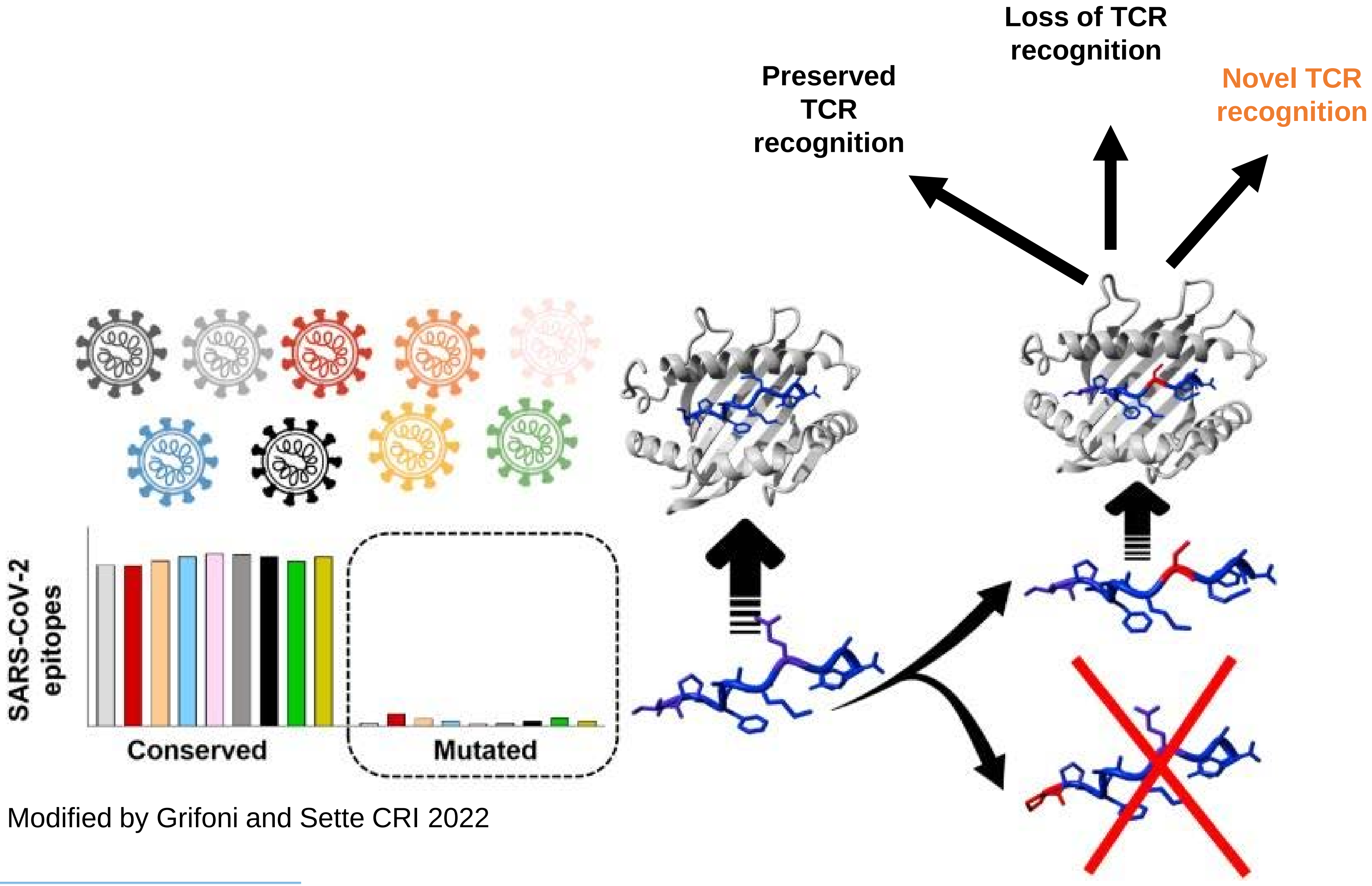
Mutated epitopes can still be presented by HLAs



