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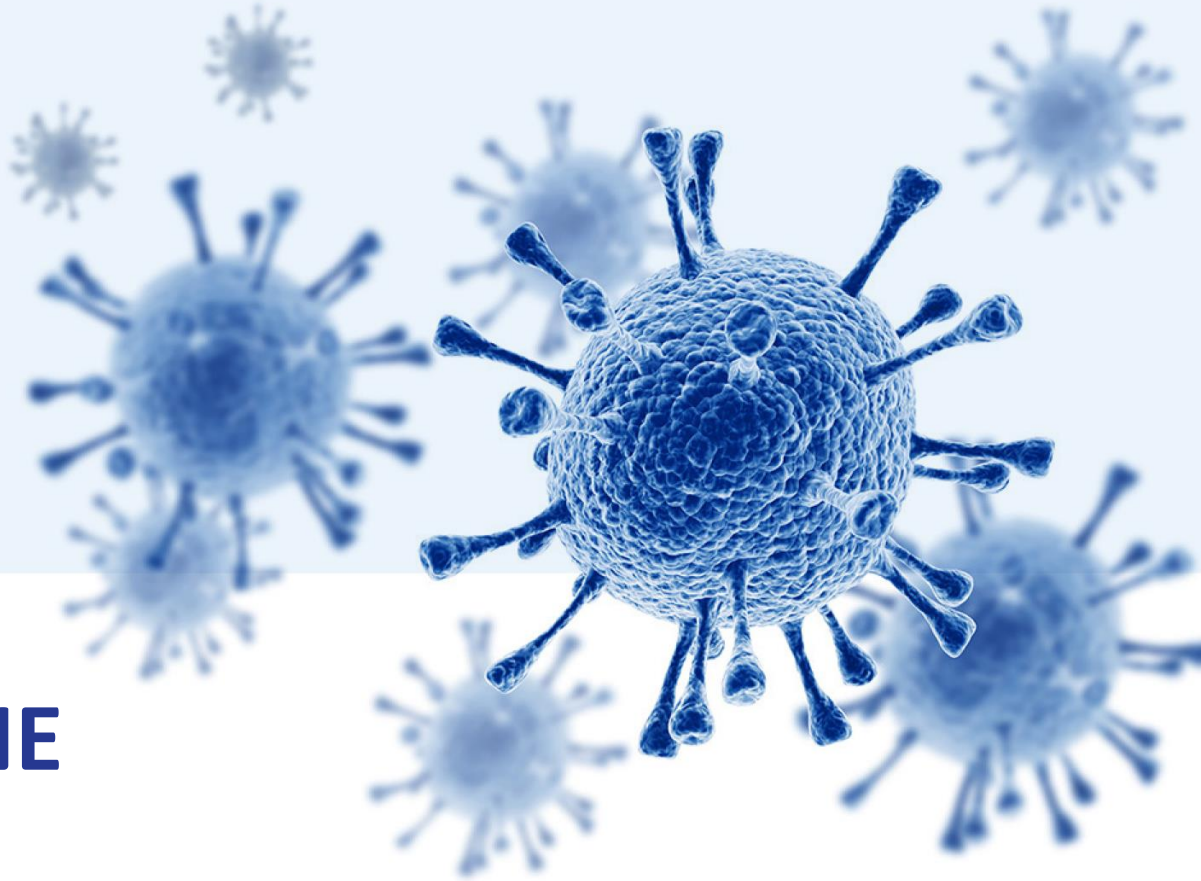

UNIVERSAL INFLUENZA VACCINE PROGRAM - BWV-101

Developing a single vaccine to protect against all influenza strains using ground-breaking mathematical models and research

Brian Price, Ph.D.

April 20, 2022 | World Vaccine & Immunotherapy Congress 2022

Forward Looking Statements

Certain statements in this presentation are forward-looking within the meaning of the Private Securities Litigation Reform Act of 1995. These statements may be identified by the use of forward-looking words such as “anticipate,” “believe,” “forecast,” “estimate,” “expect,” and “intend,” among others. These forward-looking statements are based on BWV’s current expectations and actual results could differ materially. There are a number of factors that could cause actual events to differ materially from those indicated by such forward-looking statements. These factors include, but are not limited to, risks related to the development of BWV’s vaccine candidates, including, but not limited to BWV-301; the failure to obtain FDA clearances or approvals and noncompliance with FDA regulations; delays and uncertainties caused by the global COVID-19 pandemic; risks related to the timing and progress of clinical development of our product candidates; our need for additional financing; uncertainties of patent protection and litigation; uncertainties of government or third party payor reimbursement; limited research and development efforts and dependence upon third parties; and substantial competition. As with any vaccine under development, there are significant risks in the development, regulatory approval and commercialization of new products. BWV does not undertake an obligation to update or revise any forward-looking statement. Investors should read the risk factors set forth in BWV’s Annual Report on Form 10-K for the fiscal year ended December 31, 2021 and other reports filed with the SEC on or after the date thereof. All of BWV’s forward-looking statements are expressly qualified by all such risk factors and other cautionary statements. The information set forth herein speaks only as of the date thereof.

Overview

- The continued need for a Universal Influenza Vaccine
- Blue Water Vaccines Approach
  - Technology developed at the University of Oxford
  - Mathematical model
- Epitope Identification
- H1N1 epitope data – previously presented at WVC
- H3N2 and FluB epitope identification
- Summary and Path Forward

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Why Develop an Influenza Vaccine?

- Influenza (the **flu**) is a virus that kills **290,000- 650,000** people and causes **3-5 million** cases of severe illness **each year** (WHO).

- An estimated $**87.1 billion USD** is lost through absenteeism and sickness in the US (CDC Foundation, 2014).

- **$4 billion USD** is spent on the flu vaccine each year (WHO, 2010).

The best way to protect against influenza is through vaccination.

- Vaccination in the case of flu involves a **yearly** injection of attenuated or dead influenza viruses to induce immunity in the form of the **antibodies** against the **circulating seasonal influenza strains**.

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INFLUENZA A POPULATION STRUCTURE

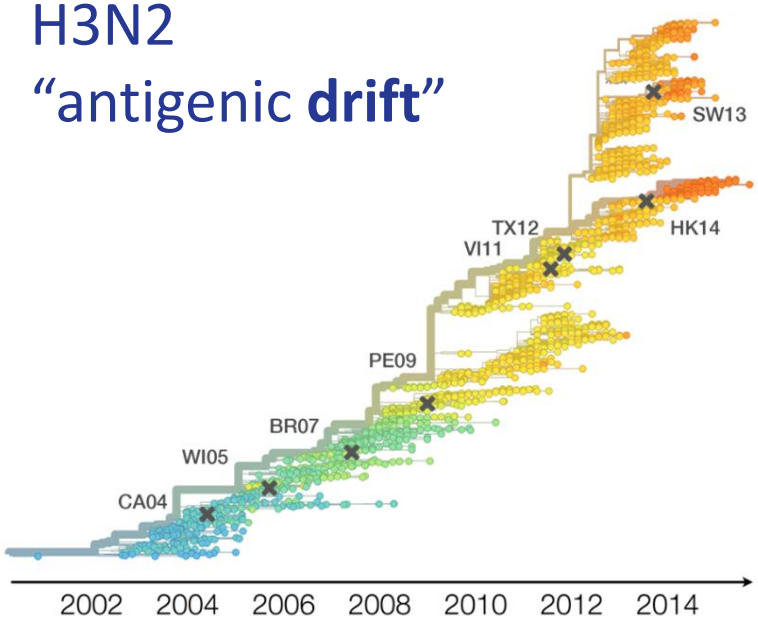
Strains of Flu A replace one another in time.
Because the vaccine targets highly variable loci of the virus, it is strain specific and thus needs constant updating.

There are two schools of thinking about flu A epidemiology and evolution: **drift** and **thrift**.

