Collaborative basic research to study viral structures for vaccines development

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Improved pandemic preparedness could be achieved by proactively managing emerging virus threats focused on four discreet activities using currently available tools:

Discovery and Surveillance

Targeted Basic Research

Translational Research and Product Development

Clinical Trial Infrastructure and Deployment Capacity

Adapted from the World Health Organization Website

Integrated pipeline for Response to Pathogen X

Discovery and Surveillance

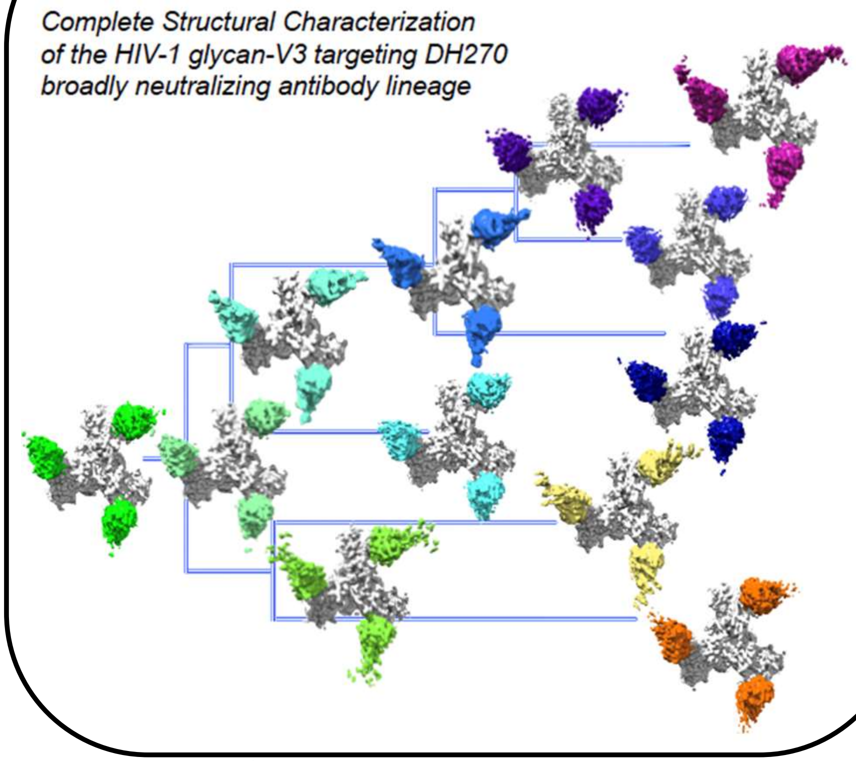
Translational Research and Product Development

Targeted Basic Research

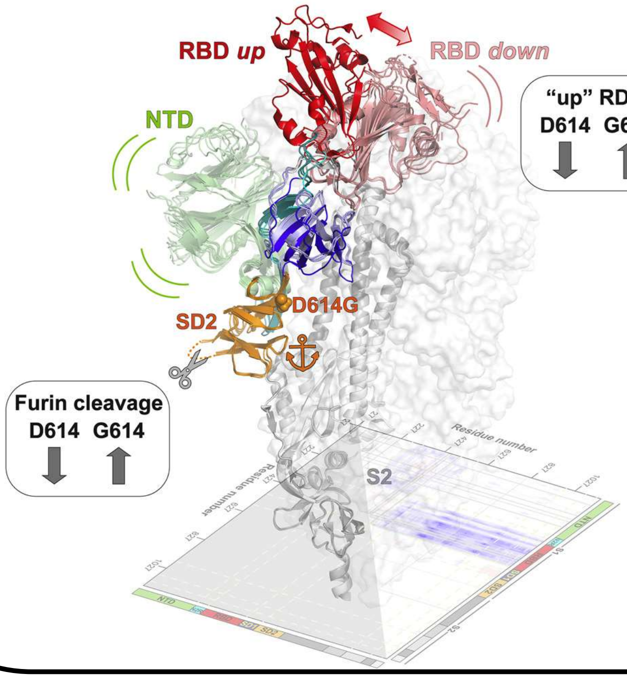
Clinical Trial Infrastructure and Deployment Capacity