Preserved TCR recognition

Loss of TCR recognition

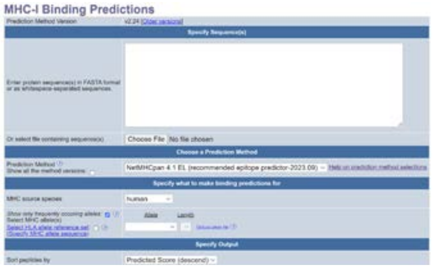
Novel TCR recognition

Modified by Grifoni and Sette CRI 2022

Recurrent BTIs and updated vaccinations bridge the gap with novel variants

Run T cell epitope predictions using:
Ancestral, BA.2. and BA.2.86 spike sequences

-27 most frequent class I and II alleles to ensure population coverage



MHC-I Binding Predictions

Prediction Method Version: v2.24 [Older versions]

Specify Sequence(s)

Enter protein sequence(s) in FASTA format or as whitespace-separated sequences.

Or select file containing sequence(s): Choose File No file chosen

Choose a Prediction Method

Prediction Method / Show all the method versions: NetMHCpan 4.1 EL (recommended epitope predictor-2023.09) Help on prediction method selections

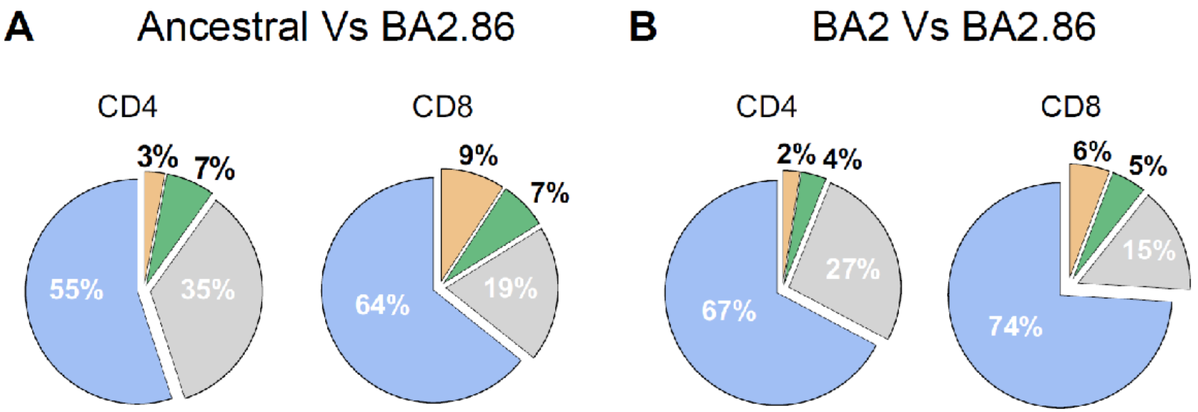
Specify what to make binding predictions for

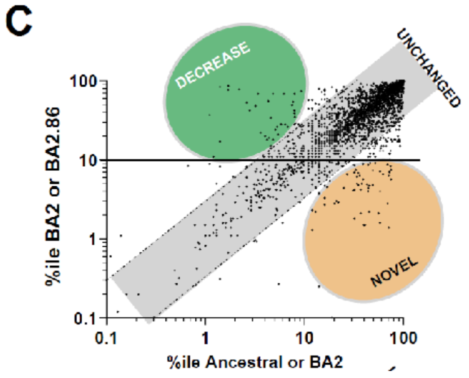
MHC source species: human

Show only frequently occurring alleles ☑
Select MHC allele(s): Allele Length
Select HLA allele reference set ○
(Specify MHC allele sequence)

Specify Output

Sort peptides by: Predicted Score (descend)





CD4

# of HLA restrictions	Anc Vs BA.2.86 #	Anc Vs BA.2.86 %	BA.2 Vs BA.2.86 #	BA.2 Vs BA.2.86 %
Conserved	358	53	358	55
Unchanged	243	36	266	41
Decrease	64	9	25	4
Novel	15	2	7	1
Total	680		656	