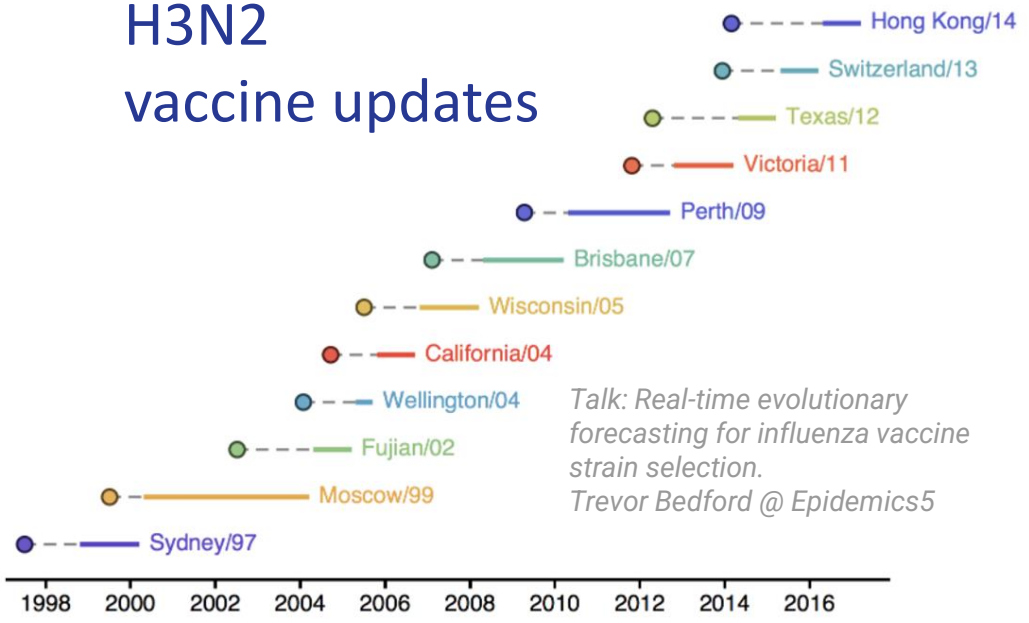
Under thrift, a universal, strain transcending vaccine is possible. But two facts need checking:

- Are there loci (possible epitopes) that cycle in time?
- Are those loci (possible epitopes) immunogenic?

H3N2 "antigenic **drift**"

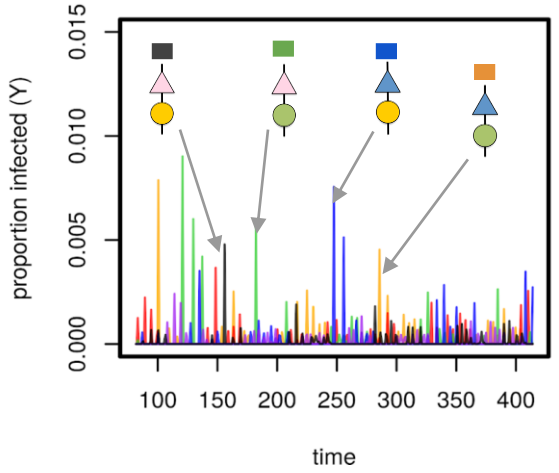


H3N2 vaccine updates



Talk: Real-time evolutionary forecasting for influenza vaccine strain selection.
Trevor Bedford @ Epidemics5

H3N2 "antigenic **thrift**"



Lourenço, J., Wikramaratna, P.S. & Gupta, S. MANTIS: an R package that simulates multilocus models of pathogen evolution. BMC Bioinformatics 16, 176 (2015)

Modeling Overview

- ✓ Epitopes of limited variability which are under STRONG immune selection exist within influenza.
- ✓ These Epitopes drive the antigenic evolution of influenza.
- ✓ These Epitopes cycle between a limited number of different conformations.

Epitopes of limited variability would make ideal vaccine targets.

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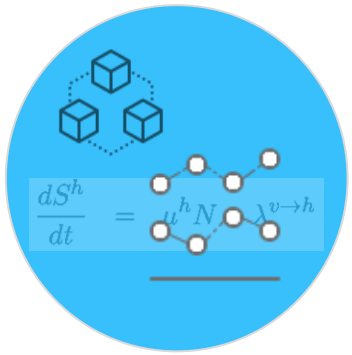
Reverse Immunodynamics of Influenza Viruses

Obtain theoretical insights on how immunity drives population dynamics and genetic structure



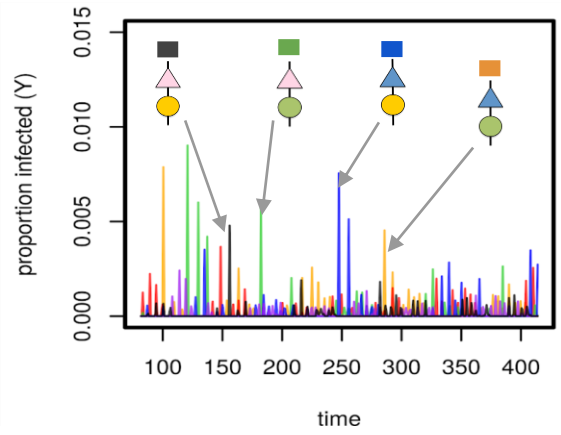
Mine genetic data for loci that are of limited variability and cycle in time

Shortlist epitopes (loci) that may be under immune pressure

Perform empirical research on shortlisted epitopes

Develop new vaccines, and contribute to public health

Influenza A



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INFLUENZA A (H1N1) CYCLIC IMMUNOGENICITY

Serum (mainly from juveniles) can be used to verify cross-reactivity and neutralization of immune responses between contemporary and historical strains.

- Are there loci (possible epitopes) that cycle in time?

Likely, yes.

Historical Microneutralization

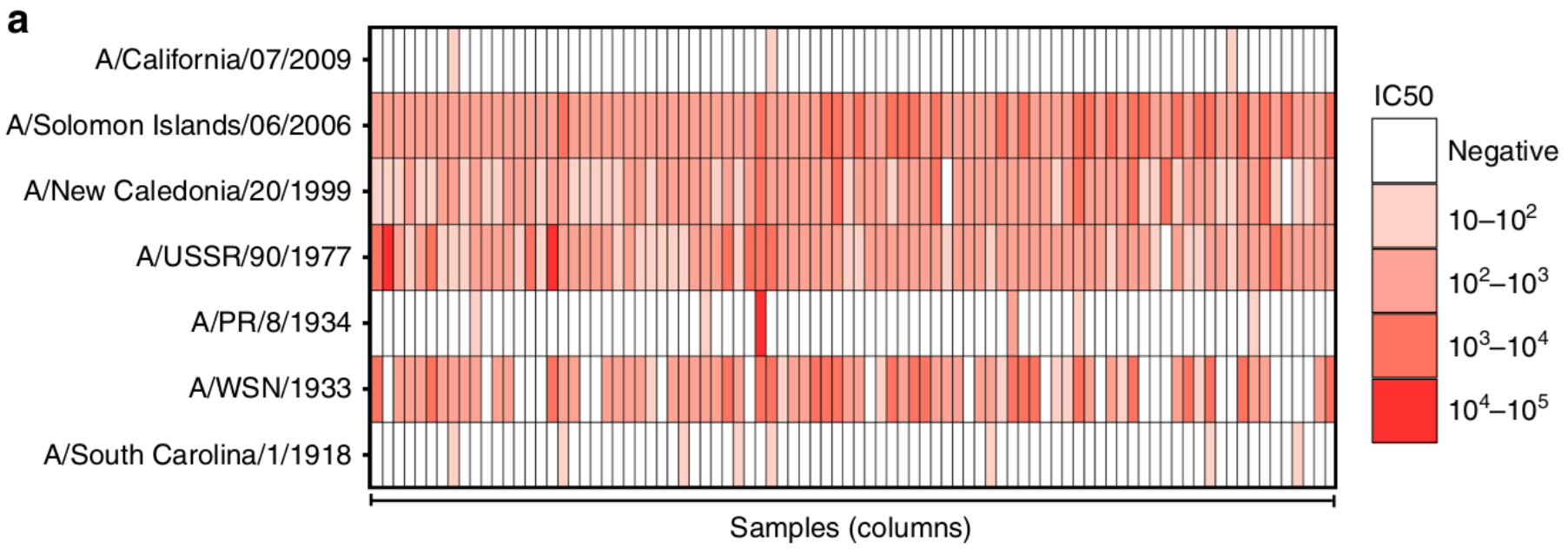
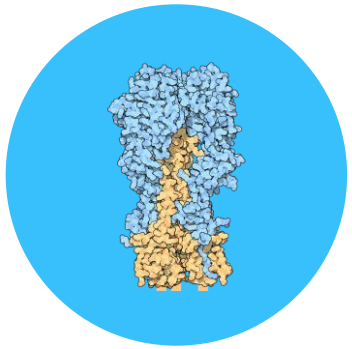