Structural biology in understanding a virus and in vaccine development

Antibody epitope visualization

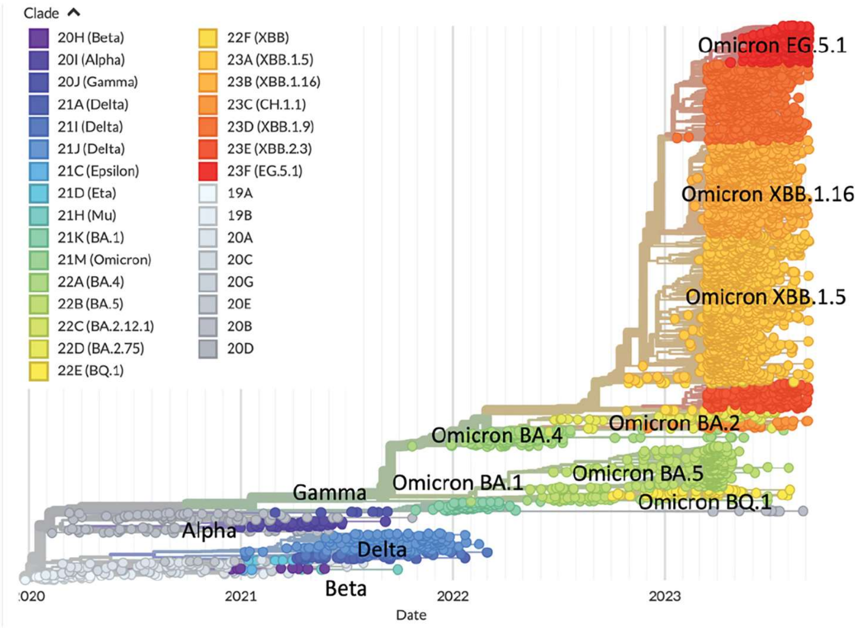


Details of protein structure and dynamics



Vaccine immunogen design

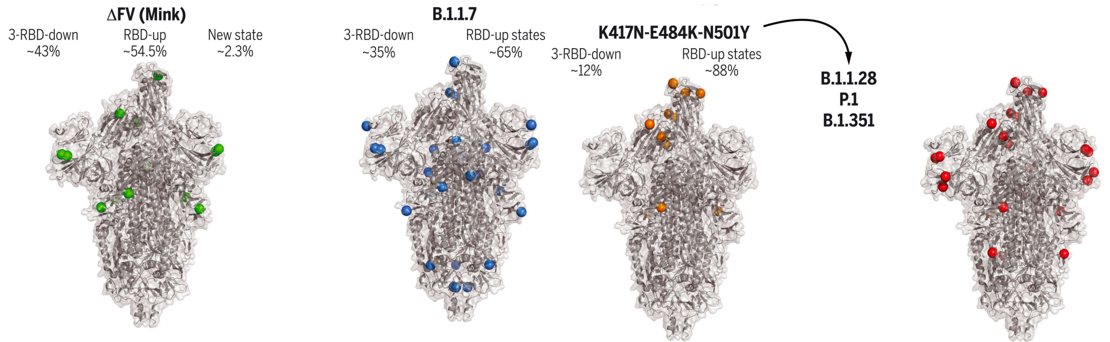
The power of structural surveillance: SARS-CoV-2 as a case study



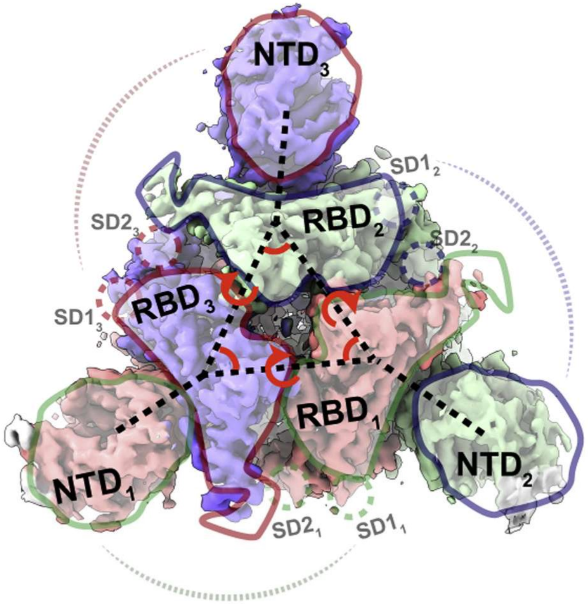
Phylogenetic tree generated from GISAID.

