Quale ruolo per gli anticorpi monoclonali in infettivologia?

Dott.ssa Lucia Taramasso

Clinica Malattie Infettive

IRCCS Policlinico San Martino di Genova

General Benefits of mAb Therapy in Clinical Practice

Effective[a,b]

- Reduce viral load
- Prevent progression to severe disease
- Could reduce morbidity and mortality

Fast[a]

- Effects are more rapid than vaccination

Provides an alternative[b]

- Important for those who are unable to be vaccinated
- Areas with low vaccine coverage
- New emerging variants

a. Marovich M, et al. *JAMA*. 2020;324:131-132; b. Lloyd EC, et al. *JAMA*. 2021;325:1015.

Antibodies (and Mab): three mechanisms of action

Complement-dependent cytotoxicity

C1q binds to the Fc region of antibody–antigen complex, initiating the classical pathway that ends in cell lysis

Antibody-dependent cellular cytotoxicity

FcγRIII binds to antibody–antigen complex, initiating signalling pathways that lead to granzyme and perforin release, killing infected cells

Antibody-dependent phagocytosis

Macrophage FcγRs recognize antibody–antigen complex, initiating signalling pathways that lead to infected-cell phagocytosis

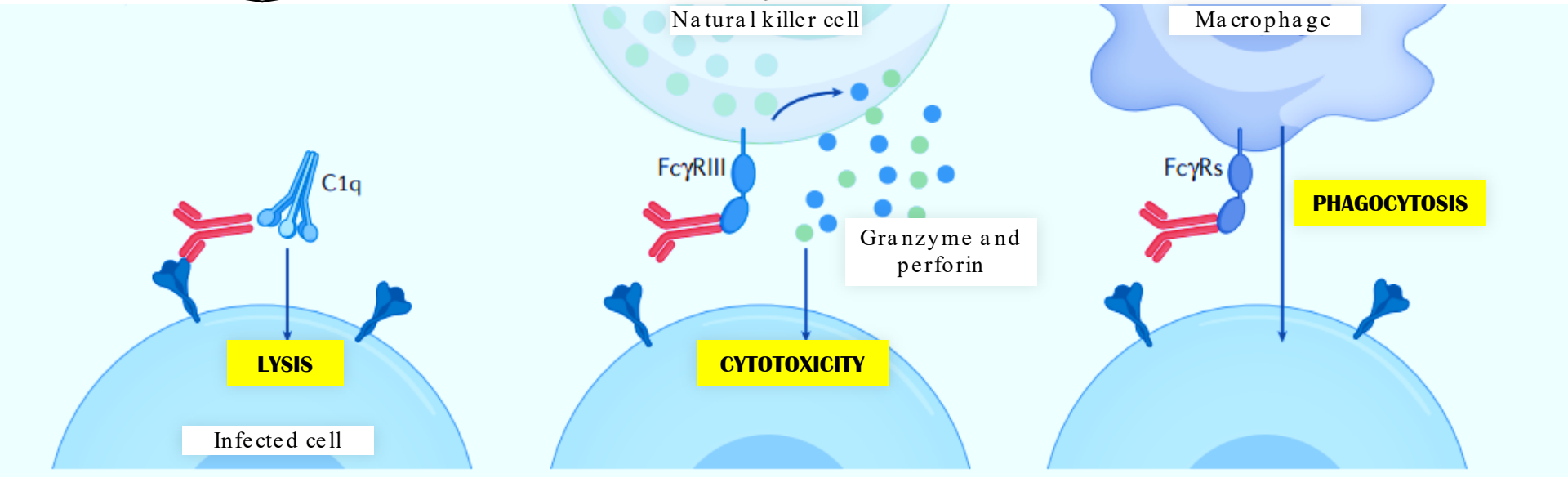
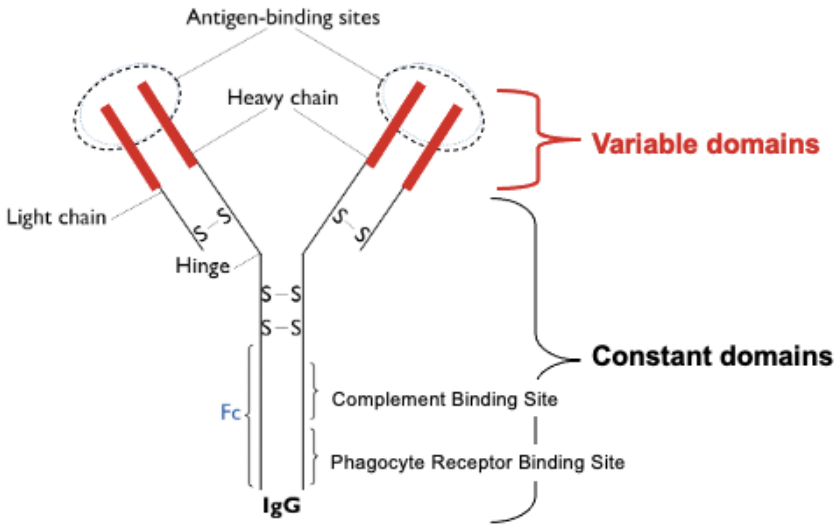
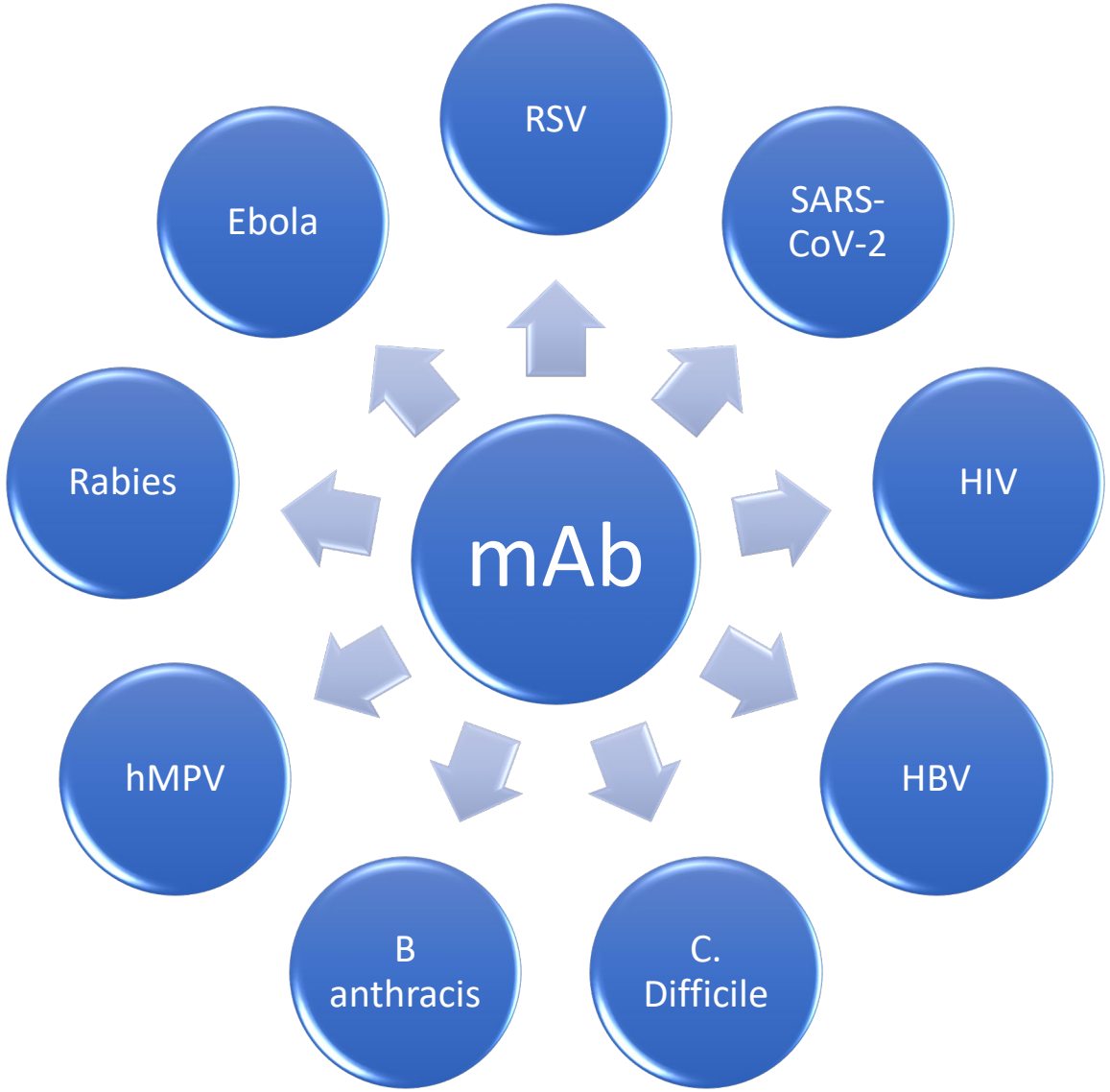


Figure 1 modified from Antibodies to combat viral infections: development strategies and progress | Nature Reviews Drug Discovery