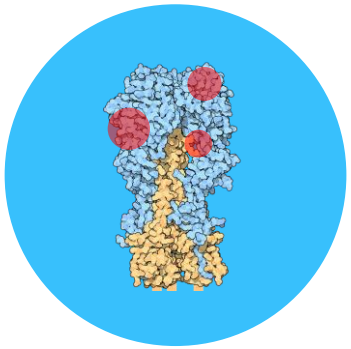
Fig. 1 Pseudotype microneutralisation data reveals a cyclic pattern of epitope recognition. **a** Serum samples from children aged between 6 and 12 years in 2006/2007. $n = 88$ were tested for their ability to neutralise a panel of pseudotyped lentiviruses representing a range of historical isolates.

Thompson, C.P., Lourenço, J., Walters, A.A. et al.
A naturally protective epitope of limited variability as an influenza vaccine target.
Nat Commun 9, 3859 (2018)

Bioinformatic and Structural Computational Pipeline



Quantify accessibility of each surface AA on the HA (H1) protein structure



For each AA, check which other AAs are accessible within the footprint of an AB centred on that AA

Define theoretical AB sites
as sets of AAs visible to an AB with specific binding site area

Identify theoretical AB sites across the HA protein structure

FluA H1N1 full genome data: extract historical genetic variation included within theoretical AB sites

Shortlist those that have limited genetic variation, to avoid candidates including highly variable AAs

Prioritize those that cycle in time (serological and neutralizing data can be used as heuristic)

Shortlist theoretical AB sites that follow theoretical expectations of limited variability and cycling in time

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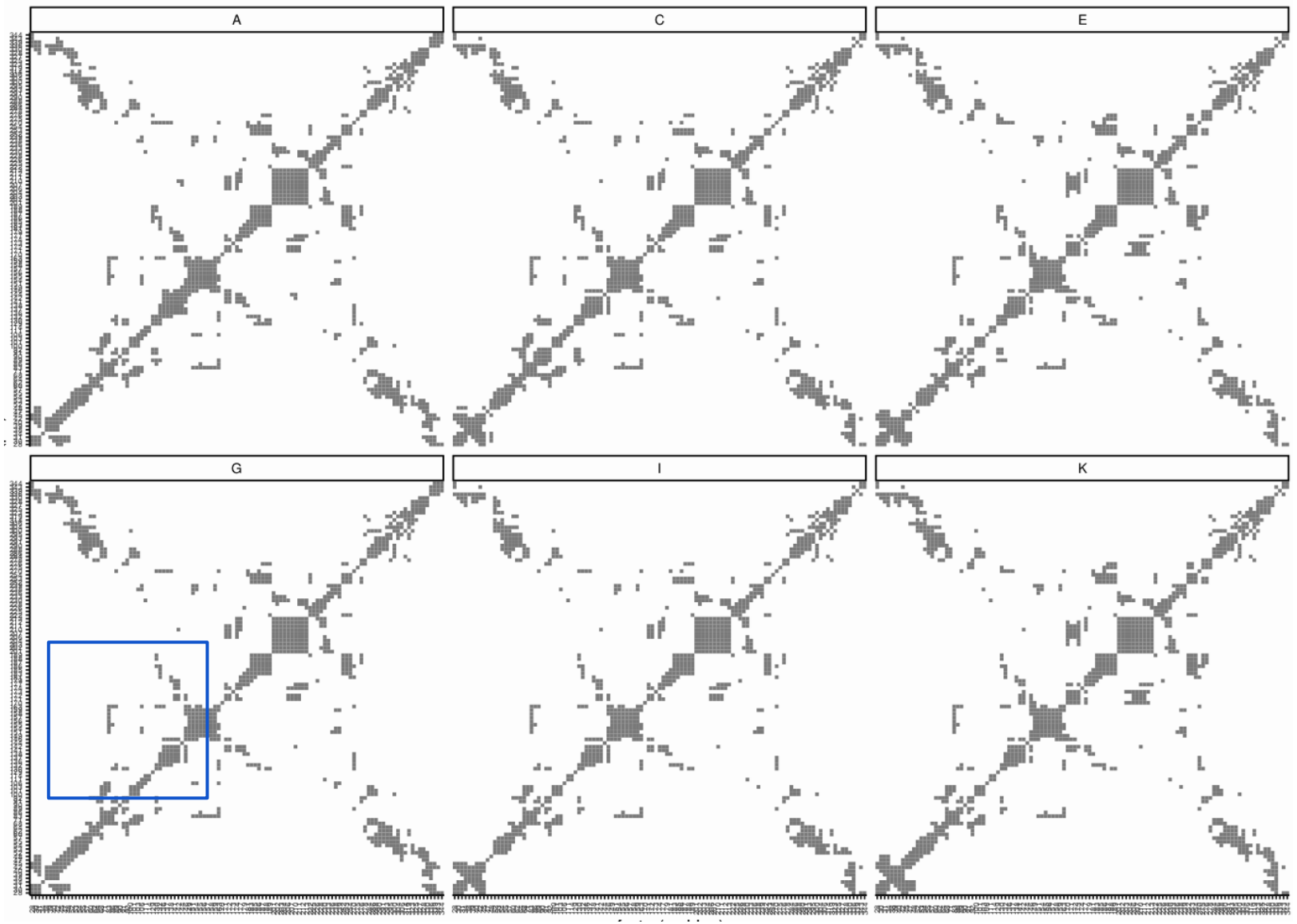
Regions visible by theoretical AB