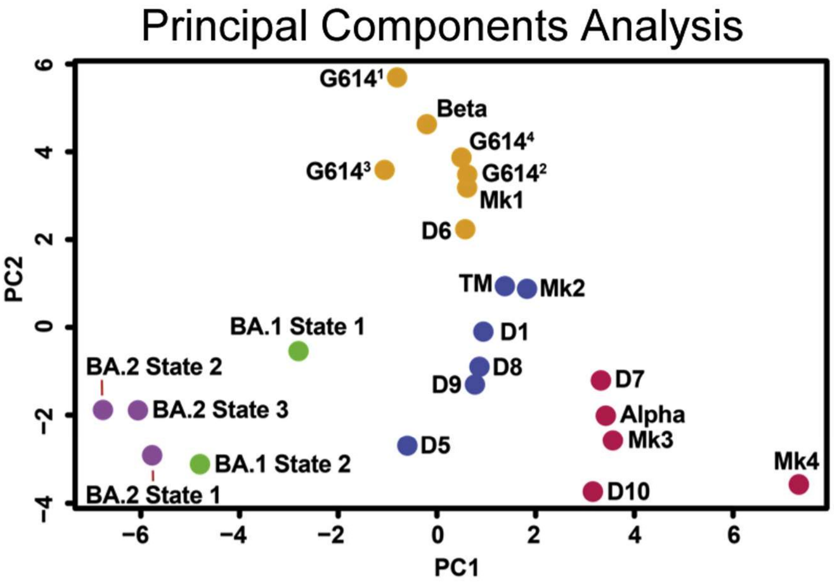
Structural Biology provides unique information on viral antigen conformation

Structural Surveillance



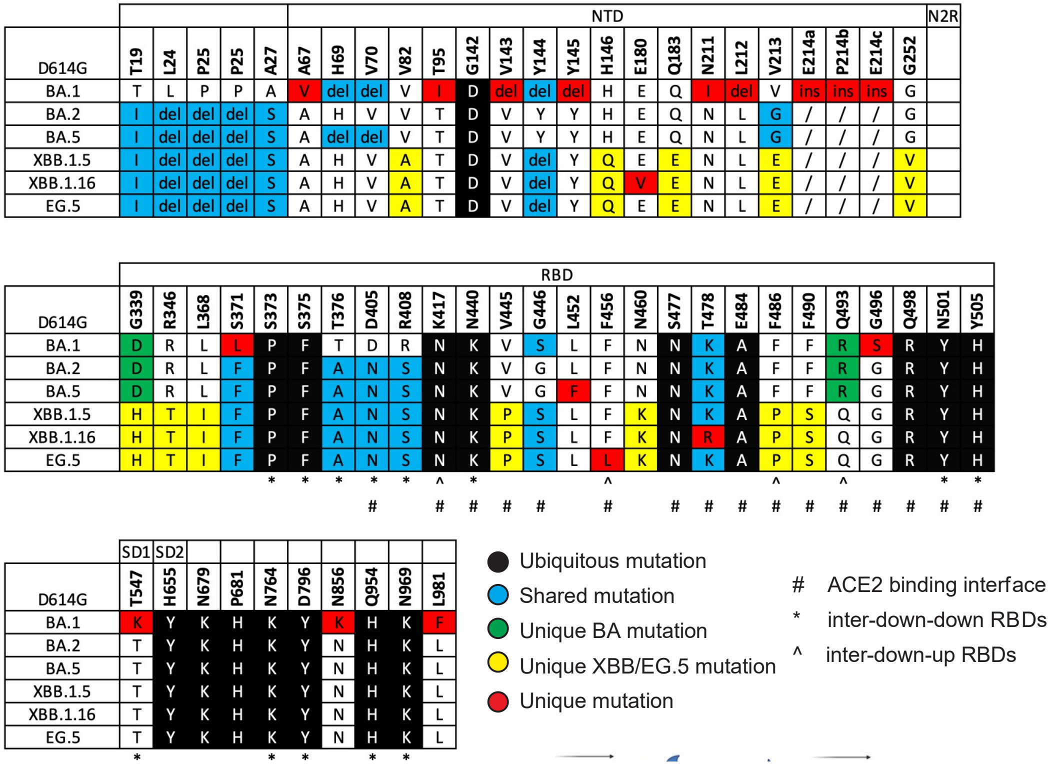
- ***All pre-Omicron variants preferred spike conformation that maximized receptor interaction and enabled transmissibility***
- ***Omicron prefers spike conformation that maximizes immune evasion***