Prophylaxis or therapy





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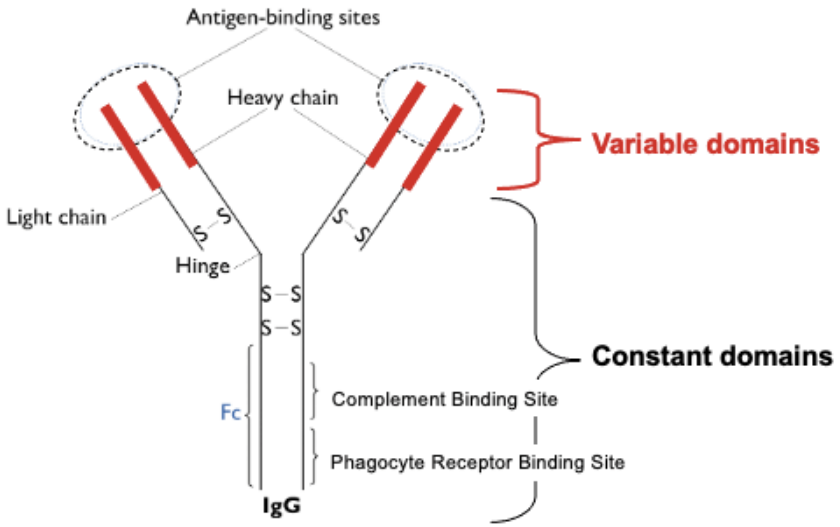
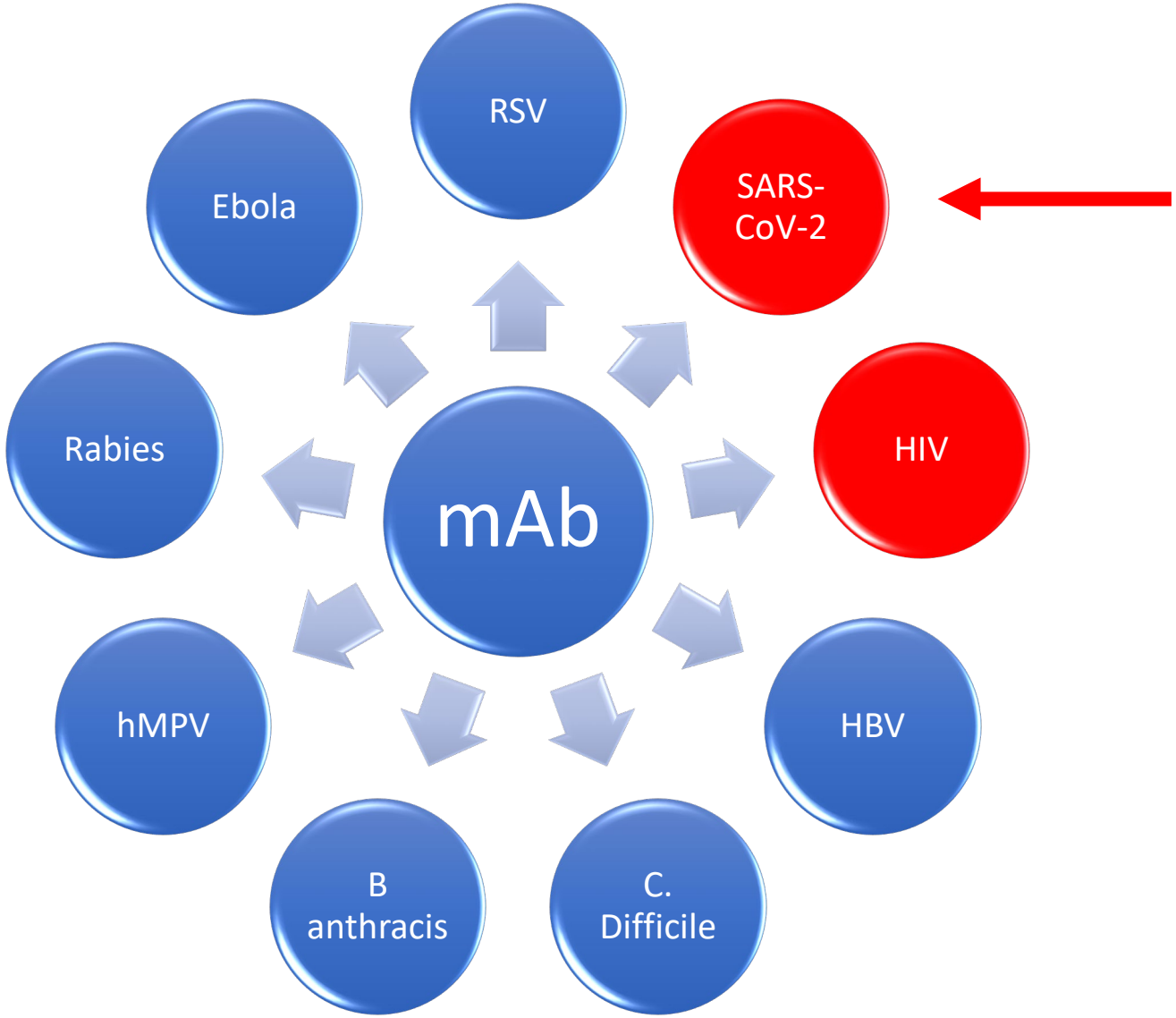
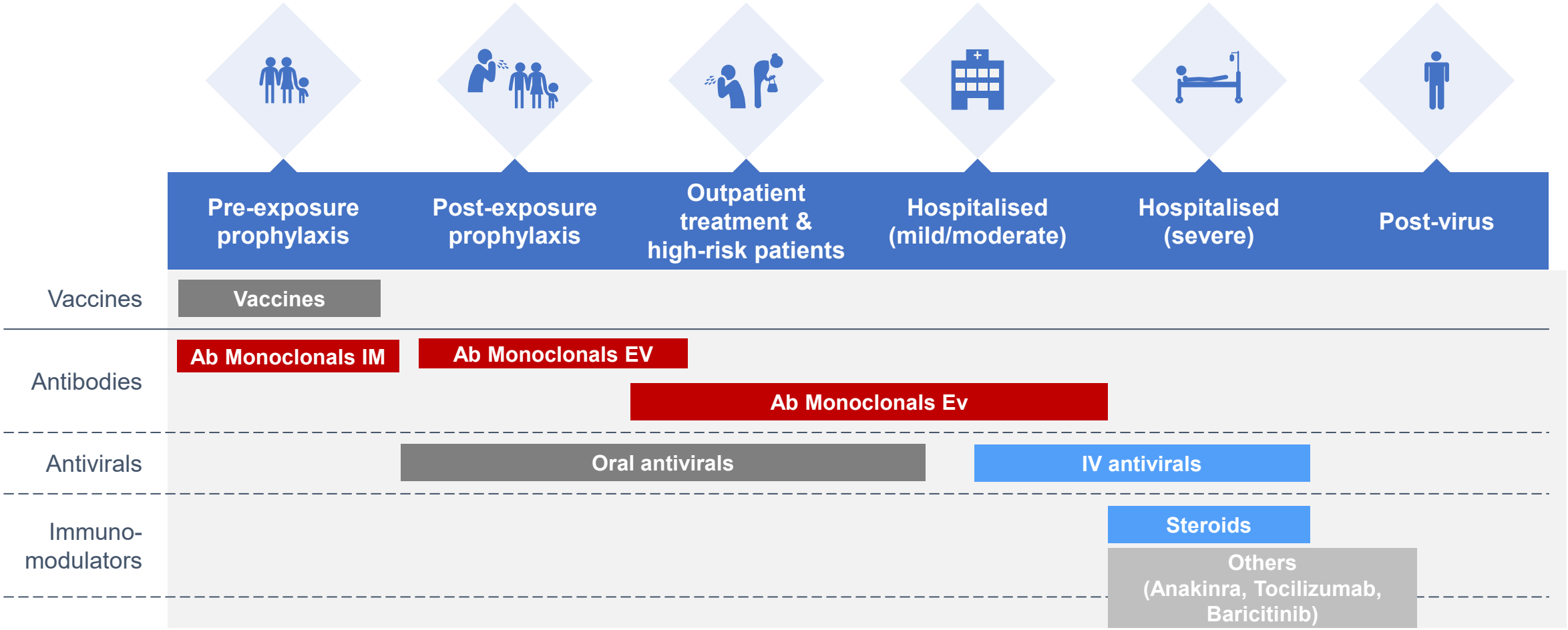




Potential role in the treatment of COVID-19

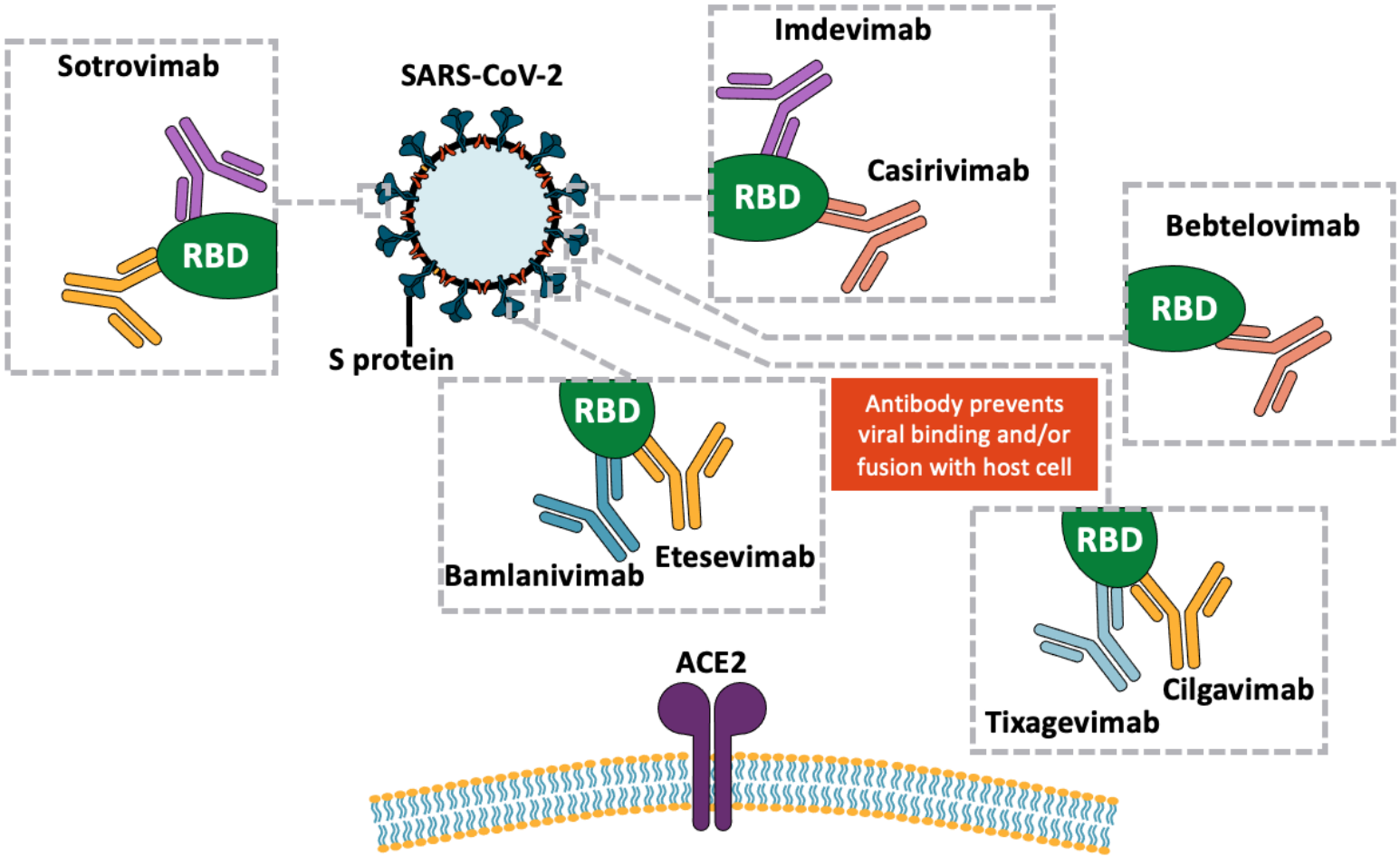
(based on available data)



*

Song. Int J Antimicrob Agents 2020; Xu. Mil Med Res 2020; Pascarella. J Intern Med 2020

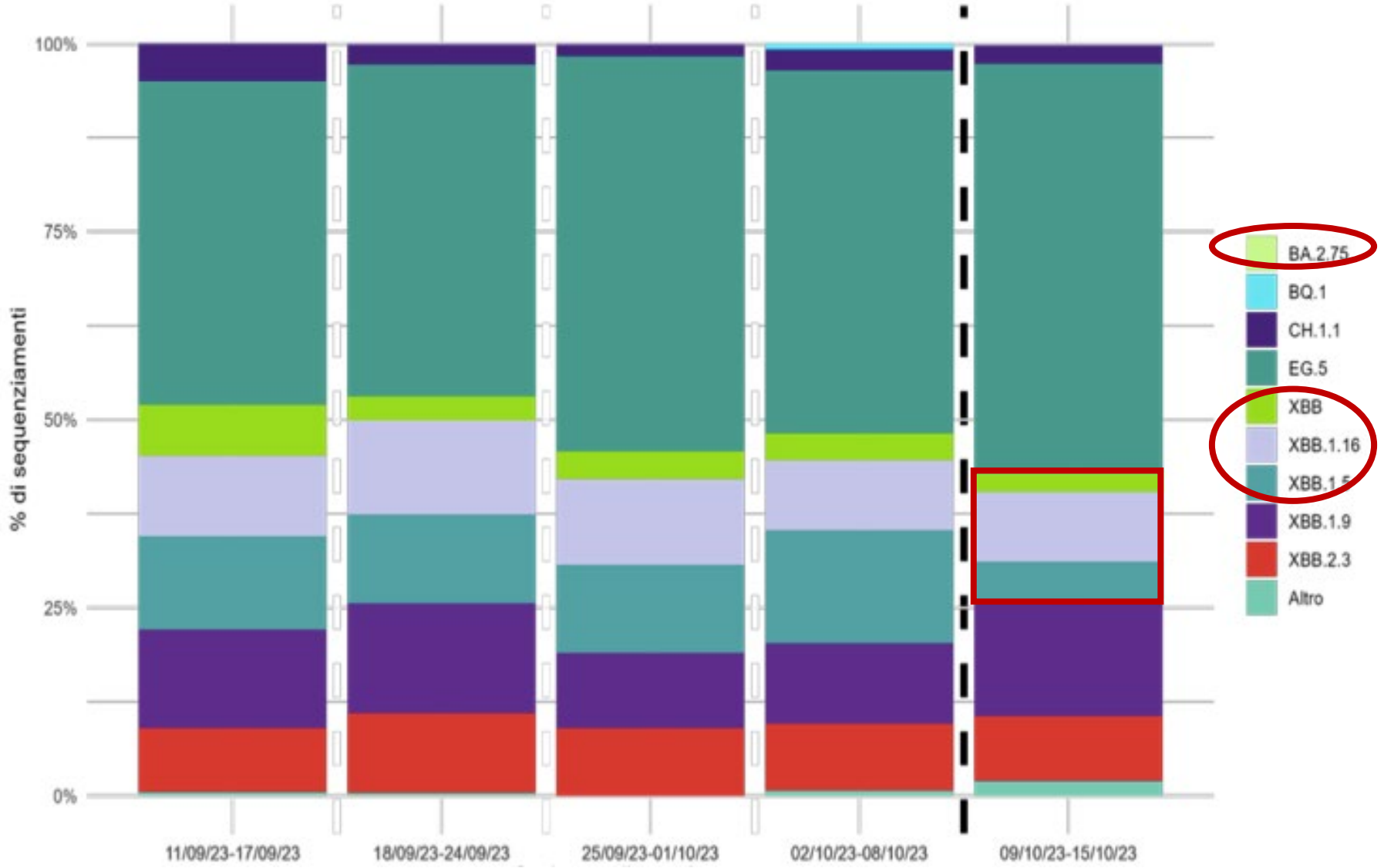
Monoclonal Antibodies Against SARS-CoV-2



Taylor. Nat Rev Immuno. 2021;21:382.