Y-axis:
for a pin on this AA…



structure
1ru7
1934
50, 800

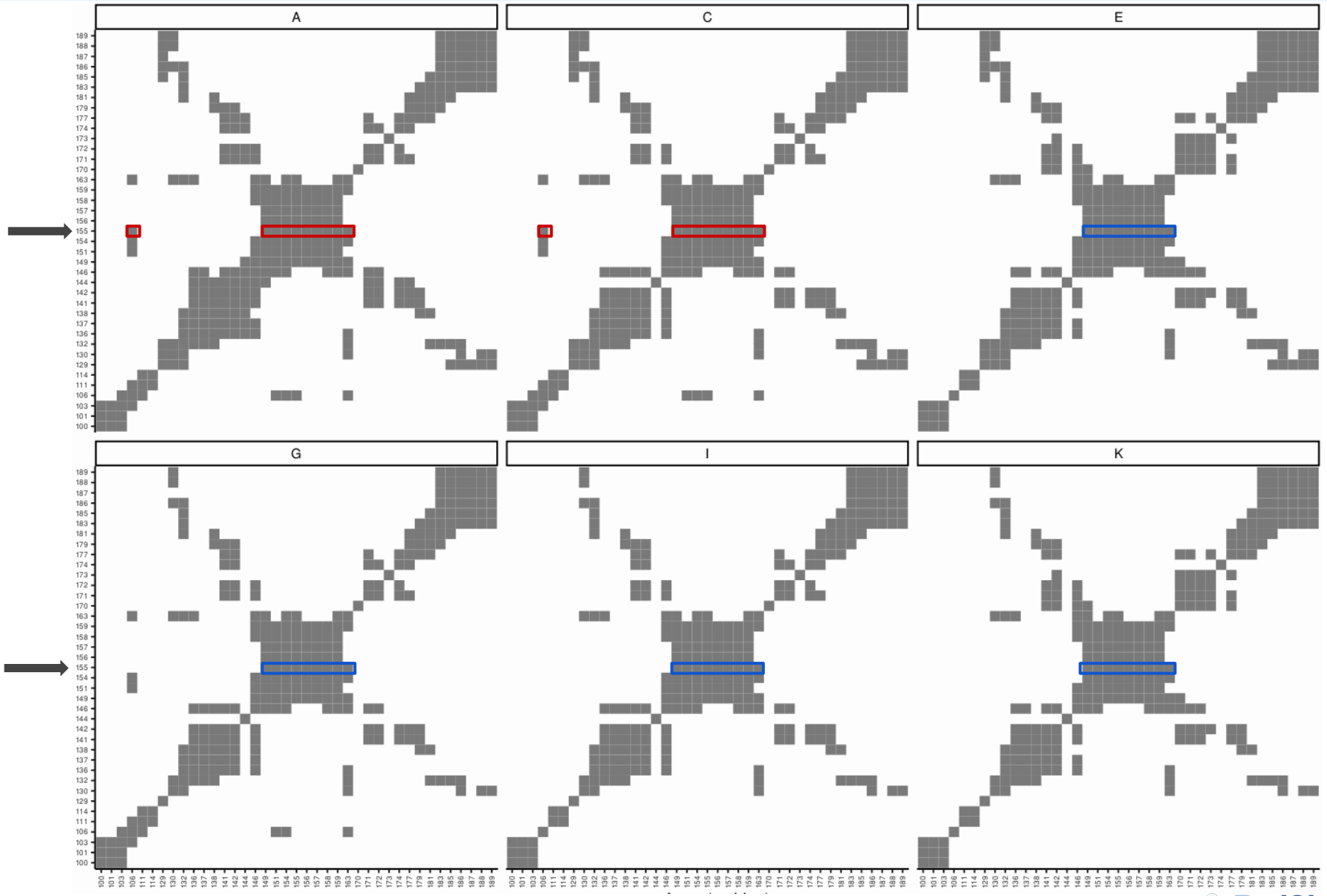
A, C, D
G, I, K

Are the copies of the protein that exist in this crystal structure

X-axis: these AAs are shortlisted.

Regions visible by theoretical AB (head region of HA): one structure

If we place a pin on 155



structure
1ru7
1934
50, 800

Selected epitopes

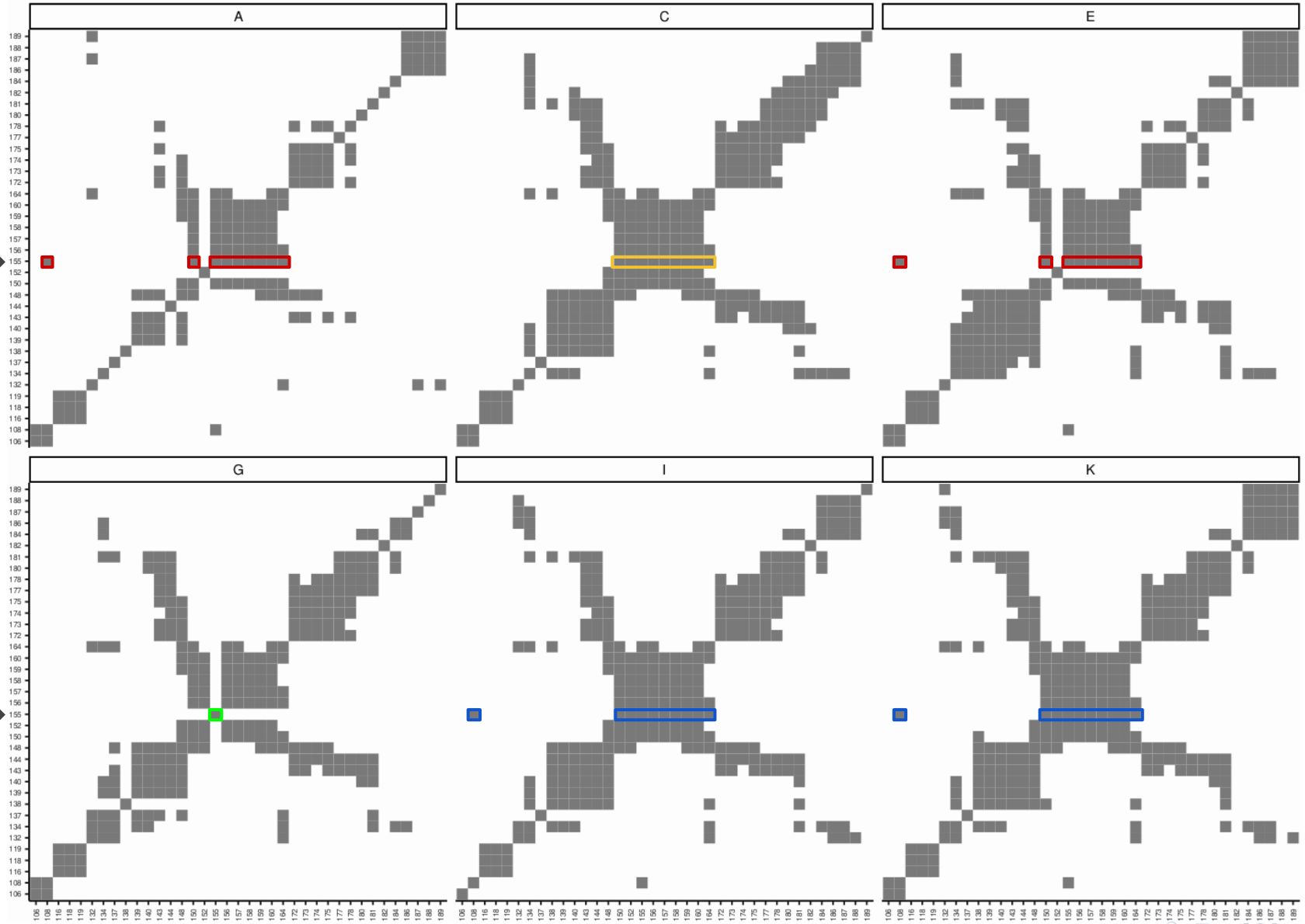
i.e. sets of AA in proximity and accessible for a “target” centered at 155

Intersection:

Takes into consideration structure (method) and biological variation.

