AI-Derived Antibodies are novel, diverse and pharmacologically active against multiple SARS-CoV-2 strains

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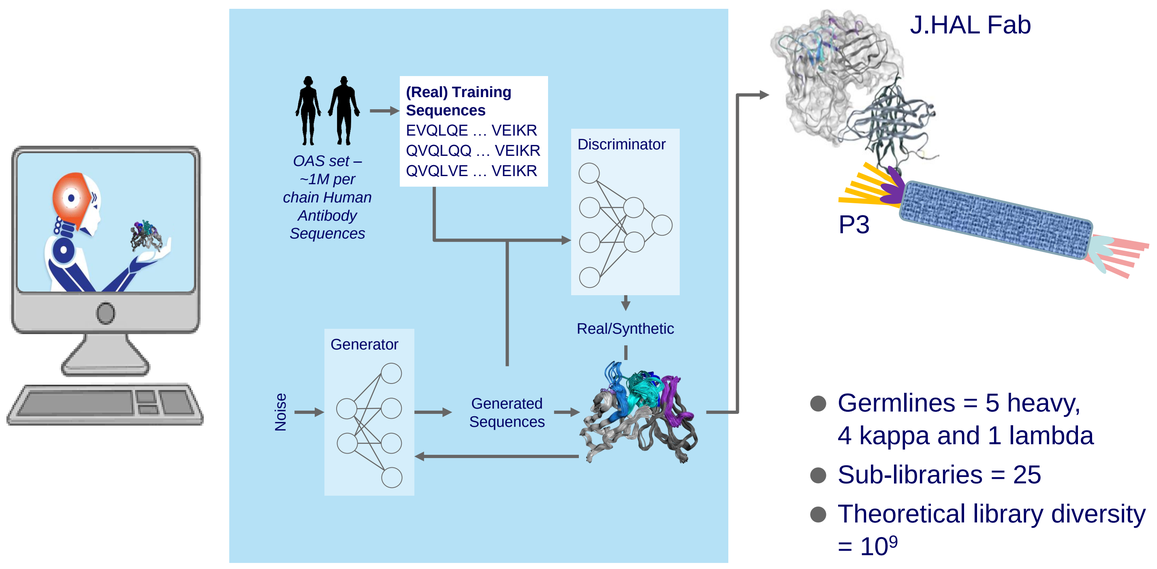
We have developed an AI-generated antibody library platform utilizing a Generative Adversarial Network (GAN) that generates novel sequences which mimic natural human response, as well biasing toward diversity and developability features.
The resulting Humanoid Antibody Library (J.HAL^{SM}) was successfully screened to obtain a panel of novel, diverse and pharmacologically active human antibodies against SARS-CoV-2.

J.HAL technology is a GAN application for antibody sequences

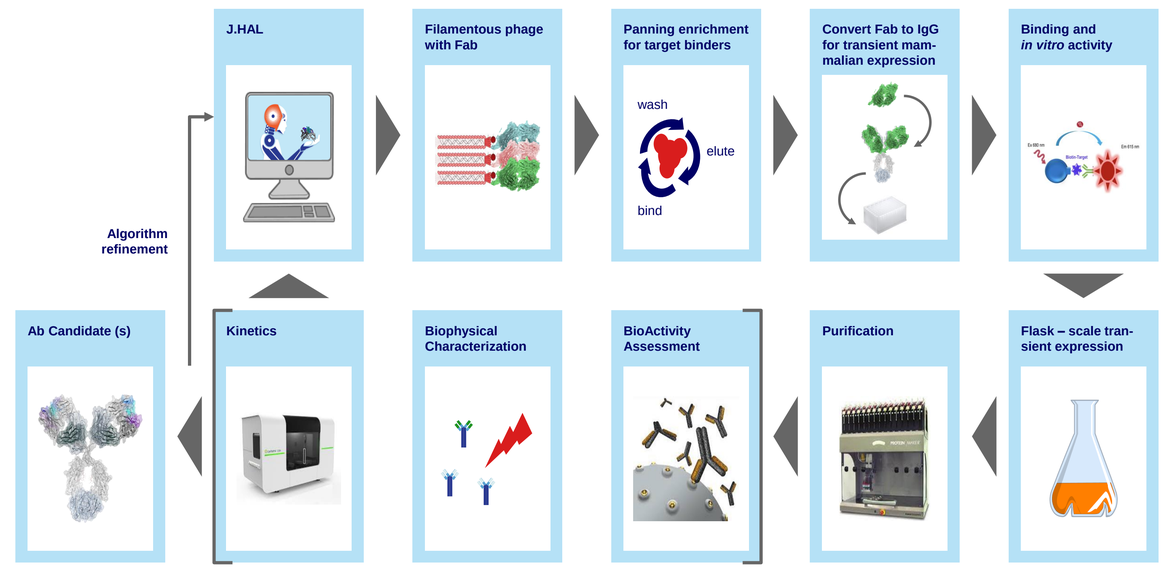


- Germlines = 5 heavy, 4 kappa and 1 lambda
- Sub-libraries = 25
- Theoretical library diversity = 10^9