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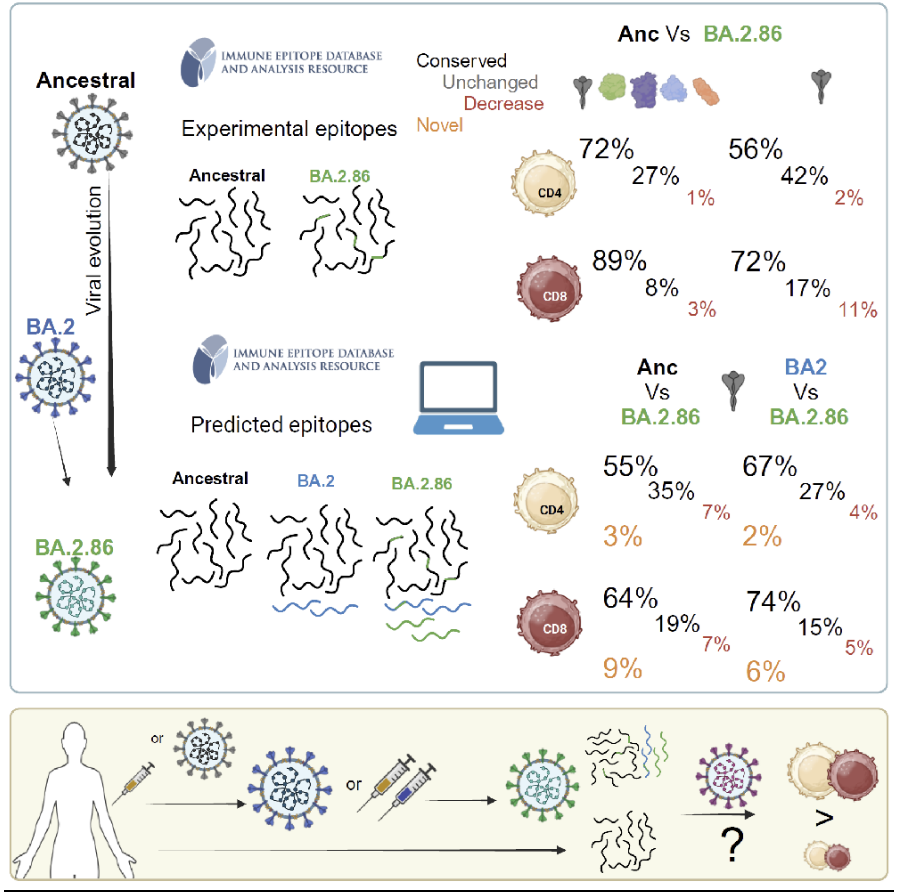
Conclusions