Regions visible by theoretical AB (head region of HA): one structure

If we place a pin on 155



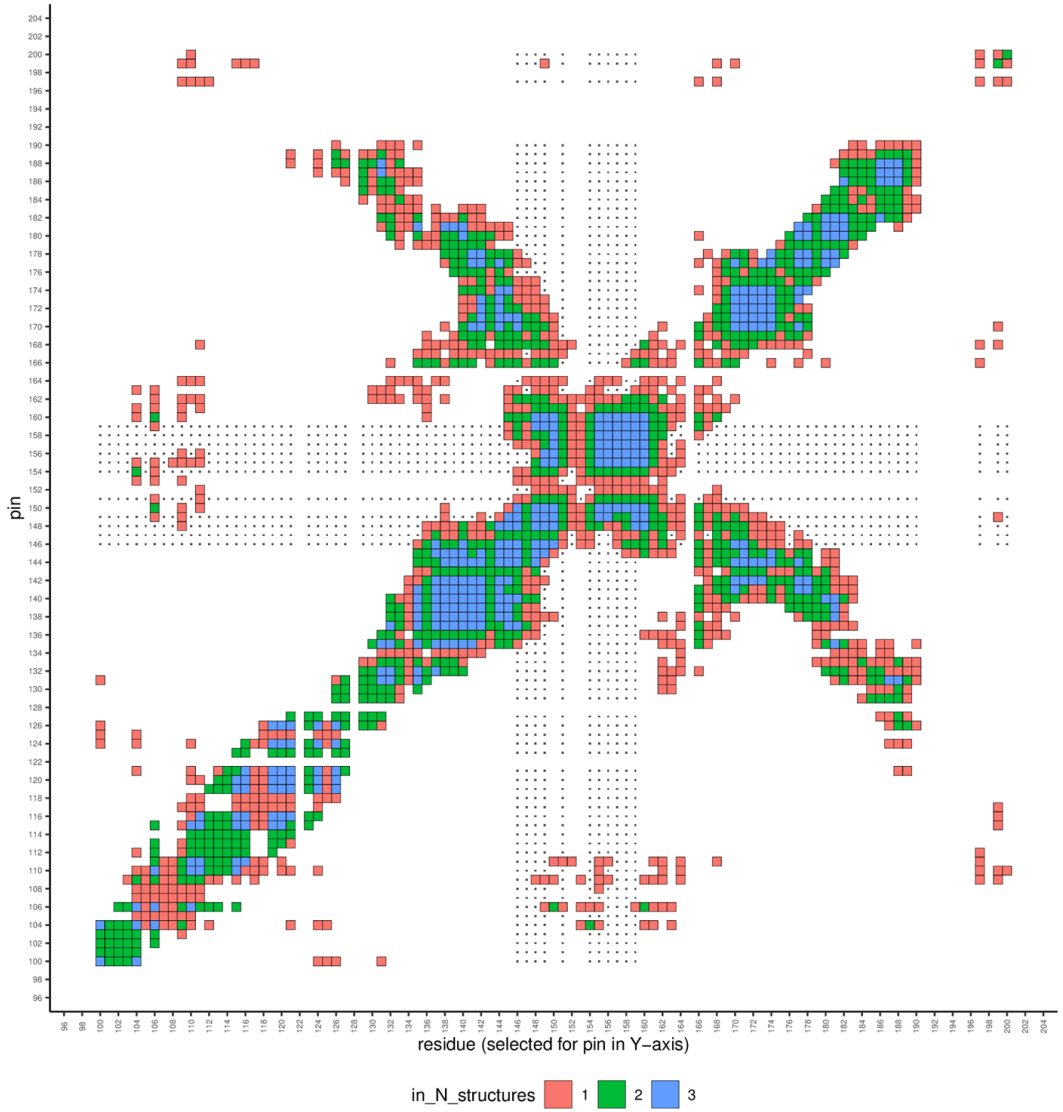
structure
3lzg
2009
50, 800

Epitopes:

Intersection:

Takes into consideration structure (method) and biological variation.

Regions visible by theoretical AB (head region of HA): across structures



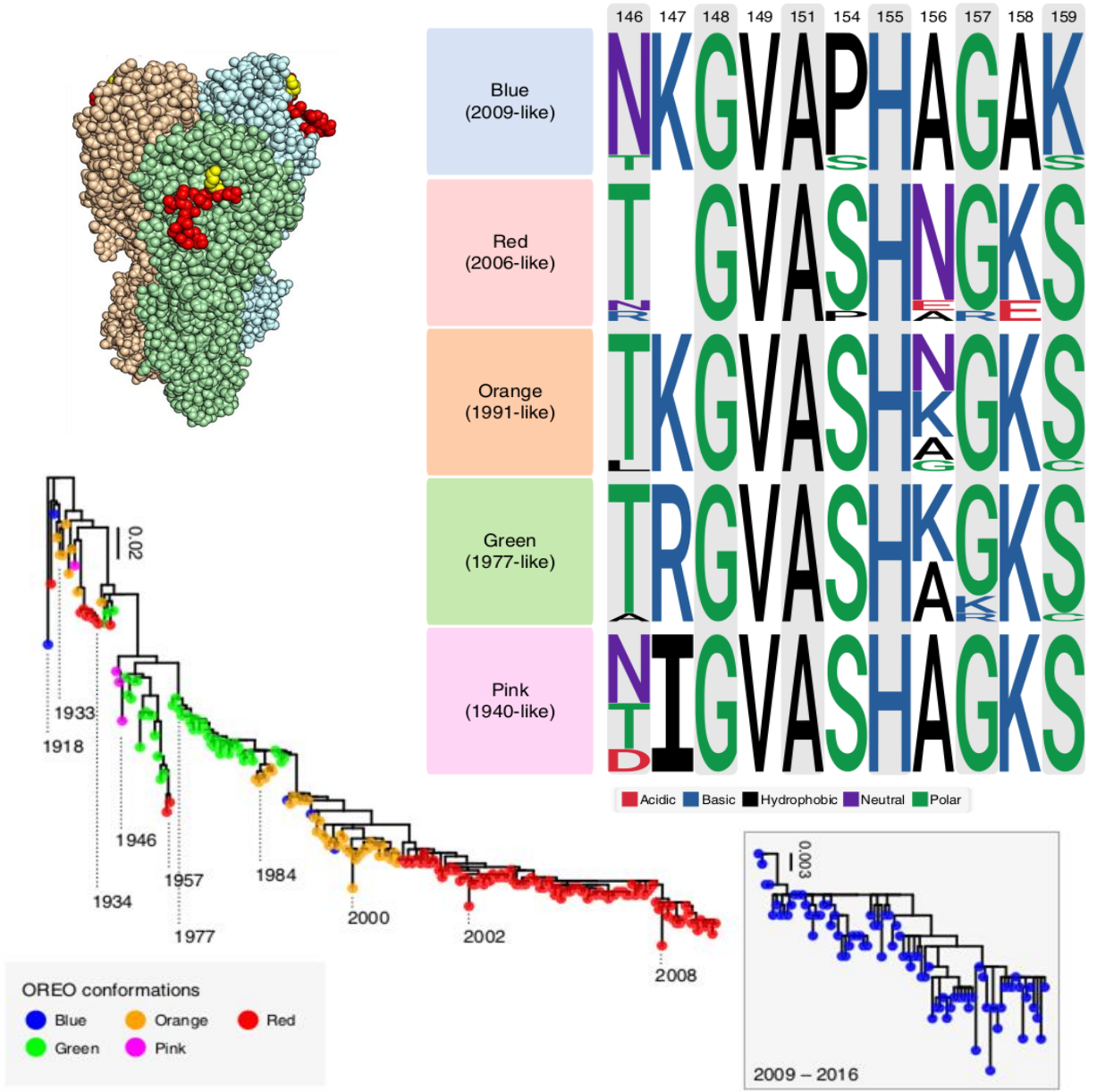
THE H1 OREO CANDIDATE

Through the computational and manual exploration of the genetic and structural data a candidate for a universal vaccine was put forward.

The candidate has preliminarily shown to have cycled in time and could explain most of the patterns observed in the serological & neutralization data.

It has been tested for immunogenicity and protection against disease and death in animal experiments.

OREO is patented and laboratory work is ongoing.



Thompson, C.P., Lourenço, J., Walters, A.A. et al. A naturally protective epitope of limited variability as an influenza vaccine target. Nat Commun 9, 3859 (2018)

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Do Epitopes of Limited Variability Exist in H3N2 and FluB?