RBD, receptor-binding domain

Monitoraggio delle varianti di SARS-CoV-2



Bollettino ISS 28/10/2023

https://www.epicentro.iss.it/coronavirus/bollettino/Bollettino-sorveglianza-integrata-COVID-19_25-ottobre-2023.pdf

Fold reduced neutralizing susceptibility to monoclonal antibodies under Emergency Use Authorization (EUA)

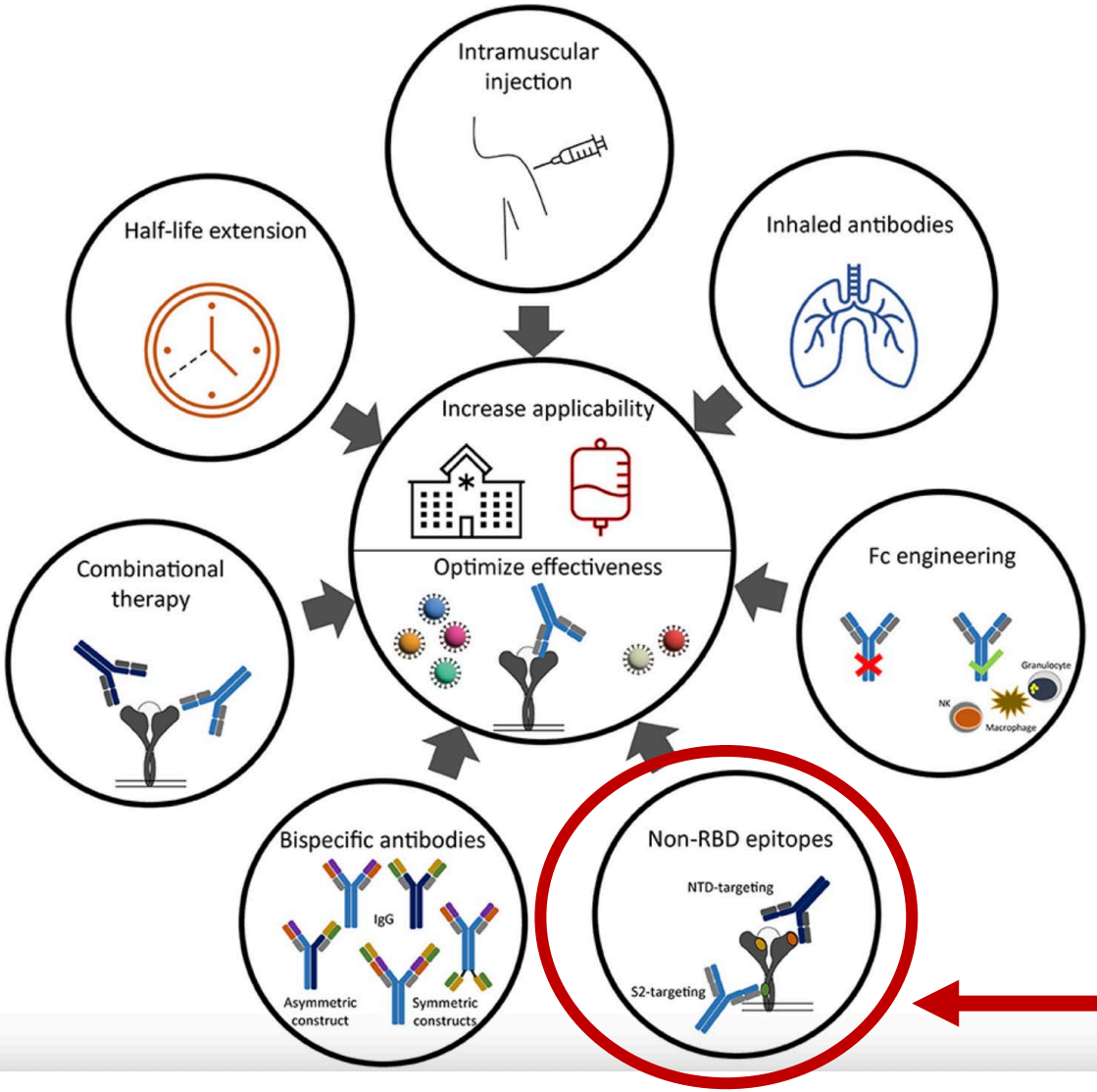
Test mAb	ETE: fold	CAS: fold	IMD: fold	CAS/IMD: fold	CIL: fold	TIX: fold	CIL/TIX: fold	SOT: fold	BEB: fold	ADI: fold
Omicron/BA.2.75	383	477	1000	1000	13	29	24	12	3.1	437
Omicron/XBB	1000	589	588	200	1000	1000	738	14	1000	1000
Omicron/XBB.1.5	-	650	572	751	433	1000	867	18	800	-
Omicron/XBB.1.16	-	420	143	615	127	448	488	5.3	149	-
Omicron/BQ.1	-	177	175	200	1000	1000	1000	26	900	-
Omicron/BQ.1.1	972	1000	1000	1000	1000	1000	1000	118	1000	1000
CH.1.1 no data	no data	no data	no data	no data	no data	no data	no data	no data	no data	no data
EG.5 no data	no data	no data	no data	no data	no data	no data	no data	no data	no data	no data
XBB.1.9	no data	no data	no data	no data	no data	no data	no data	no data	no data	no data
XBB.2.3	no data	no data	no data	no data	no data	no data	no data	no data	no data	no data

Stanford University database last accessed November 3, 2023

Optimization of Anti-SARS-CoV-2 Neutralizing Antibody Therapies: Roadmap to Improve Clinical Effectiveness and Implementation

*Karlijn van der Straten [1,2], Marit J. van Gils [1], Steven W. de Taeye [1] and Godelieve J. de Bree [2]**

[1] Department of Medical Microbiology and Infection Prevention, Amsterdam Institute for Infection and Immunity, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands, [2] Department of Internal Medicine, Amsterdam Institute for Infection and Immunity, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands

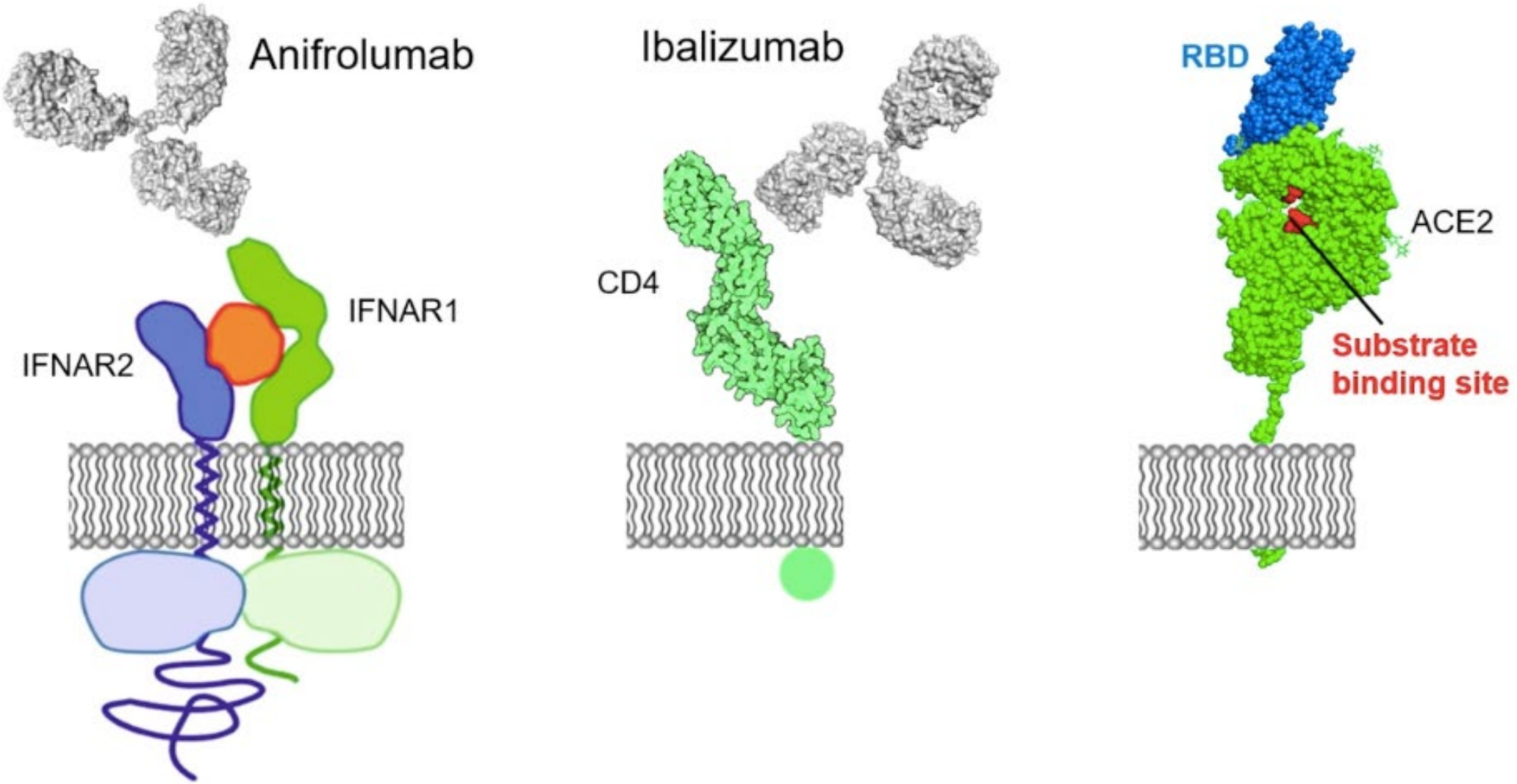


two main drawbacks

mAbs developed for therapy are produced by human immune systems, and the most potent of them are very similar to neutralizing antibodies commonly elicited by infection or vaccination

not feasible to pre-emptively generate spike-targeting mAb therapeutics or prophylactics that offer reliable and effective protection against an emergent virus

Can we use monoclonal antibody therapeutics against a highly variable target?