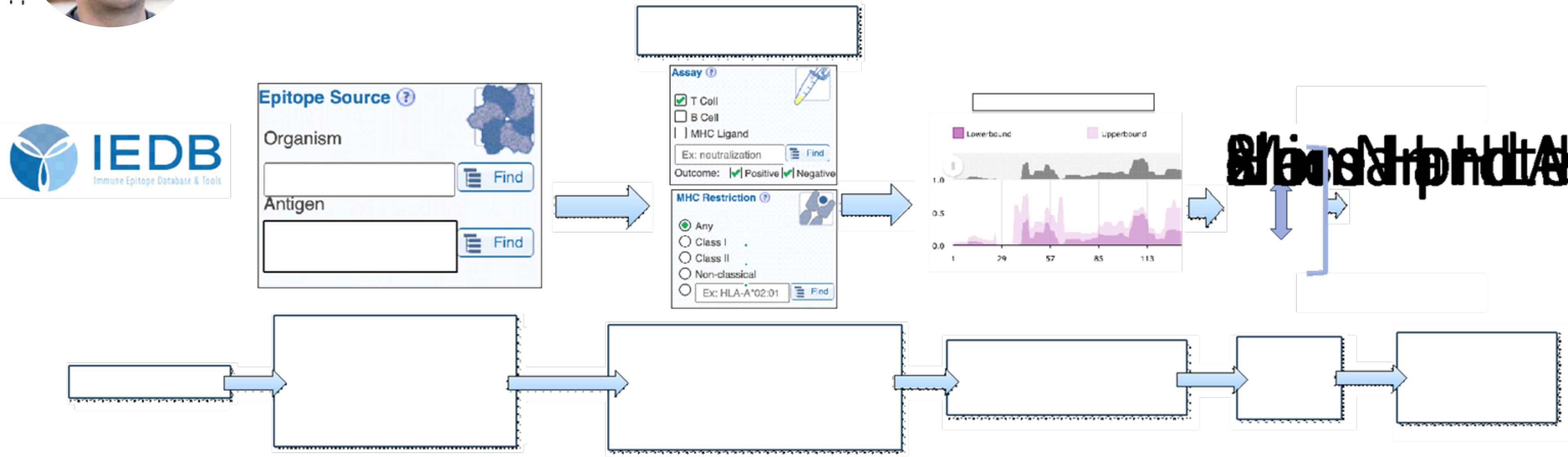


Non-spike regions are less effected by mutations thus are ideal additional vaccine candidates to induce a stable T cell response

Novel variant epitopes induced following BTI or bivalent vaccination can bridge the gap between ancestral immunization and upcoming circulating variants

How animal models reflect human T-cell immunogenicity?

Tertuliano Alves Pereira Neto

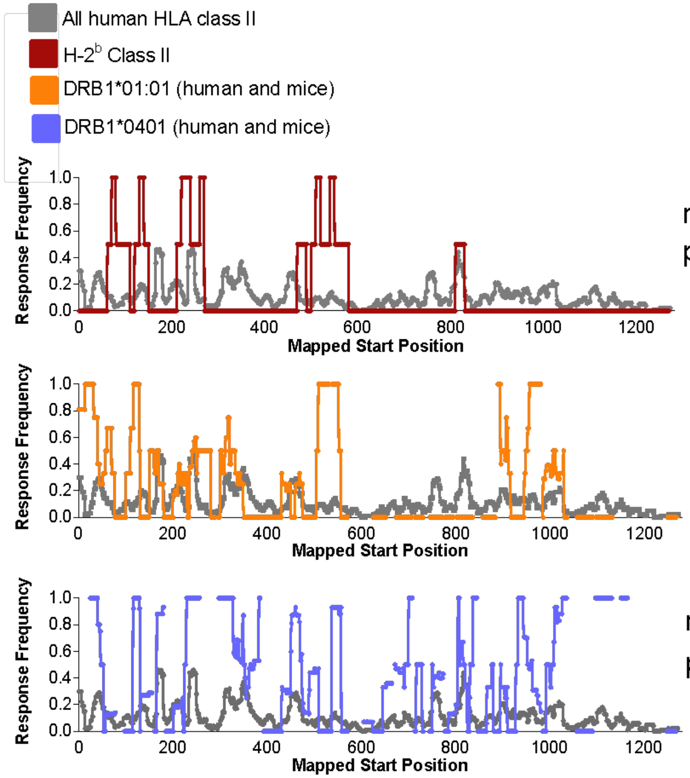


☑ T Cell
☐ B Cell
☐ MHC Ligand
Ex: neutralization
Outcome: ☑ Positive ☑ Negative

● Any
○ Class I
○ Class II
○ Non-classical
○ Ex: HLA-A*02:01

Neto et al., 2023 Cellular & Molecular Immunology

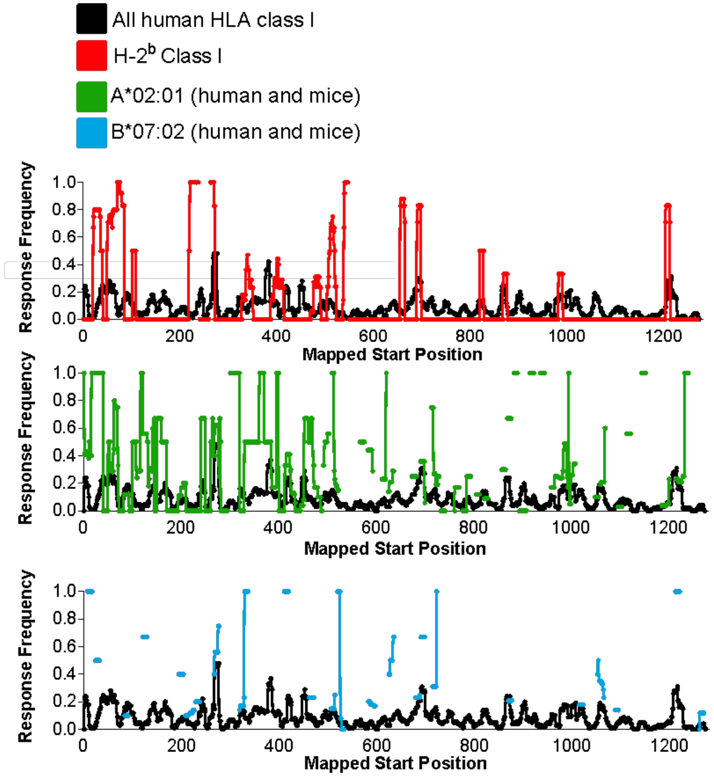
How animal models reflect human T-cell immunogenicity?