H3N2

12-18 months taken in 2012/2013

Strains pre-1995 (IC50)

0	5427	438.7
0	3089	617.4
0	1315	811.6
0	3411	1609
0	8054	3981
0	0	0
0	6157	525.8
0	4304	457.5
0	2031	520.9
0	5562	451.8
0	2851	483.5
0	4588	1634
0	2581	2701
0	5990	1852
0	11958	857.6
0	7093	589.3
0	8429	327.3
0	7479	648.6
0	6270	524.3
0	12346	349.7
0	3459	17169
0	8646	1427
0	7820	1281
0	1898	786.9
0	5298	849
0	3459	810.8
0	4413	534.2
0	2414	879.1
0	1201	919.9
0	3788	488.5

FluB

6 to 12 years taken in 2009

Recent strains		(IC50) Historical strains	
0	28.74	0	0
0	71.84	0	0
0	0	0	0
0	20.88	0	0
0	59.76	0	0
0	72.35	0	0
0	46.39	0	0
108.6	98.24	90.33	0
0	94.55	0	0
0	19.42	0	0
0	8.3	223.8	0
0	131.7	0	0
504.2	34.58	836.5	201.5
7.671	35.47	0	160.7
0	0	0	90.56
19.67	0	88.02	156
0	0	0	0
0	25.23	0	87.37
0	12.73	897	29.89
0	121.6	0	89.5
0	171.9	0	0
0	189	0	0
0	0	0	20.47
0	239.6	0	0
47.49	16.61	0	25.3
102.8	0	715	79.19
12.74	41.61	0	30.1
0	113.7	0	14.3
731.3	33.32	377.5	14.22
33.46	24.67	35.53	39.29
1429	145	1387	48.76
250.3	131.5	217.1	0
845.5	71.59	1587	717.2
56.91	84.08	62.2	30.25
139.2	252.7	179	0
167	195.5	393.4	26.7
319.3	185.1	415.3	0
0	27.25	0	0
173.4	87.83	166.4	0
263.7	21.23	374.1	0
306.5	57.8	452.4	37.11

Unpublished work – Blue Water Vaccines / Oxford University.

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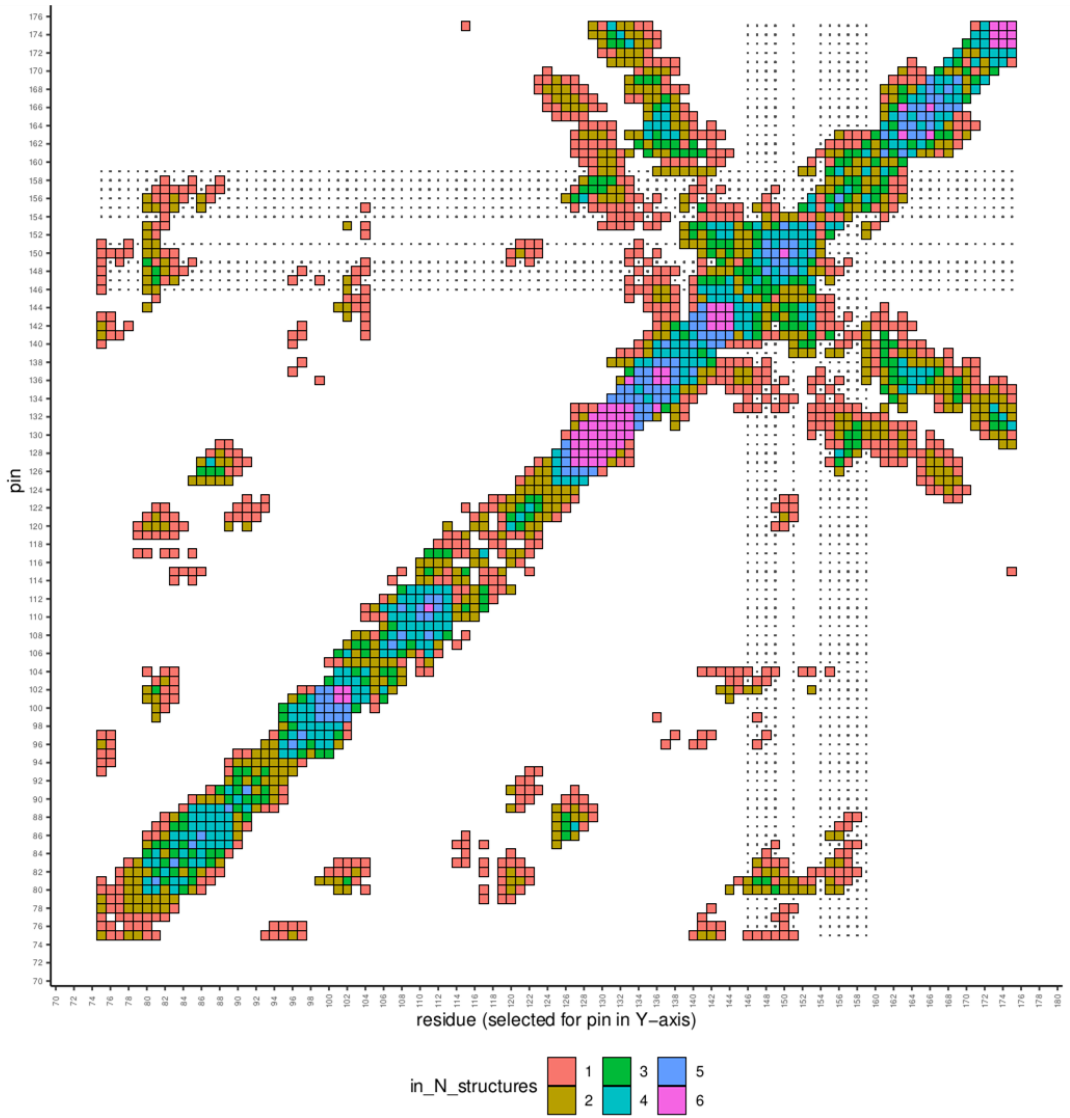
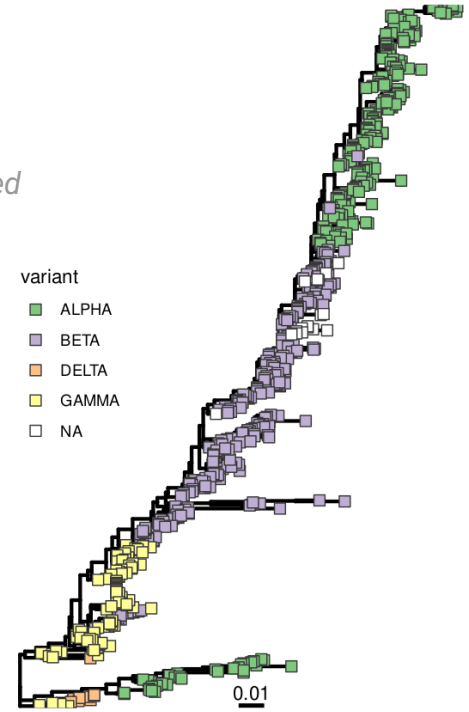
H3 theoretical AB maps



The INDY and MAIZ candidates for Influenza A H3

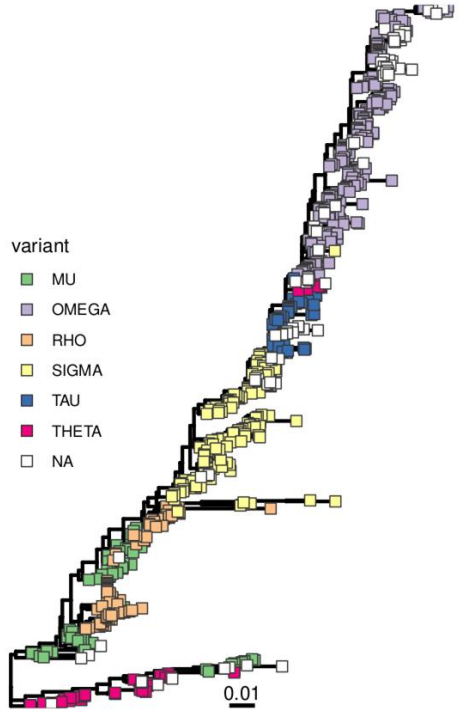
INDY by variant



Patent
OU Innovation Limited
Blue Water Vaccines
No: GB2204478.8
Ref: 489.143574

sequence numbering																													
STANDARD	128	129	130	131	132	173	174	175	176	177	178	179	180	181	182	183	184	213	214	215	242	243	245	246	247	248	249	251
LINEAR	142	143	144	145	146	187	188	189	190	191	192	193	194	195	196	197	198	227	228	229	256	257	259	260	261	262	263	265
variant																												
ALPHA	N	W	T	G	V	K	E	Q	F	D	K	L	Y	I	W	G	V	Q	A	V	G	D	L	L	I	N	S	G
BETA	N	W	T	G	V	N	E	K	F	D	K	L	Y	I	W	G	V	Q	T	V	G	D	L	L	I	N	S	G
GAMMA	N	W	T	G	V	N	G	K	F	D	K	L	Y	I	W	G	V	Q	T	V	G	D	L	L	I	N	S	G
DELTA	N	W	T	G	V	N	G	N	F	D	K	L	Y	I	W	G	V	Q	T	I	G	D	L	L	I	N	S	G