Bieniasz PD, Abstract # 107, CROI 2023

nature microbiology

Article

https://doi.org/10.1038/s41564-023-01389-9

Pan-sarbecovirus prophylaxis with human anti-ACE2 monoclonal antibodies

Received: 29 September 2022

Accepted: 19 April 2023

Published online: 15 May 2023

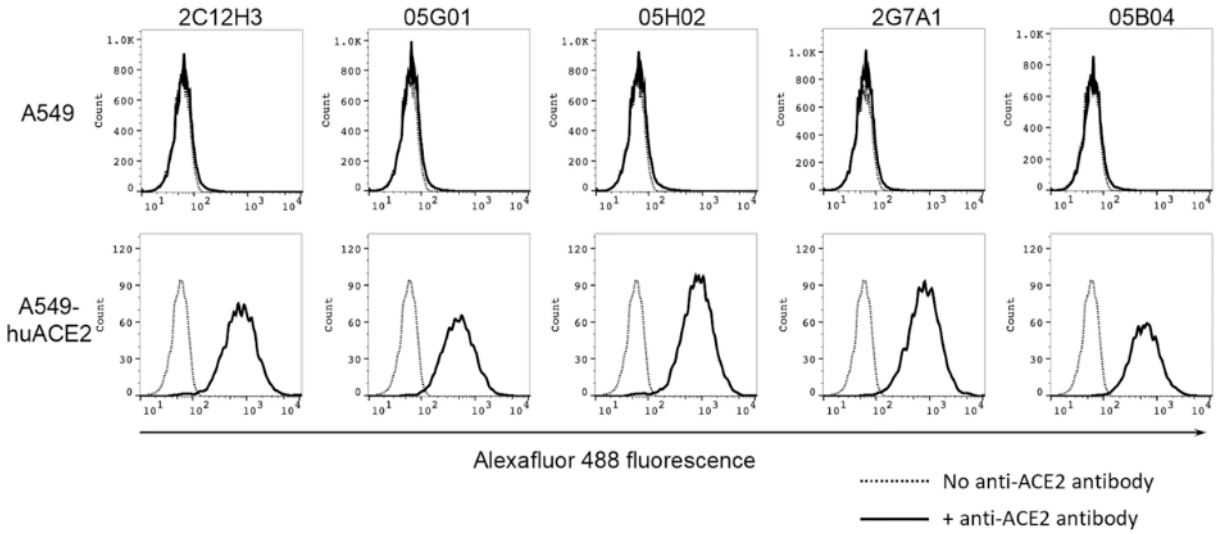
Check for updates

Fengwen Zhang[1], Jesse Jenkins[1], Renan V. H. de Carvalho[2], Sandra Nakandakari-Higa[2], Teresia Chen[3], Morgan E. Abernathy[3], Viren A. Baharani[1], Elisabeth K. Nyakatura[4], David Andrew[4], Irina V. Lebedeva[4], Ivo C. Lorenz[4], H.-Heinrich Hoffmann[5], Charles M. Rice[5], Gabriel D. Victora[2], Christopher O. Barnes[3,6], Theodora Hatziioannou[1] & Paul D. Bieniasz[1,7]

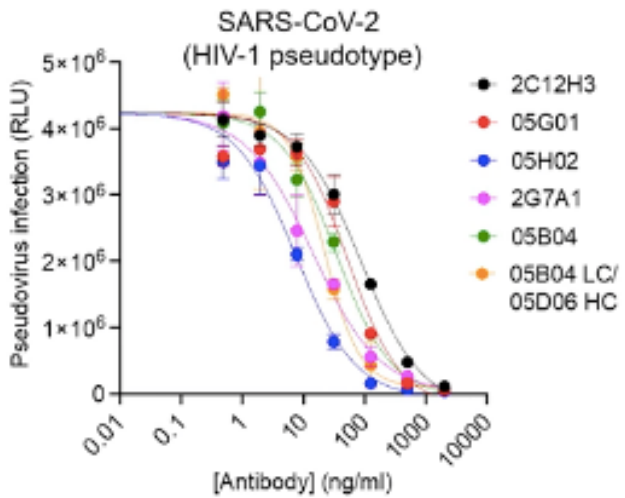
This work reports the generation of a set of six human mAbs that bind the human angiotensin-converting enzyme-2 (hACE2) receptor, rather than the SARS-CoV-2 spike protein.

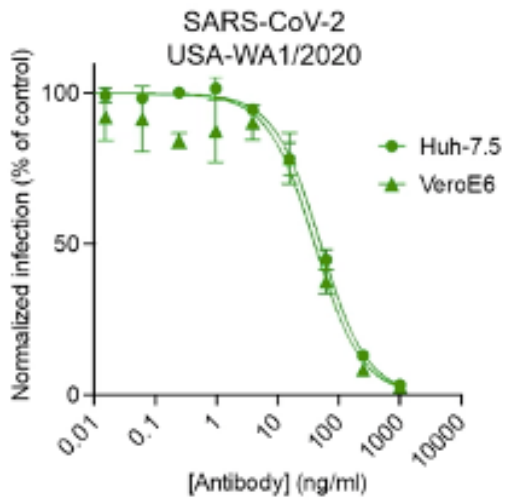
Zhang et al., Nat Microbiol. 2023;8(6):1051-1063

Human anti-human hACE2 antibodies



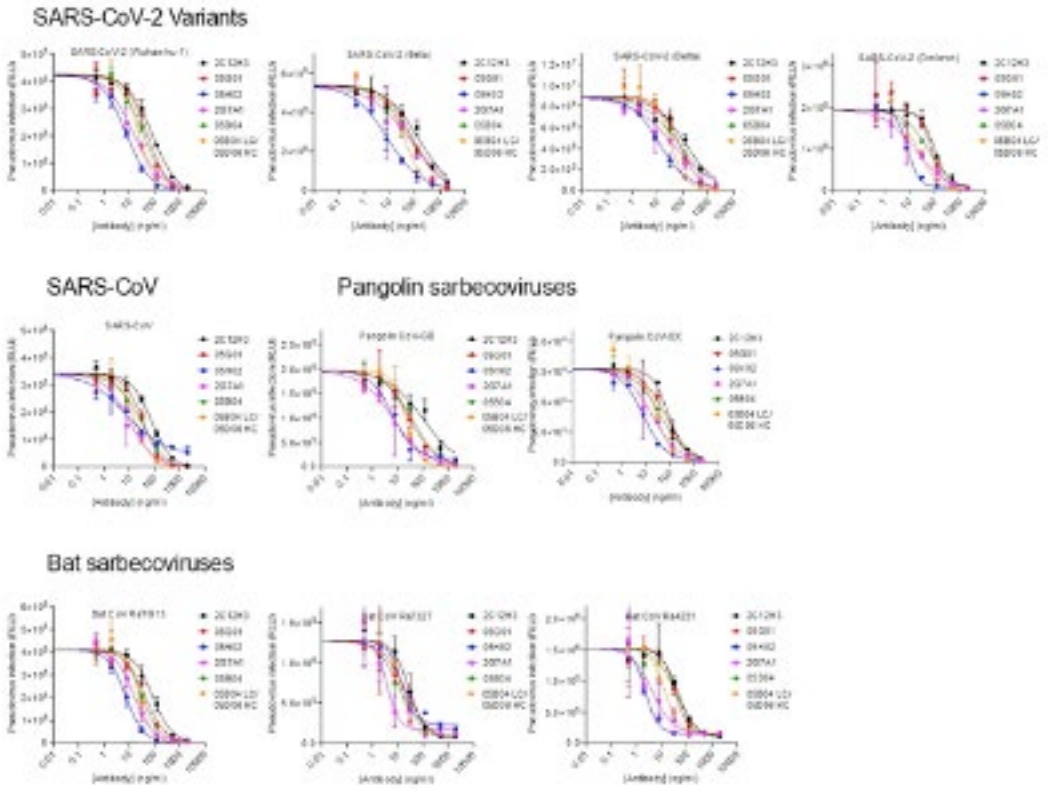
Inhibition of SARS-CoV-2 infection by human anti-human hACE2 antibodies



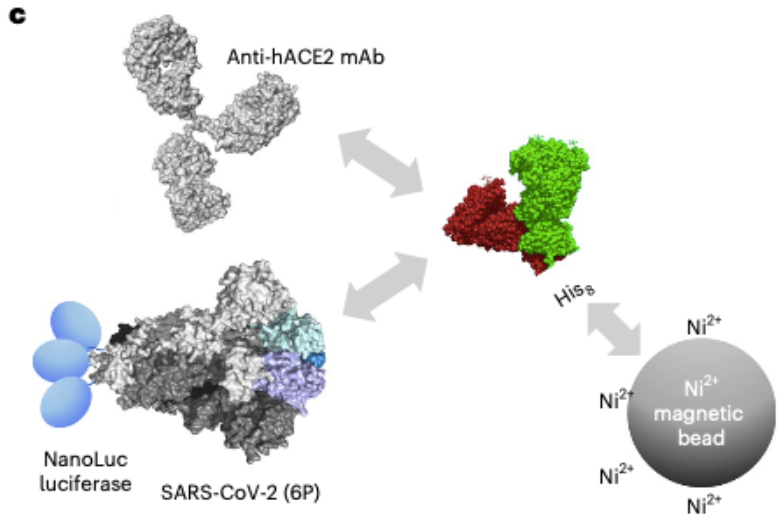


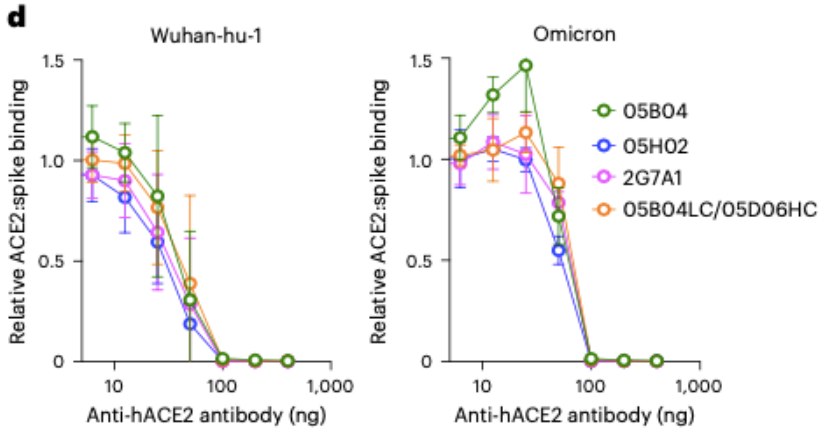
- Selective binding to cells that express ACE-2 and not to cells that don't
- High affinity
- IC50 mantained across SARS-CoV-2 variants

Broad inhibition of sarbecovirus pseudotype infection

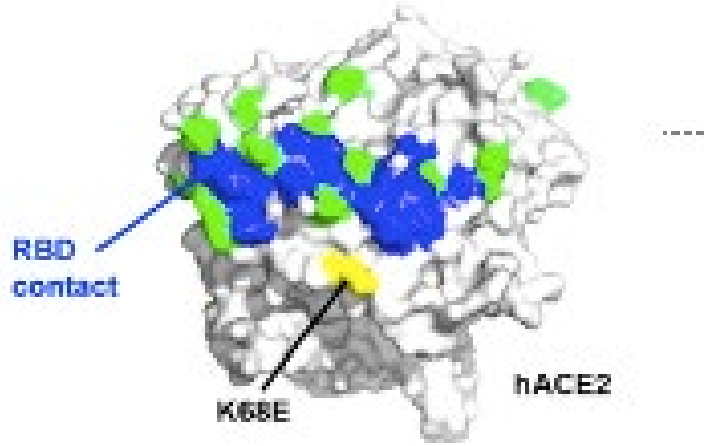


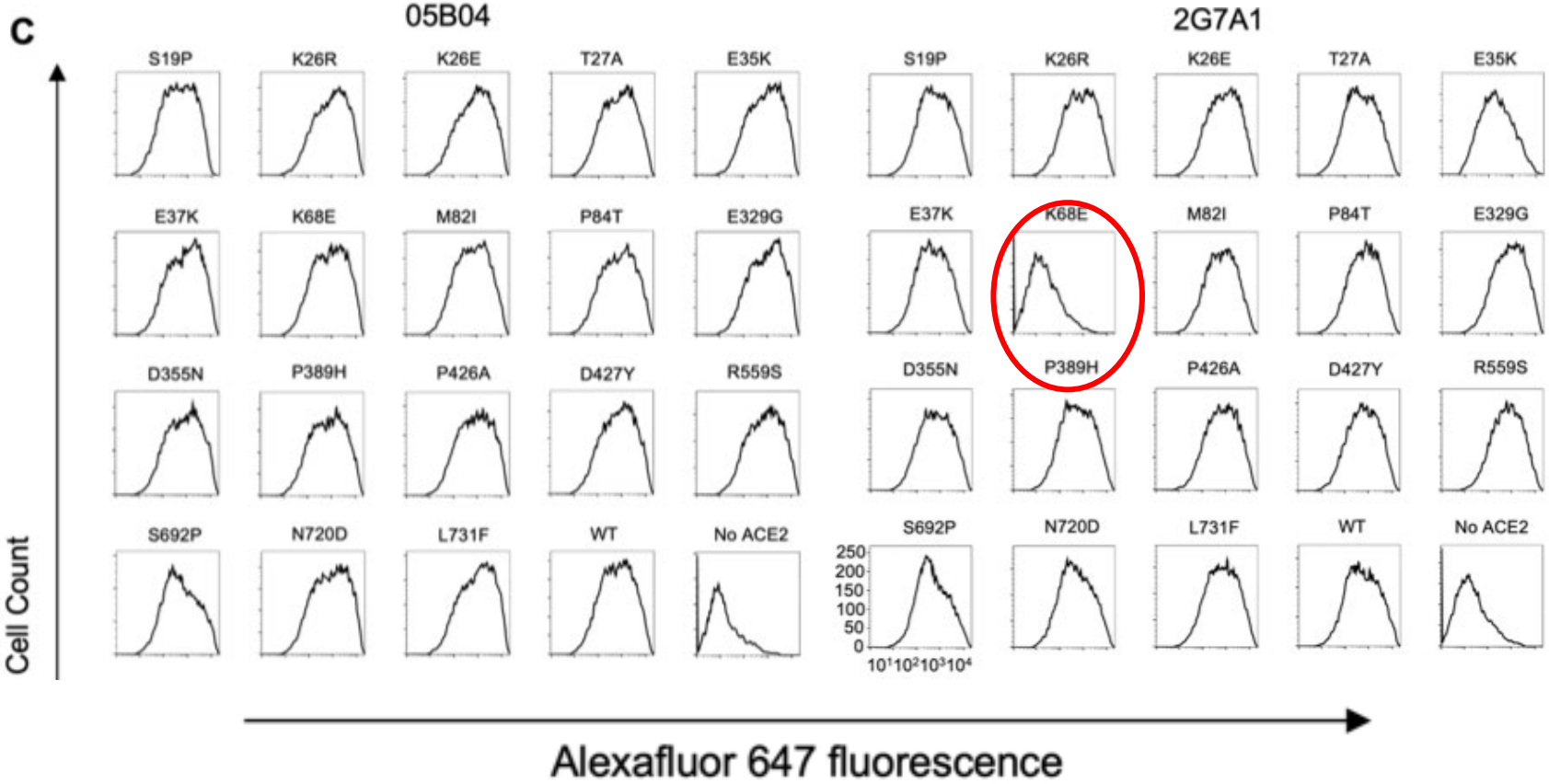
Zhang et al., Nat Microbiol. 2023;8(6):1051-1063