- Trained on **real** mature human antibody sequences and built as a phage library
- Large, human-derived antibody sequence training set extracted from OAS
- GAN training models are germline specific
- Ability to generate synthetic humanoid large, diverse, combinatorial germline pairings for library creation
- GAN-generated **antibodies represent B-cell response – including full SHM**

Preprint available at bioRxiv *(https://www.biorxiv.org/content/10.1101/2020.04.12.024844v2)*

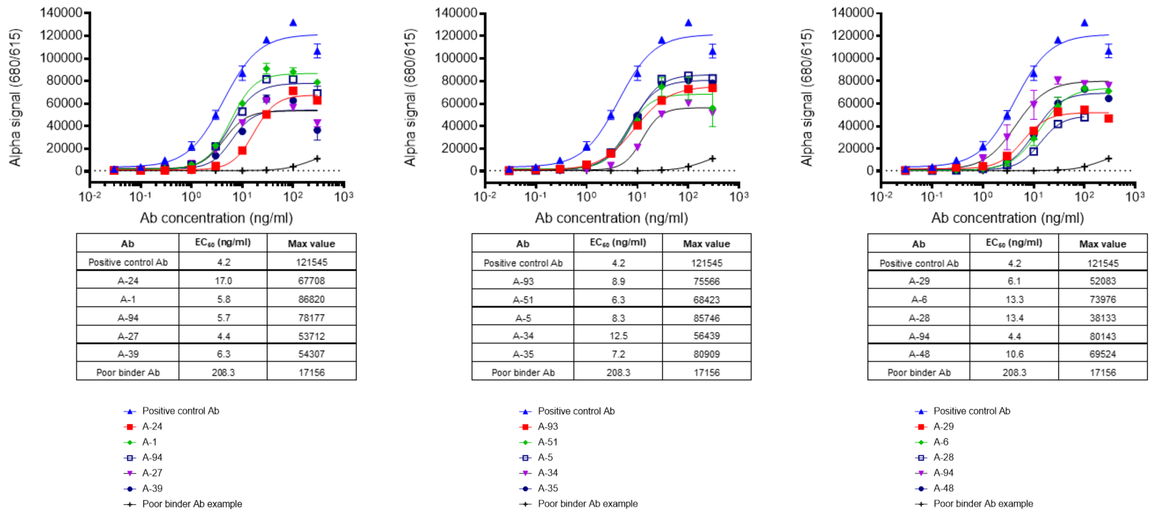
SARS-CoV-2 Antibody Discovery Workflow



- J.HAL Fab on phage panned on Wuhan RBD or on UK S1 antigens with increasing stringency
- Enriched Fab converted to IgG and transiently expressed in 293F cells at 96 deep well scale
- Unpurified transfection supernatants used for screening binding and activity assays
- Top candidates expressed at flask scale, purified and tested for SARS-CoV-2 neutralization ability across multiple strains

J.HAL IgG antibodies exhibit good binding to SARS-CoV-2 spike protein

Dose-dependent antibody binding to spike protein



Ab	EC_{50} (ng/ml)	Max value
Positive control Ab	4.2	121545
A-24	17.0	67708
A-1	5.8	86820
A-94	5.7	78177
A-27	4.4	53712
A-39	6.3	54307
Poor binder Ab	208.3	17156

Ab	EC_{50} (ng/ml)	Max value
Positive control Ab	4.2	121545
A-93	8.9	75566
A-51	6.3	68423
A-5	8.3	85746
A-34	12.5	56439
A-35	7.2	80909
Poor binder Ab	208.3	17156