MAIZ by variant



Patent
OU Innovation Limited
Blue Water Vaccines
No: GB2204478.8
Ref: 489.143574

sequence numbering															
STANDARD	141	142	143	144	145	146	147	148	149	150	151	152	153	154	155
LINEAR	155	156	157	158	159	160	161	162	163	164	165	166	167	168	169
variant															
OMEGA	C	I	R	R	S	S	S	S	F	F	S	R	L	N	W
TAU	C	K	R	R	S	N	N	S	F	F	S	R	L	N	W
SIGMA	C	K	R	R	S	N	K	S	F	F	S	R	L	N	W
RHO	C	K	R	G	S	V	K	S	F	F	S	R	L	N	W
MU	C	K	R	G	S	V	N	S	F	F	S	R	L	N	W
THETA	C	K	R	G	S	D	N	S	F	F	S	R	L	N	W

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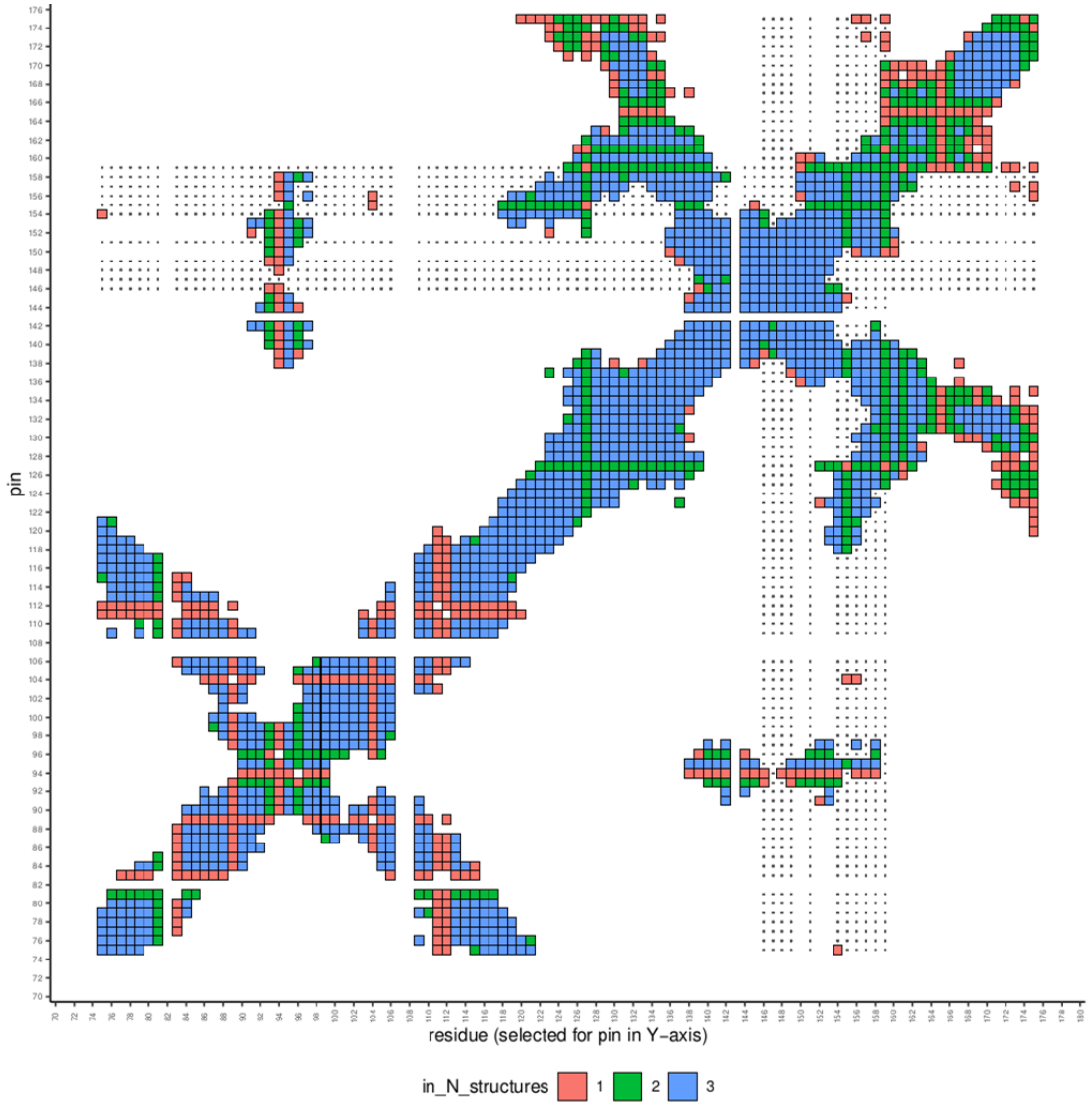
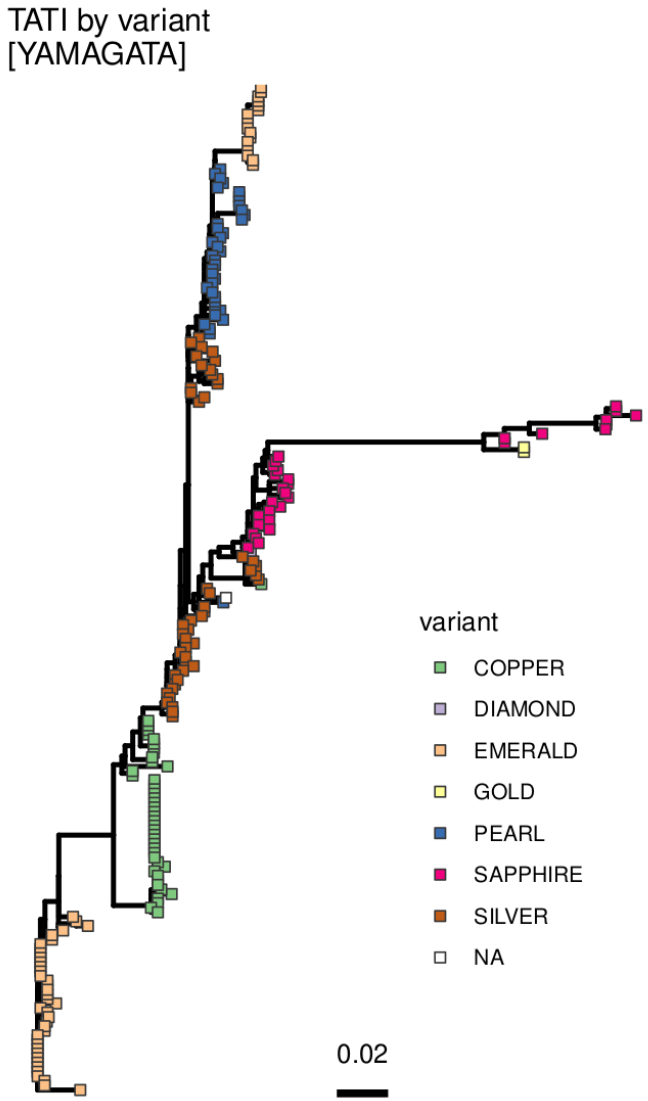
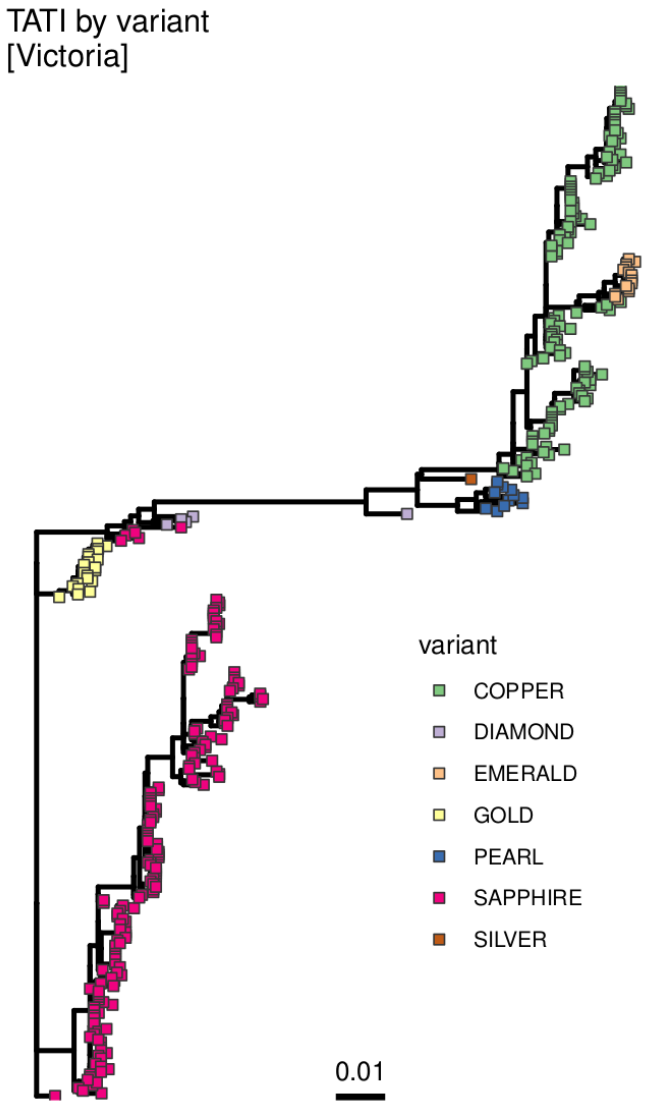
Flu B theoretical AB maps