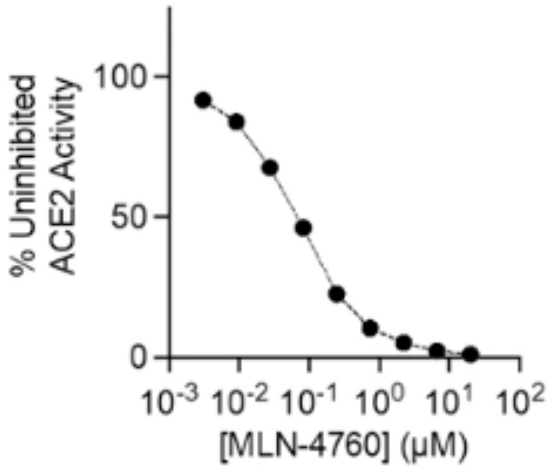
Human anti-human hACE2 antibodies block spike-ACE2 binding

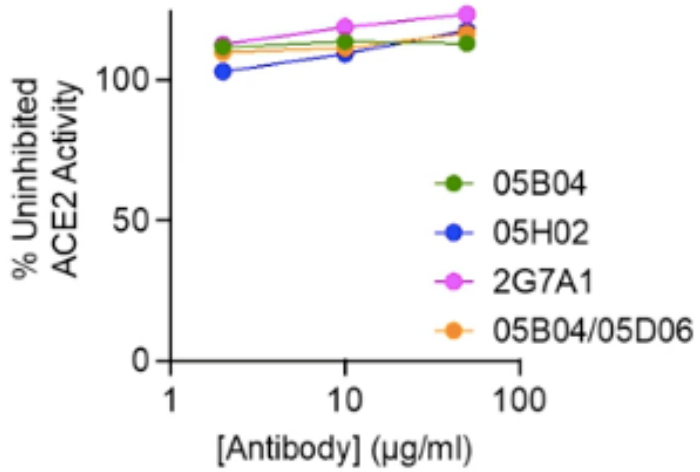


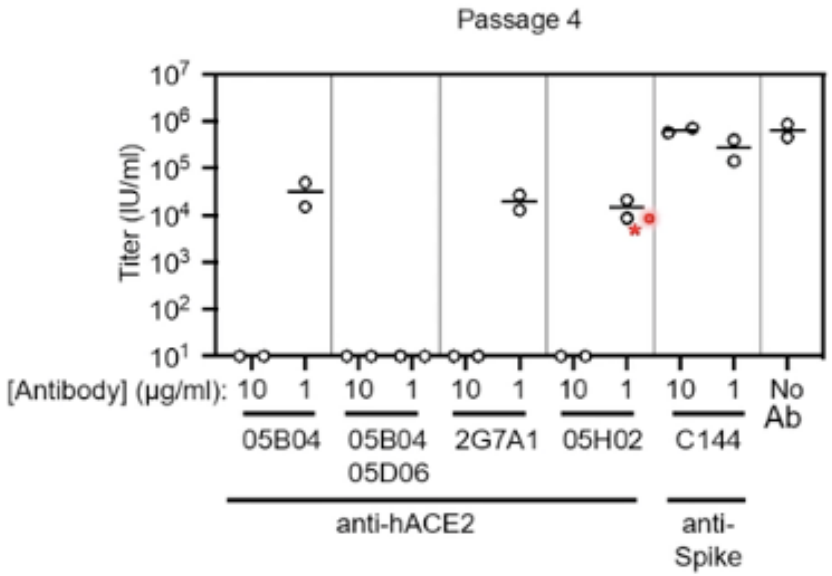


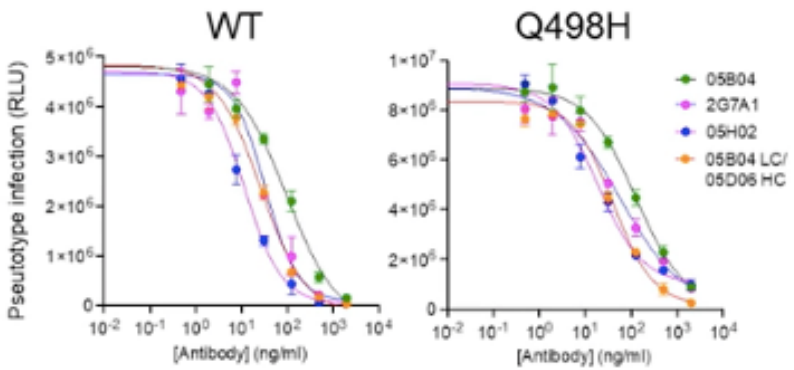
Human ACE2 polymorphisms rarely affect anti-ACE2 binding

Human anti-human ACE2 antibodies do not inhibit ACE2 activity

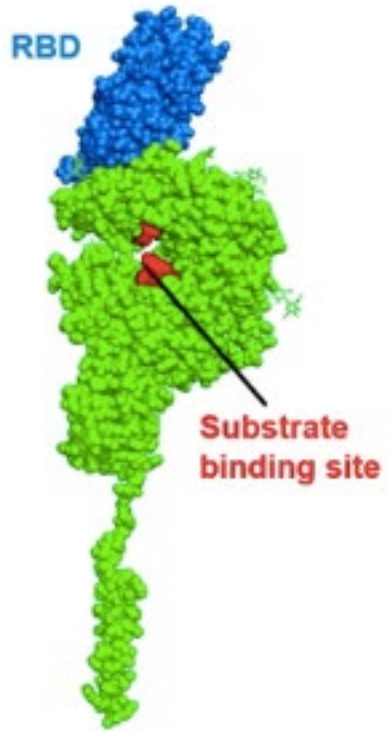






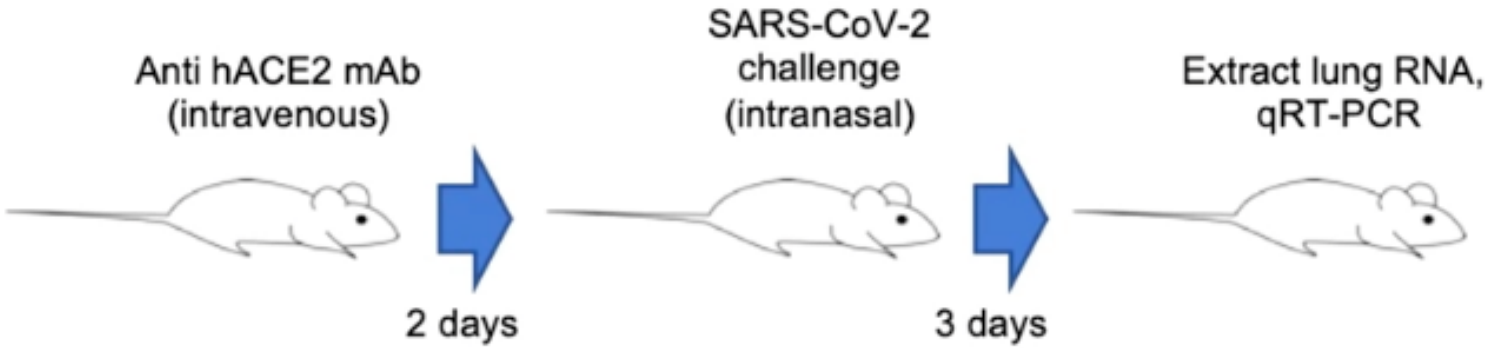


		05B04	05B04 LC/ 05D06 HC	2G7A1	05H02
IC50 (ng/ml)	WT	97	27	33	12
	Q498H	124	40	57	18

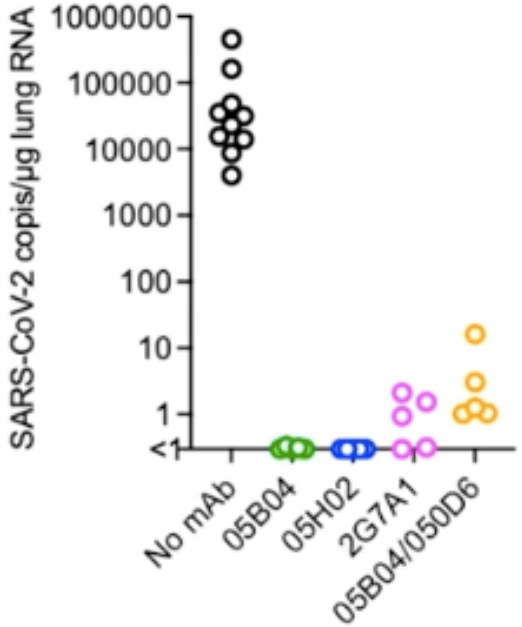


They have high genetic barrier to anti ACE2 antibody resistance

Human anti-human ACE2 antibodies protect human ACE2 knock-in mice from SARS-CoV-2



Pre-treatment of the mice with any one of the four anti-hACE2 mAbs, reduced SARS-CoV-2 replication in lungs, to levels below or close to the limit of detection (~1 copy of viral RNA per µg total RNA)