r: 0.118
p: 2.63e-005

r: 0.436
p: 2.82e-060

r: 0.594
p: 3.04e-122



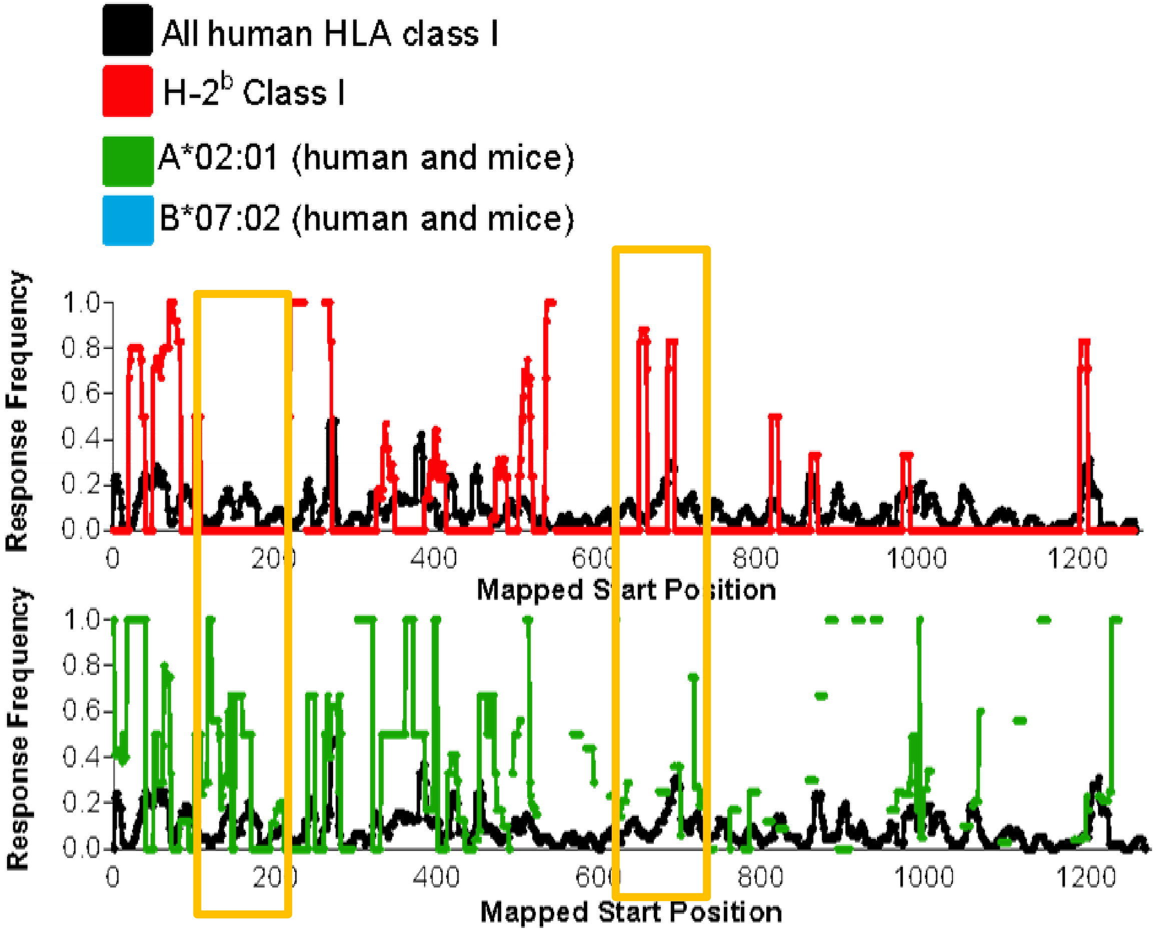
r: 0.206
p: 1.37e-013

r: 0.410
p: 7.42e-053

r: 0.189
p: 1.17e-011

Neto et al., 2023 Cellular & Molecular Immunology

How animal models reflect human T-cell immunogenicity?