The TATI candidate for Influenza B (Yamagata & Victoria)





Patent
OU Innovation Limited
Blue Water Vaccines
No: GB2204478.8
Ref: 489.143575

sequence numbering															
STANDARD	139	140	141	142	144	145	146	147	148	149	150	151	152	153	154
variant															
SILVER	G	Y	E	N	R	L	S	T	Q	N	V	I	N	A	E
COPPER	G	Y	E	N	R	L	S	T	Q	N	V	I	D	A	E
DIAMOND	G	Y	E	N	R	L	S	T	H	N	V	I	N	A	E
PEARL	G	Y	E	K	R	L	S	T	Q	N	V	I	N	A	E
EMERALD	G	Y	E	K	R	L	S	T	Q	N	V	I	D	A	E
SAPPHIRE	G	Y	E	H	R	L	S	T	H	N	V	I	N	A	E
GOLD	G	Y	E	R	R	L	S	T	H	N	V	I	N	A	E

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Progress to date and Next Steps

1. Identified **two epitopes** of limited variability in H3N2 influenza A and **one epitope** in influenza B.
2. Sites to be evaluated to confirm immunogenicity experimentally.
   - ✓ **Generating** antigen specific sera and evaluating for strain cross-reactivity and neutralization.
   - ✓ **Evaluating** sera from cohorts of young children to confirm cross-reactivity in historical strains
   - ✓ **Animal vaccination** and challenge studies to demonstrate that protective immunogenicity can be induced.

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Summary

- ✓ The **large seasonal burden** warrants the development of improved influenza vaccines.
- ✓ Improved influenza vaccines should **provide broad protection** without the need for annual immunization.
- ✓ We have focused our development efforts on identified **epitopes of limited variability** in the head region of the HA.
- ✓ These epitopes are **highly immunogenic** and have been shown to provide protection against challenge (H1).

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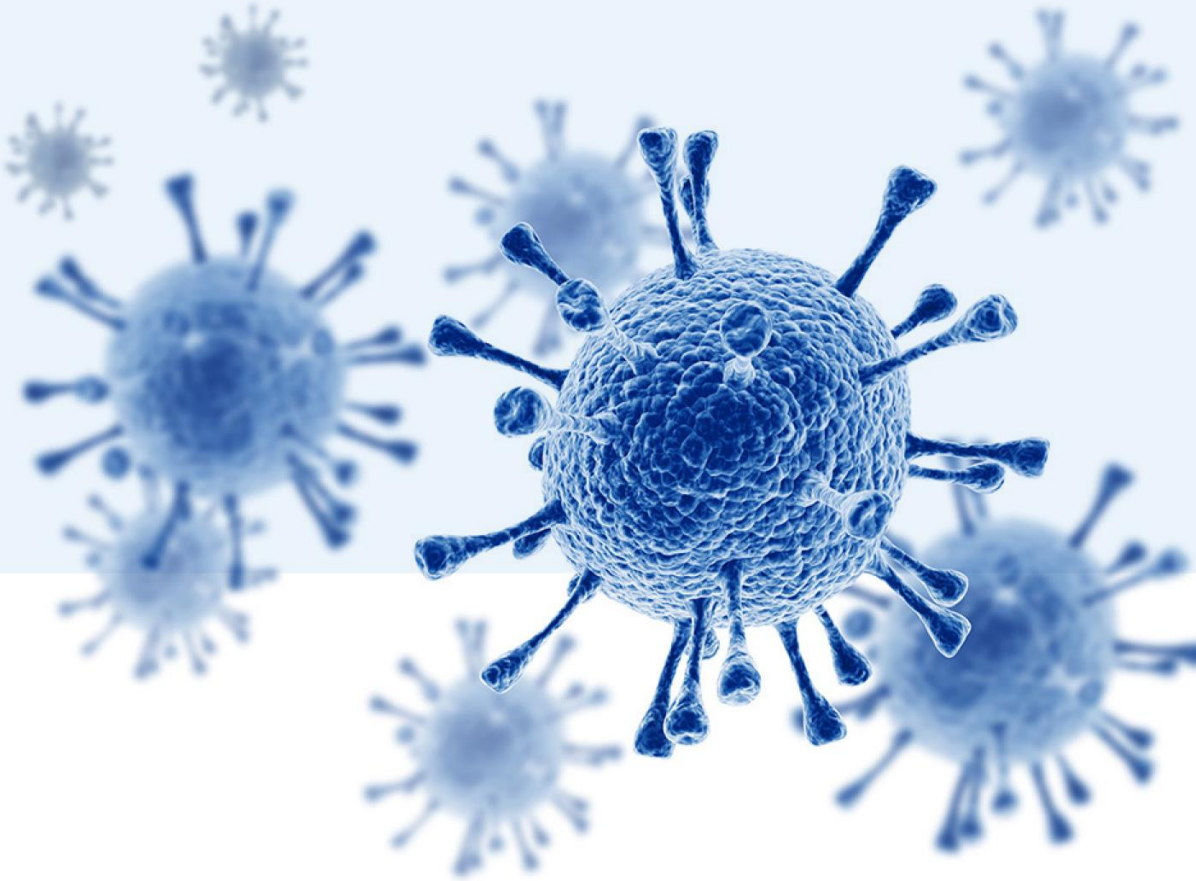
vaccines



Thank you!

Brian Price, Ph.D.
Blue Water Vaccines