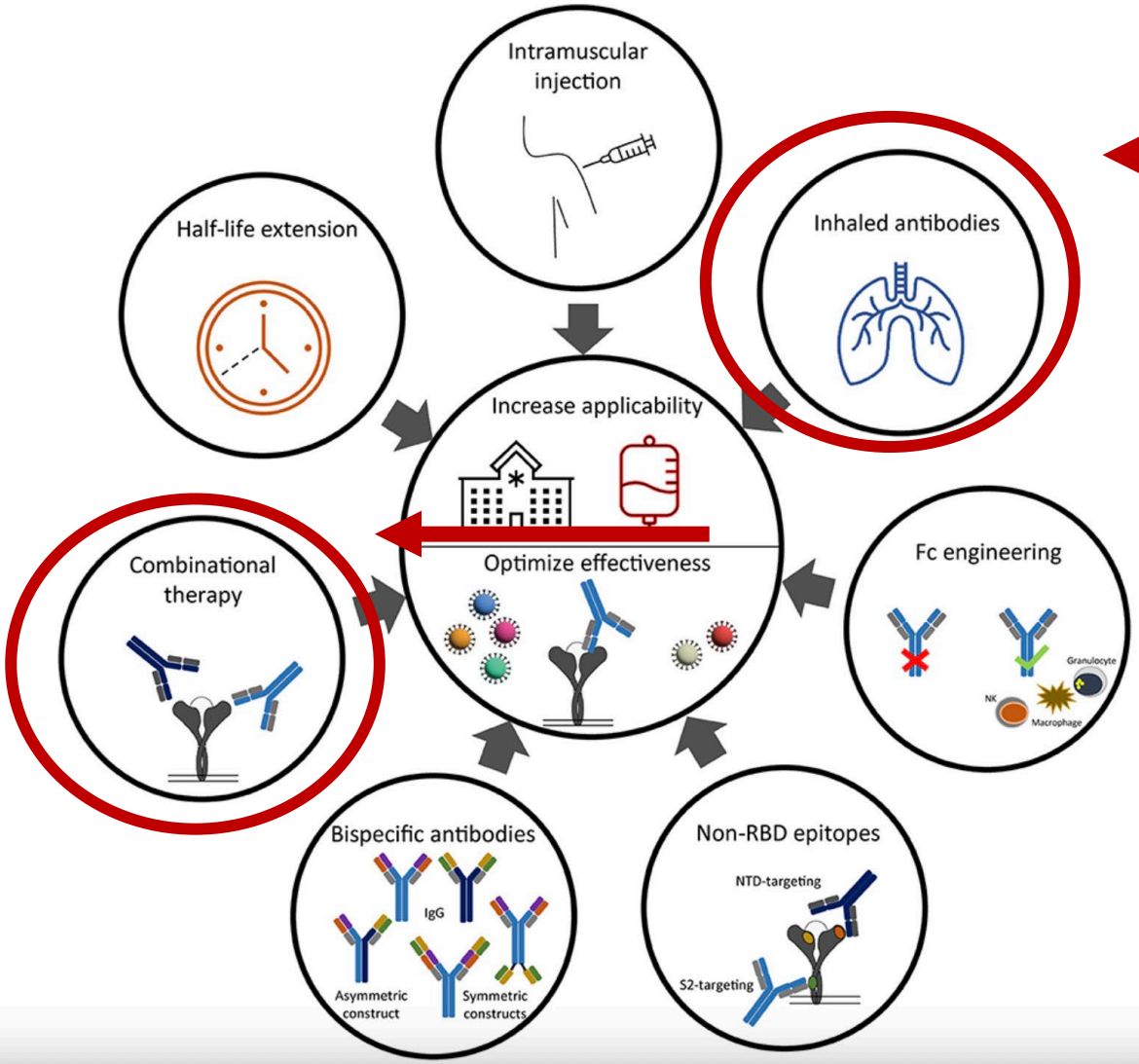


These antibodies might be useful prophylactic and treatment agents against any current or future SARS-CoV-2 variants and might be useful to treat infection with any hACE2-binding sarbecoviruses that emerge in the future.

Optimization of Anti-SARS-CoV-2 Neutralizing Antibody Therapies: Roadmap to Improve Clinical Effectiveness and Implementation

*Karlijn van der Straten [1,2], Marit J. van Gils [1], Steven W. de Taeye [1] and Godelieve J. de Bree [2]**

[1] Department of Medical Microbiology and Infection Prevention, Amsterdam Institute for Infection and Immunity, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands, [2] Department of Internal Medicine, Amsterdam Institute for Infection and Immunity, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands



two main drawbacks

mAbs developed for therapy are produced by human immune systems, and the most potent of them are very similar to neutralizing antibodies commonly elicited by infection or vaccination

not feasible to pre-emptively generate spike-targeting mAb therapeutics or prophylactics that offer reliable and effective protection against an emergent virus

Safety and efficacy of inhaled IBIO123 for mild-to-moderate COVID-19: a randomised, double-blind, dose-ascending, placebo-controlled, phase 1/2 trial

Bruno Maranda, Sébastien M Labbé*, Magali Lurquin, Pascal Brabant, Alexandre Fugère, Jean-François Larrivée, Djordje Grbic, Annie Leroux, Frédéric Leduc, Andrés Finzi, Simon Gaudreau, Yolandi Swart, on behalf of the IBIO-INH-001 Investigators†*

Lancet Infect Dis 2023

Published Online
August 21, 2023
https://doi.org/10.1016/
S1473-3099(23)00393-6

IBIO123 is a cocktail of three, fully human, neutralising monoclonal antibodies against SARS-CoV-2. This work aims to assess the safety and efficacy of inhaled IBIO123 in individuals with mild-to-moderate COVID-19.

Double-blind, dose-ascending, placebo-controlled, first-in-human, phase 1/2 trial

Recruited symptomatic and non-hospitalised participants with COVID-19 in South Africa and Brazil across 11 centres

In phase 1, the primary outcome was the safety assessment in the safety population (ie, all participants who received an intervention). In phase 2, the primary outcome was the mean absolute change from baseline to day 5 in SARS-CoV-2 viral load

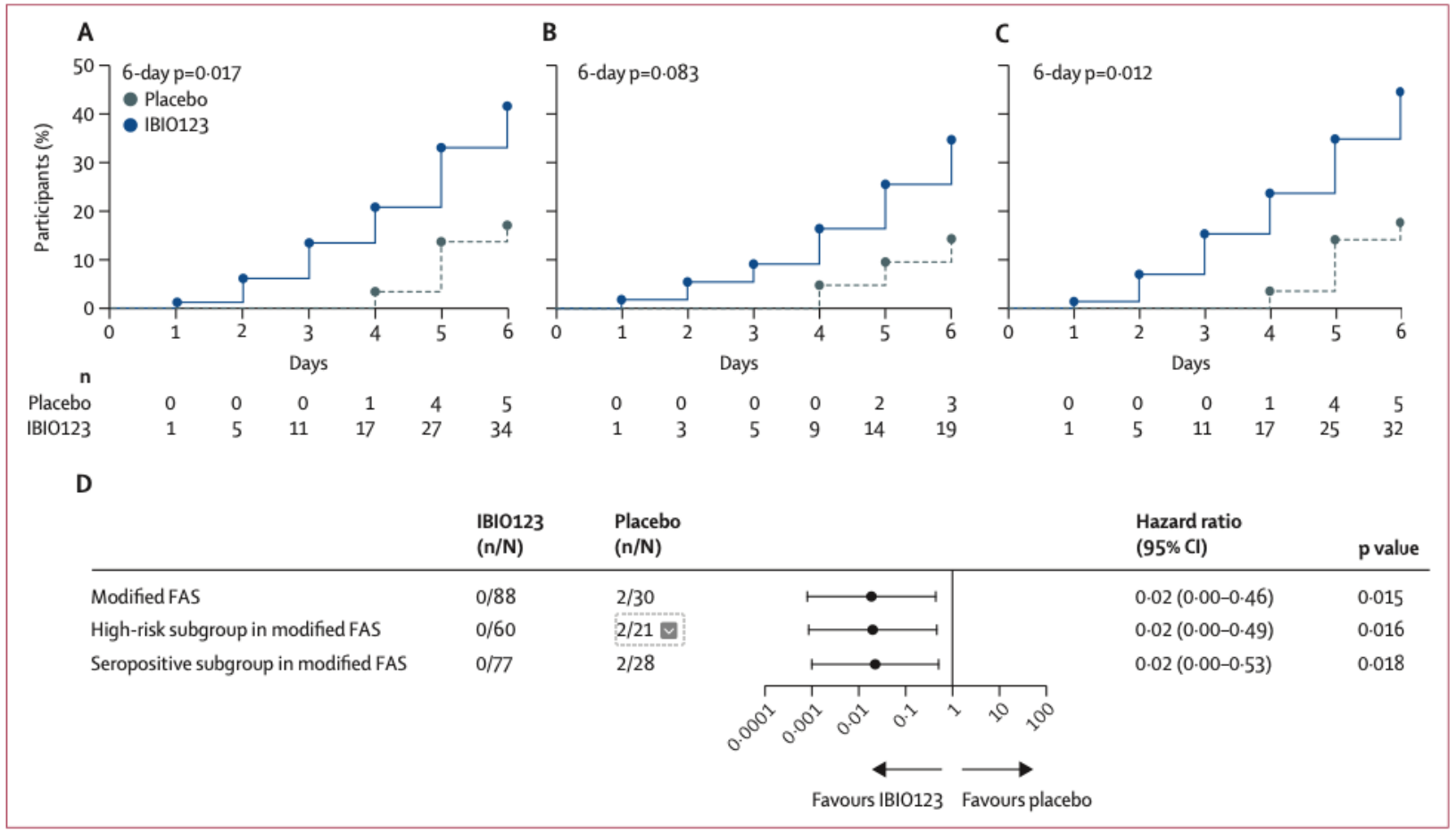
IBIO123 is a mixture of three—IBIO-1 (63%), IBIO-2 (5%), and IBIO-3 (32%)—fully human, recombinant, monoclonal IgGs with a specific activity against SARS-CoV-2
formulated to be administered by inhalation.

Both IBIO-1 (also known as CV3-1) and IBIO-3 (also known as EH-3) bind non-competitively to the **receptor binding domain in the S1 subunit,**
IBIO-2 (also known as CV3-25) binds to a highly conserved epitope of the **S2 subunit.**

neutralisation potency of IBIO123 against multiple strains, from the original strain isolated in Wuhan, China, to omicron (XBB.1.5), has been shown in in-vitro assays

RESULTS

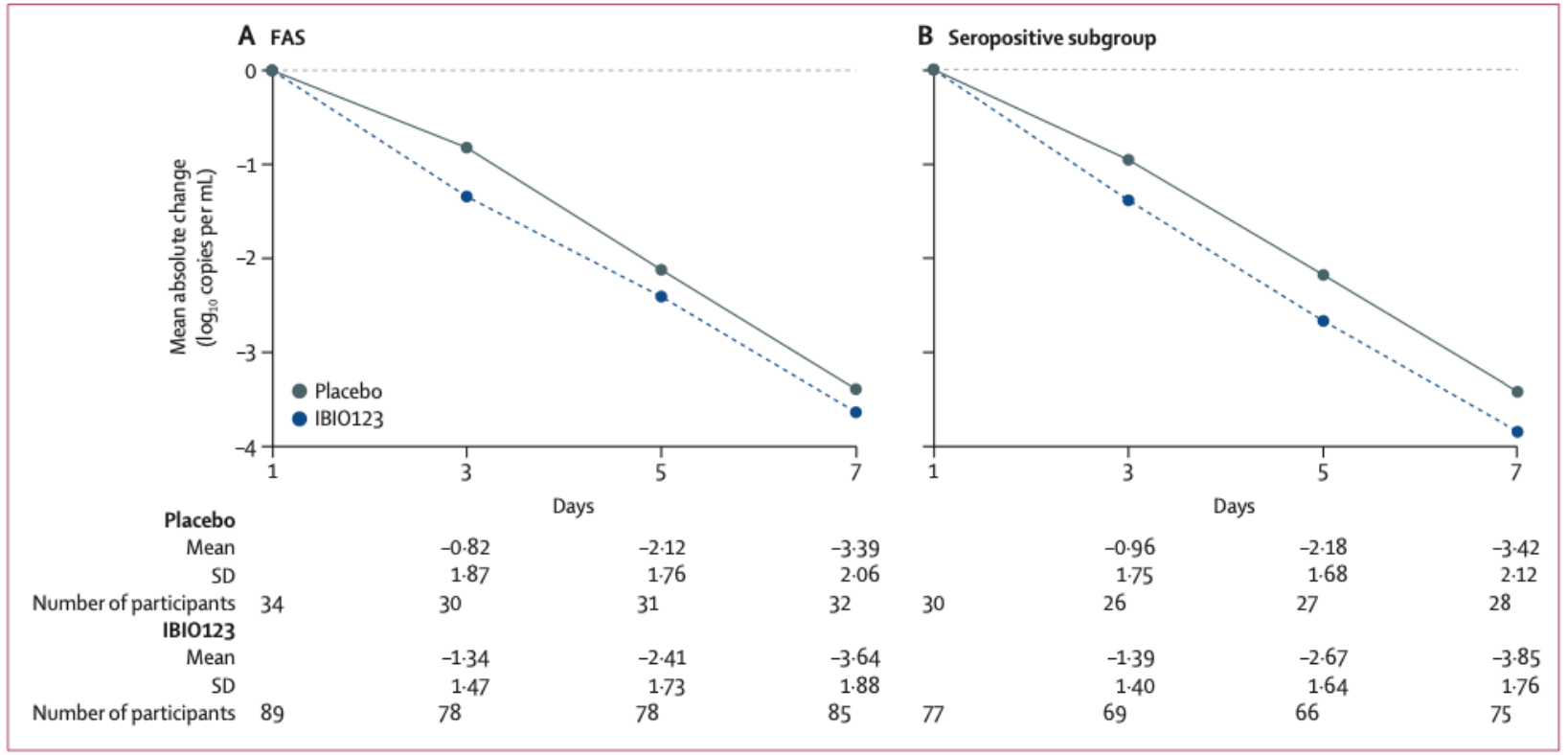
- Between Dec 4, 2021, and May 23, 2022, 24 participants were enrolled in phase 1→ No safety issues were observed.
- Between July 20, 2022, and Jan 4, 2023, 138 participants were enrolled in phase 2 and randomly assigned to receive IBIO123 (n=104) or placebo (n=34)



Resolution of respiratory symptoms at day 6 :
- 34 (42%) of 81 in IBIO123 group
- 5 (17%) of 29 in placebo group (p=0·017) in the modified FAS

- 19 (35%) of 55
- 3 (14%) of 21 among participants at high risk (p=0·083).