Information from structure of viral antigens can help predict the course of an epidemic while informing a response in the form of a vaccine or a therapeutic

Structure-guided sequence surveillance predicted structures of emerging variants



D614G						NTD																		N2R
	T19	L24	P25	P25	A27	A67	H69	V70	V82	T95	G142	V143	Y144	Y145	H146	E180	Q183	N211	L212	V213	E214a	P214b	E214c	G252
BA.1	T	L	P	P	A	V	del	del	V	I	D	del	del	del	H	E	Q	I	del	V	ins	ins	ins	G
BA.2	I	del	del	del	S	A	H	V	V	T	D	V	Y	Y	H	E	Q	N	L	G	/	/	/	G
BA.5	I	del	del	del	S	A	del	del	V	T	D	V	Y	Y	H	E	Q	N	L	G	/	/	/	G
XBB.1.5	I	del	del	del	S	A	H	V	A	T	D	V	del	Y	Q	E	E	N	L	E	/	/	/	V
XBB.1.16	I	del	del	del	S	A	H	V	A	T	D	V	del	Y	Q	V	E	N	L	E	/	/	/	V
EG.5	I	del	del	del	S	A	H	V	A	T	D	V	del	Y	Q	E	E	N	L	E	/	/	/	V

D614G	RBD																								
	G339	R346	L368	S371	S373	S375	T376	D405	R408	K417	N440	V445	G446	L452	F456	N460	S477	T478	E484	F486	F490	Q493	G496	Q498	N501	Y505
BA.1	D	R	L	L	P	F	T	D	R	N	K	V	S	L	F	N	N	K	A	F	F	R	S	R	Y	H
BA.2	D	R	L	F	P	F	A	N	S	N	K	V	G	L	F	N	N	K	A	F	F	R	G	R	Y	H
BA.5	D	R	L	F	P	F	A	N	S	N	K	V	G	F	F	N	N	K	A	F	F	R	G	R	Y	H
XBB.1.5	H	T	I	F	P	F	A	N	S	N	K	P	S	L	F	K	N	K	A	P	S	Q	G	R	Y	H
XBB.1.16	H	T	I	F	P	F	A	N	S	N	K	P	S	L	F	K	N	R	A	P	S	Q	G	R	Y	H
EG.5	H	T	I	F	P	F	A	N	S	N	K	P	S	L	L	K	N	K	A	P	S	Q	G	R	Y	H
					*	*	*	*	*	^	*				^					^		^			*	*
								#		#	#	#	#		#		#	#	#	#	#	#	#	#	#	#

D614G	SD1	SD2								
	T547	H655	N679	P681	N764	D796	N856	Q954	N969	L981
BA.1	K	Y	K	H	K	Y	K	H	K	F
BA.2	T	Y	K	H	K	Y	N	H	K	L
BA.5	T	Y	K	H	K	Y	N	H	K	L
XBB.1.5	T	Y	K	H	K	Y	N	H	K	L
XBB.1.16	T	Y	K	H	K	Y	N	H	K	L
EG.5	T	Y	K	H	K	Y	N	H	K	L
	*				*	*		*	*	

- ● Ubiquitous mutation
- 🟦 Shared mutation
- 🟩 Unique BA mutation
- 🟨 Unique XBB/EG.5 mutation
- 🟥 Unique mutation

\# ACE2 binding interface
* inter-down-down RBDs
^ inter-down-up RBDs

AI-enabled structural analysis to further bridge between structure and sequence

<u>Information and Assessment</u>

Structure

Sequence

Biochemistry

Biophysics

Virology

<u>Computational Methods for Accelerated Antigen Design</u>

Structure Prediction

Protein Language Models

Molecular Dynamics based approaches

AI-accelerated Antigen Design

Predictive Immunology

Prediction of escape and translation efficacy

Pathogen X

<u>Translational Candidate Development</u>

Animal Models

ex vivo models (organoids)

Vaccine Delivery Technology

Clinical Trials!

What priority research should be triggered immediately after the declaration of a pandemic?

- Sequence surveillance
- Population level sequence surveillance (for example, wastewater)
- Immune surveillance
- Structural surveillance
    - Expedite structural research.
    - Leverage existing knowledge on related viruses: we may know more than we think we do.
    - AI-enabled structural biology.
    - Facilitate cross-talk between different arms of a required response.