r: 0.206

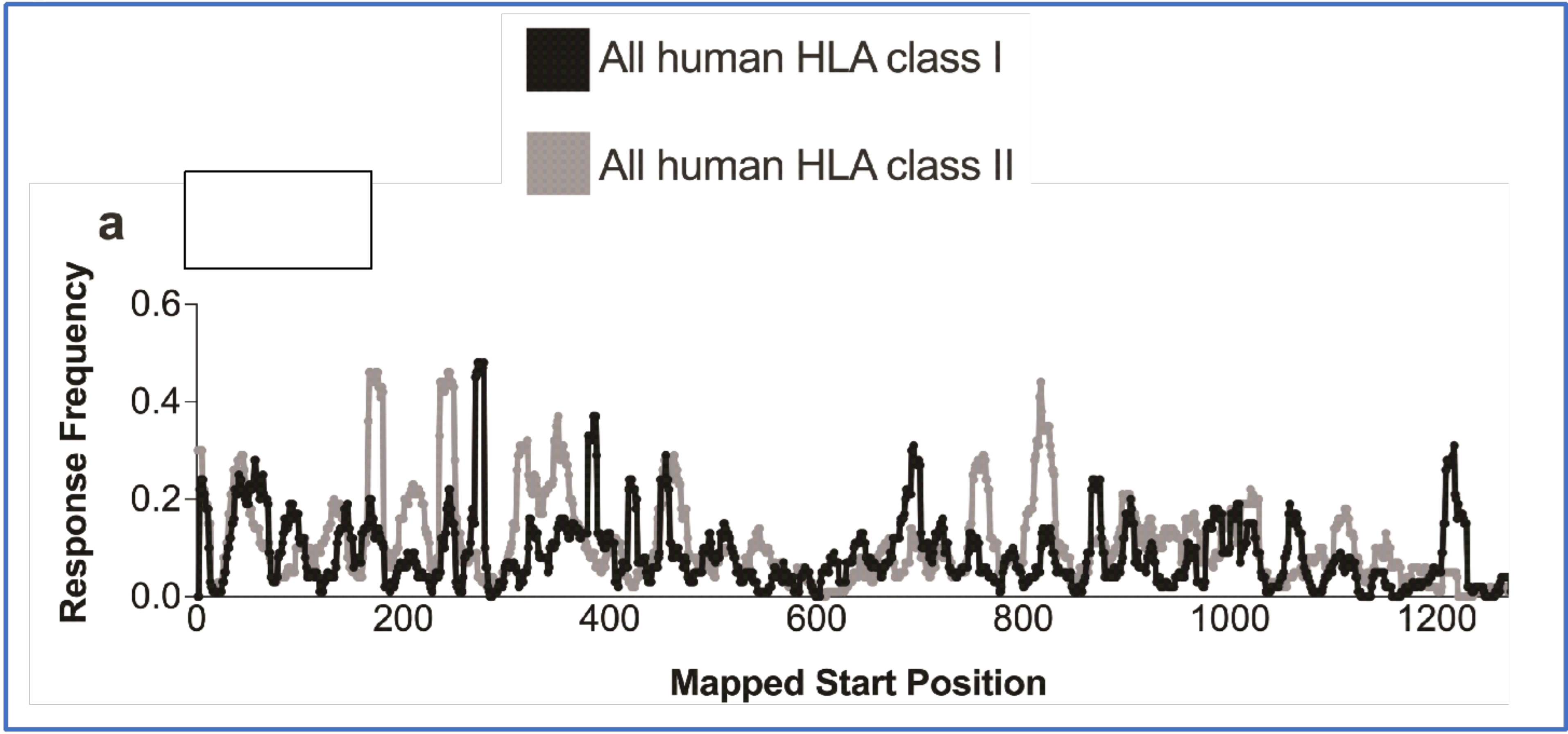
p: 1.37e-013

r: 0.410

p: 7.42e-053

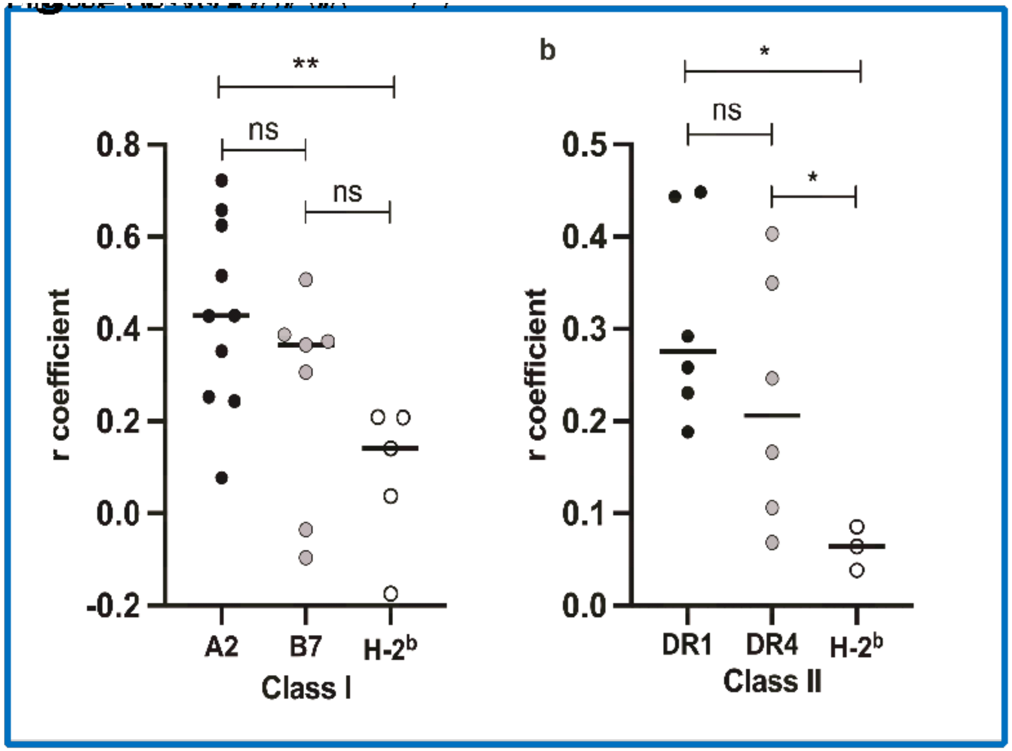
Neto et al., 2023 Cellular & Molecular Immunology

Are there common regions recognized by CD4 and CD8 T cells?



Neto et al., 2023 Cellular & Molecular Immunology

Is this applicable to other viral systems?



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Conclusions: implications for preclinical testing

- The weak correlation observed on mouse H-2b T cell responses suggest non-HLA transgenic mice can be used to evaluate immunogens destined for humans, but this happens more rarely.

- HLA transgenic mice show better correlation and can be used to evaluate immunogens destined for humans.

- Mouse strains or HLA transgenic need to be selected to be matched to the specific immunogenic regions to be tested.

- In several cases the same regions were targeted by CD8 and CD4 T-cells. Thus, specific antigen subregions could be used as immunogens, selected to be broadly immunogenic and conserved across different viral species

- This findings are applicable to different viral systems

….Science is teamwork

Tertuliano Alves Pereira Neto

Prof. Alex Sette

John Sidney

NIH National Institute of Allergy and Infectious Diseases

SAVE initiative: 75N93021C00016
P01A1168347

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