One participant died and one was hospitalised in the placebo group, whereas no deaths/hospitalisations in the IBIO123 group.



	A FAS				B Seropositive subgroup			
Placebo								
Mean		−0·82	−2·12	−3·39		−0·96	−2·18	−3·42
SD		1·87	1·76	2·06		1·75	1·68	2·12
Number of participants	34	30	31	32	30	26	27	28
IBIO123								
Mean		−1·34	−2·41	−3·64		−1·39	−2·67	−3·85
SD		1·47	1·73	1·88		1·40	1·64	1·76
Number of participants	89	78	78	85	77	69	66	75

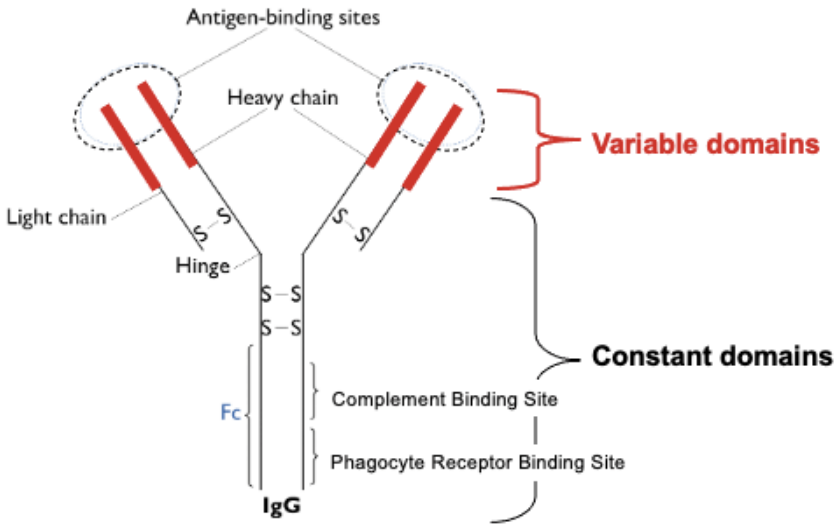
Figure 2: **SARS-CoV-2 viral load over time**

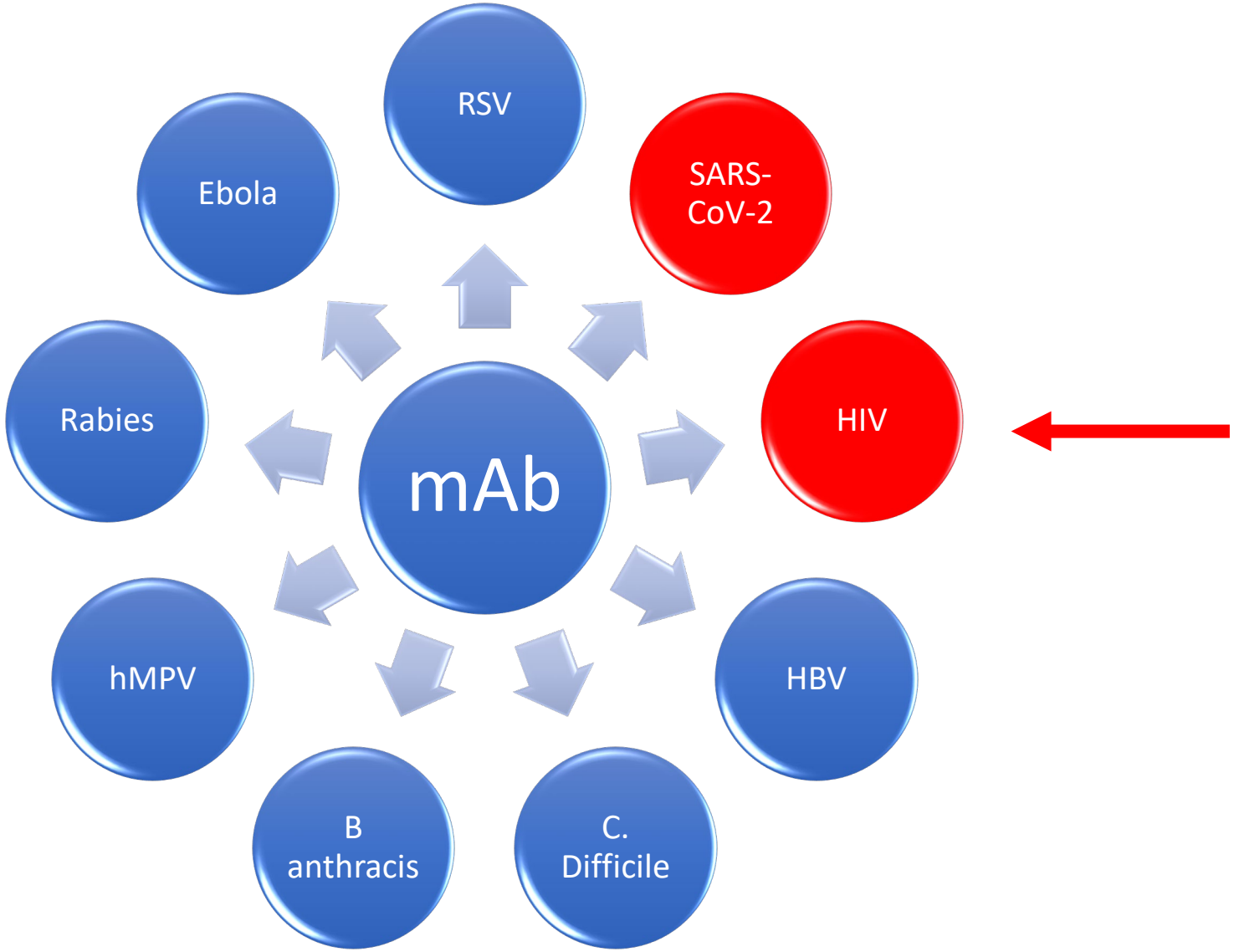
The difference in mean absolute change from baseline viral load to day 5 between participants in the IBIO123
group and participants in the placebo group was –0·29 log10 in the full analysis set (FAS) population and –0·49 log10 copies per mL (−1·56 to 0·58; p=0·20) in seropositive participants. In the modified FAS, 81 (69%) of 118 participants were at high risk of severe disease progression.

CONCLUSIONS

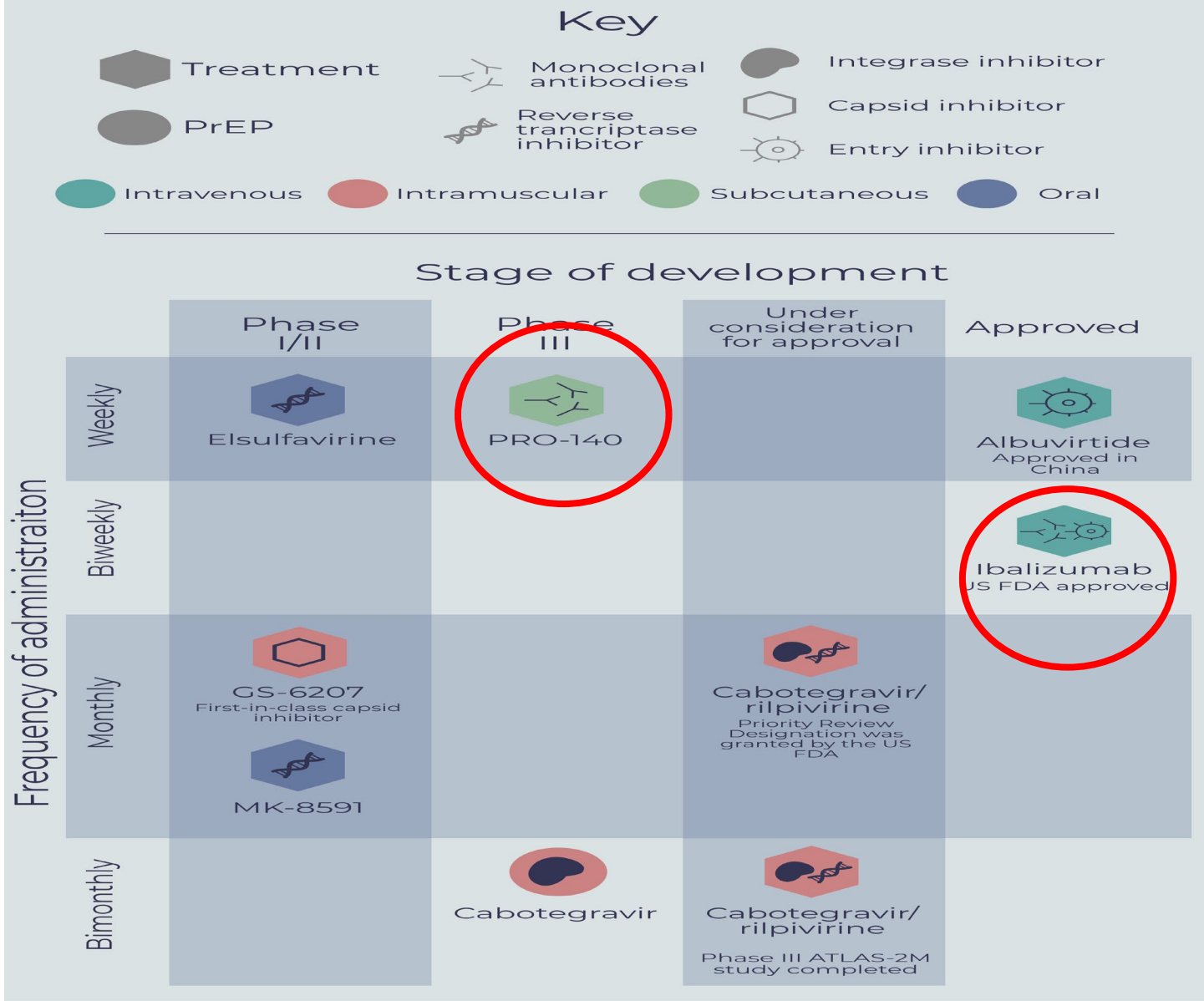
Inhalation of IBIO123 was safe. Despite the lack of significant reduction of viral load at day 5, treatment with IBIO123 resulted in a higher proportion of participants with complete resolution of respiratory symptoms at day 6. This study supports further clinical research on inhaled monoclonal antibodies in COVID-19 and respiratory diseases in general.