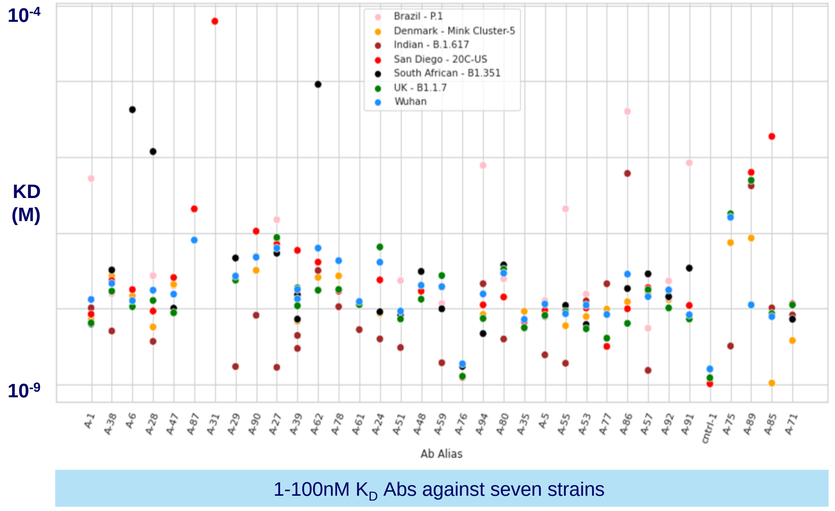
Ab	EC_{50} (ng/ml)	Max value
Positive control Ab	4.2	121545
A-29	6.1	52083
A-6	13.3	73976
A-28	13.4	38133
A-94	4.4	80143
A-48	10.6	69524
Poor binder Ab	208.3	17156

- Candidates that specifically bound SARS-CoV-2 spike protein and did not bind an irrelevant antigen were further characterized for dose-dependent binding using AlphaLISA technology
- A total of 73 unique antibody sequences specific for SARS-CoV-2 Spike protein were identified in the primary “yes/no” binding screen
- Binding assays were performed using unpurified transfection supernatants and later reproduced with purified material
- All antibody data are from **native library candidates without any affinity maturation**
- **Feasible to screen unpurified transfection supernatants to accelerate discovery timelines**

J.HAL IgG antibodies cross-react across multiple SARS-CoV-2 strains

Binding affinity measurements to spike protein from 7 SARS-CoV-2 strains

SPR conducted on Carterra LSA – purified material, averaged replicates shown

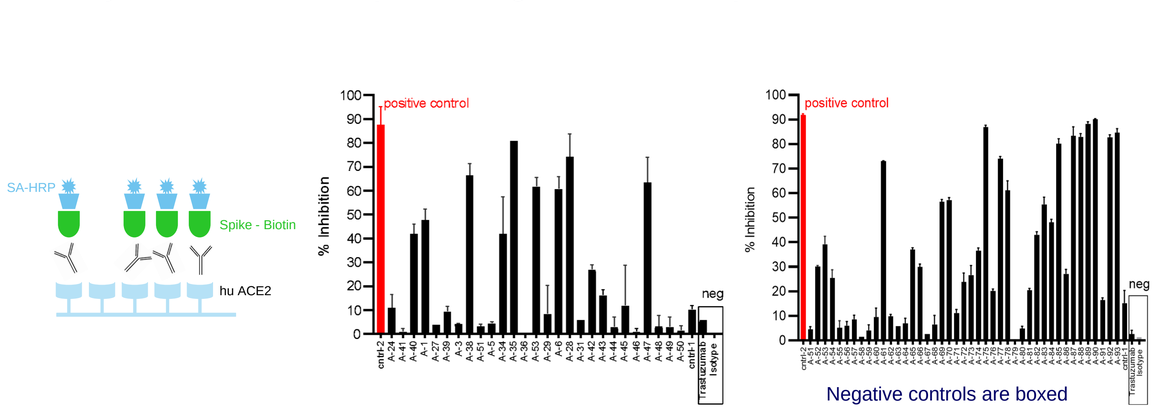


1-100nM K_D Abs against seven strains

- Binding of selected candidates to the spike protein from seven viral strains was characterized by SPR conducted on Carterra LSA
- SPR binding profiles of purified candidates matched the binding profiles of unpurified transient transfection supernatants
- All antibody data are from **native library candidates without any affinity maturation**
- **Feasible to utilize SPR technology to assess pan cross-reactivity of unpurified transfection supernatants to accelerate discovery timelines**

J.HAL IgG antibodies effectively block spike:huACE2R interaction

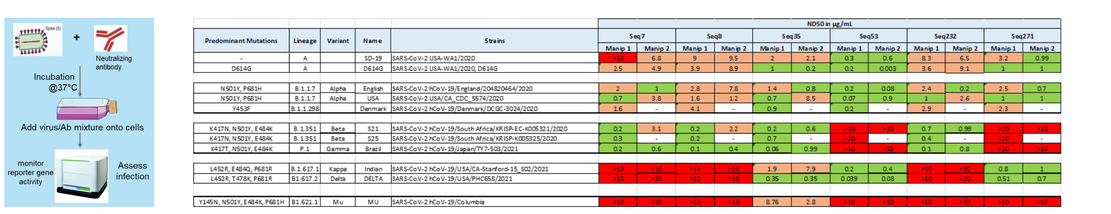
Antibody Blockade of SARS spike binding to hu ACE2 receptor



- Candidate antibody supernatants that specifically bound SARS-CoV-2 Spike protein were tested for their ability to block binding of SARS-CoV-2 spike protein to human ACE-2 receptor
- Multiple antibodies identified that effectively block spike: human ACE2 receptor interaction
- **Feasible to screen unpurified transfection supernatants for functional activity**

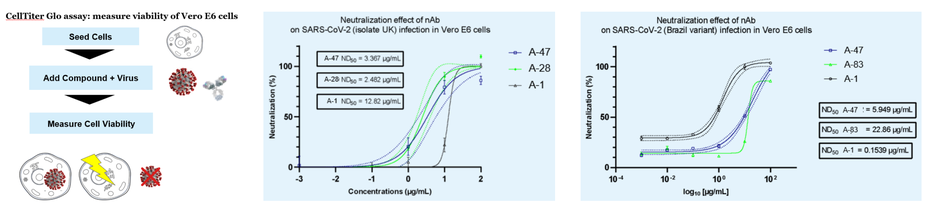
J.HAL IgG antibodies neutralize multiple strains of SARS-CoV-2

Spike-pseudotyped VSV model and J.HAL Abs summary of activity



Predominant Mutations	Lineage	Variant	Name	Strains	ND50 in µg/mL Seq7 M1	Seq7 M2	Seq8 M1	Seq8 M2	Seq35 M1	Seq35 M2	Seq53 M1	Seq53 M2	Seq232 M1	Seq232 M2	Seq271 M1	Seq271 M2
-	A		SD-19	SARS-CoV-2 USA-WA1/2020	>10	6.8	9	9.5	2	2.1	0.3	0.6	8.3	6.5	3.2	0.99
D614G	A		D614G	SARS-CoV-2 USA-WA1/2020, D614G	2.5	4.9	3.9	8.9	1	0.2	0.2	0.003	3.6	9.1	1	1
N501Y, P681H	B.1.1.7	Alpha	English	SARS-CoV-2 hCoV-19/England/204820464/2020	2	1	2.8	7.8	1.4	0.8	0.2	0.08	2.4	0.2	2.5	0.7
N501Y, P681H	B.1.1.7	Alpha	USA	SARS-CoV-2 USA/CA_CDC_5574/2020	0.7	3.8	1.6	1.2	0.7	8.5	0.07	0.9	1	2.6	1	1
Y453F	B.1.1.298		Denmark	SARS-CoV-2 hCoV-19/Denmark/DCOC-3024/2020	1.6	-	4.1	-	0.9	-	0.2	-	2.9	-	2.3	-
K417N, N501Y, E484K	B.1.351	Beta	S21	SARS-CoV-2 hCoV-19/South Africa/KRISP-EC-K005321/2020	0.2	3.1	0.2	2.2	0.2	0.6	>10	>10	0.7	0.99	>10	>10
K417N, N501Y, E484K	B.1.351	Beta	S25	SARS-CoV-2 hCoV-19/South Africa/KRISP-K005325/2020	0.3	-	0.2	-	0.7	-	>10	-	0.4	-	>10	-
K417T, N501Y, E484K	P.1	Gamma	Brazil	SARS-CoV-2 hCoV-19/Japan/TY7-503/2021	0.2	0.6	0.1	0.4	0.06	0.99	>10	>10	0.1	0.8	>10	>10
L452R, E484Q, P681R	B.1.617.1	Kappa	Indian	SARS-CoV-2 hCoV-19/USA/CA-Stanford-15_S02/2021	>10	>10	>10	>10	1.9	7.9	0.2	0.4	>10	>10	0.8	1
L452R, T478K, P681R	B1.617.2	Delta	DELTA	SARS-CoV-2 hCoV-19/USA/PHC658/2021	>10	>10	>10	>10	0.35	0.35	0.039	0.08	>10	>10	0.51	0.7
Y145N, N501Y, E484K, P681H	B1.621.1	Mu	MU	SARS-CoV-2 hCoV-19/Columbia	>10	>10	>10	>10	8.76	2.8	>10	>10	>10	>10	>10	>10

SARS-CoV-2 infection model and examples of J.HAL Abs neutralization activity



Positive control Ab:UK, ND_{50} = 0.223 ug/mL

- Neutralization ability of candidate antibodies was assessed using VSV pseudotyped-system harboring the spike envelope glycoprotein of SARS-CoV-2; multiple strains were evaluated
- Multiple candidates were demonstrated to have neutralizing activity against several strains of SARS-CoV-2
- All antibody data are from **native library candidates without any affinity maturation**

Acknowledgements: Danielle van Citters, Kathryn McLean, Lindsay Pautsch, Caroline Carbonelle, Fred Hutch Carterra LSA SPR facility

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