Prophylaxis or therapy





The pipeline for long-acting HIV formulations



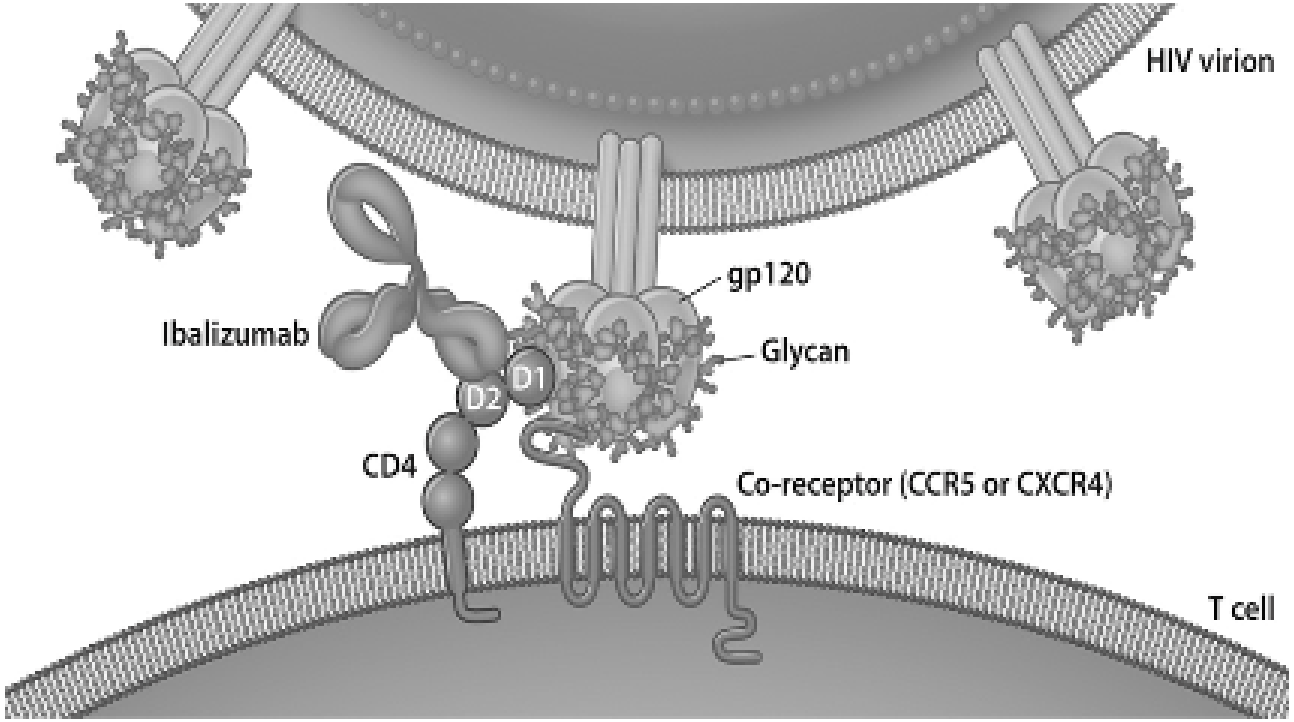
INFECTIOUS DISEASES HUB

Sources: http://i-base.info/htb/wp-content/uploads/2018/07/PIPELINE-2018-full-version.pdf; https://aidsinfo.nih.gov/drugs/513/cabotegravir/0/patient; https://clinicaltrials.gov/

Ibalizumab (Trogarzo®)

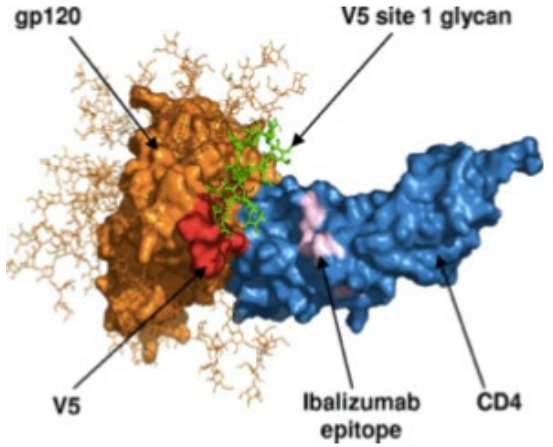
Humanized IgG4 monoclonal antibody, blocks receptor-mediated virus entry by binding to extracellular domain 2 of the HIV-1 receptor CD4 with high affinity

this epitope is comprised of 5 amino acid residues in CD4 domain 2 and two residues in the C-terminal region of domain 1



Located at the interface between domains 1 and 2 of the CD4 molecule, the ibalizumab binding epitope is on the opposite side of CD4 from the domain 1 binding sites that are required for major histocompatibility complex class II (MHCII) receptor binding and gp120 attachment.

Ibalizumab exploits this unique mechanism to inhibit infection by a broad spectrum of HIV-1 isolates, including all major subtypes, irrespective of coreceptor tropism



Beccari et al., Antimicrob Agents Chemother. 2019;63(6):e00110-19;
Toma et al., J Virol. 2011 Apr;85(8):3872-80

The clinical trial that led to FDA approval of ibalizumab was a phase III, single-group, open-label study that enrolled **40 patients** from 30 centers throughout the United States and Taiwan (TMB-301, NCT02475629)

1) control period (days 0-6), patients were monitored while they received their current ART regimen →1/40 0.5 log
2) functional monotherapy period (days 7-13), 2000-mg i.v. loading dose of ibalizumab + prior ART regimen → 33/40 0.5 log
3) maintenance period (day 14-week 25), initiated OBR + i.v. ibalizumab at 800 mg every 14 days → 25/40 0.5 log

At the end of the maintenance period, plasma HIV-1 RNA values of <50 and <200 copies/ml occurred in 17 (43%) and 20 (50%) patients, respectively.
7 (18%) patients had virologic failure, which was defined as two consecutive measurements after day 14 that showed a <0.5-$\log_{10}$ reduction in plasma HIV-1 RNA copies/ml.
3 (8%) patients had viral rebound, which was defined as an increase of at least 1.0 log10 copies/ml in plasma HIV-1 RNA

Mean increase in CD4 T cell count was 62 cells/mm^3

Virologic response	Control period (days 0–6)	End of functional monotherapy period (day 14)	*P*	End of maintenance period (wk 25)
Decrease in viral load of at least 0.5 $\log_{10}$ copies/ml, *n* (%)	1 (3)	33 (83)	<0.001[b]	25 (63)
Decrease in viral load of at least 1.0 $\log_{10}$ copies/ml, *n* (%)	0 (0)	24 (60)	NA	22 (55)
Change in viral load, mean $\log_{10}$ copies/ml ± SD	0.0 ± 0.2	−1.1 ± 0.6	<0.001	−1.6 ± 1.5
HIV-1 RNA level of <50 copies/ml, *n* (%)	NA	NA	NA	17 (43)
HIV-1 RNA level of <200 copies/ml, *n* (%)	NA	NA	NA	20 (50)

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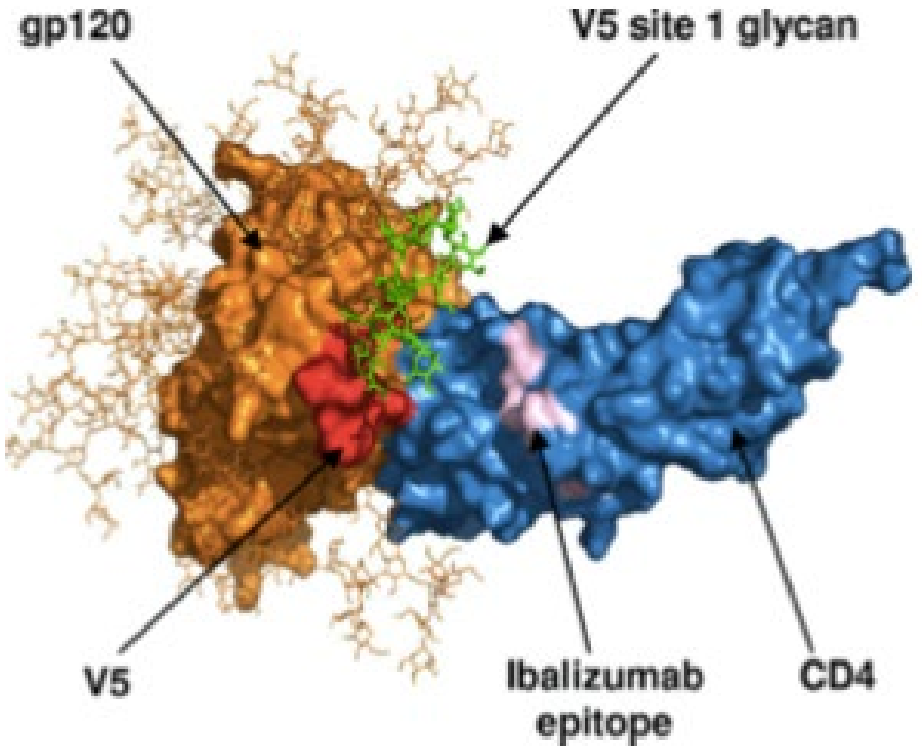
Of the 10 (25%) patients with virologic failure or viral rebound, 9 demonstrated reduced susceptibility to ibalizumab compared to baseline, which was related to the loss of potential N-linked glycosylation sites (PNGS) in the V5 loop of HIV-1 envelope gp120 in 8 of the 9 (89%) patients.

The V5 loop is present as an external portion of gp120

Reduced expression or loss of V5 PNGS and the specific positions of PNGS appear to be the primary mechanisms of resistance to ibalizumab

however, a reduced MPI from baseline was not predictive of virologic failure or rebound



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Article

Combination anti-HIV antibodies provide sustained virological suppression

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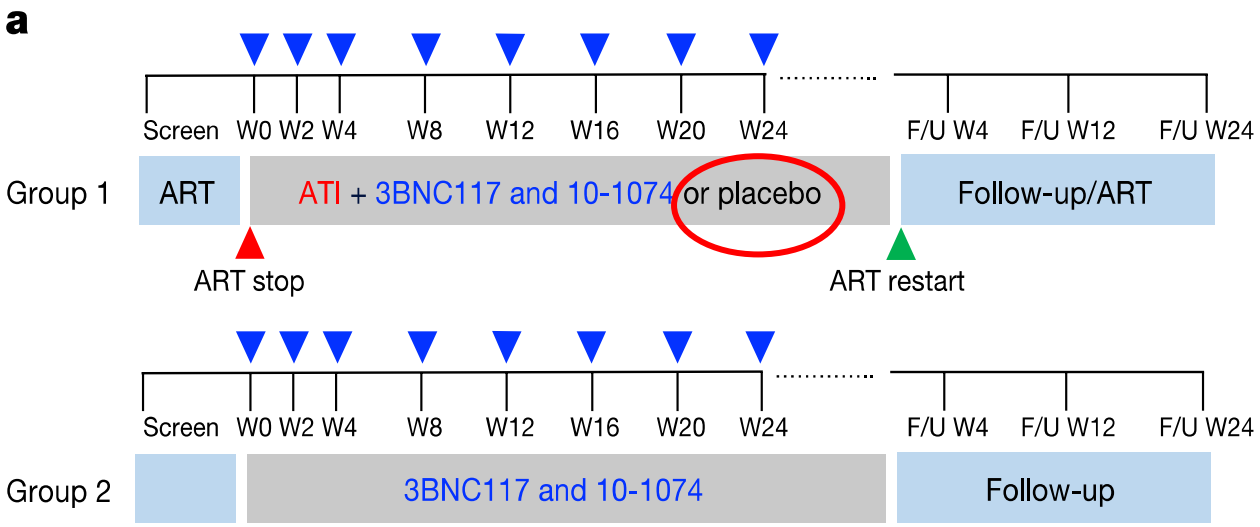
Table 1 | Baseline characteristics of the study participants.

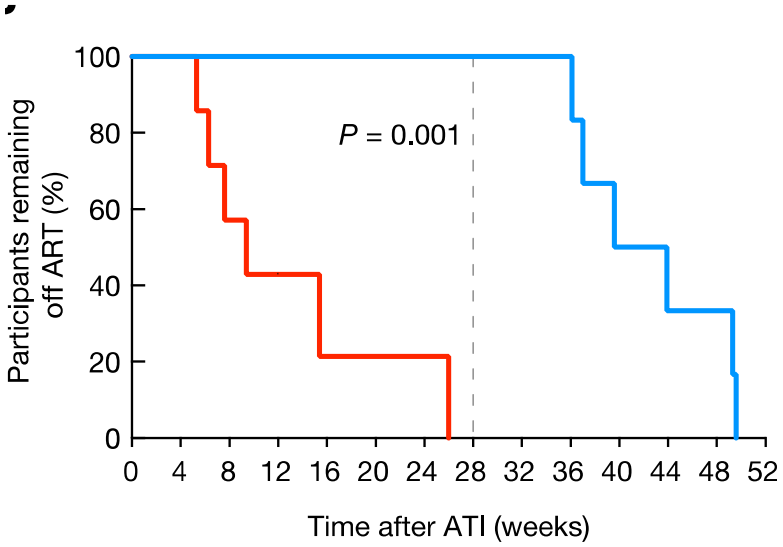
Characteristic		Group 1 Antibody arm (*n*=7)	Group 1 Placebo arm (*n*=7)	Group 2 *n*=5
Sex, number (%)	Male	7 (100)	7 (100)	5 (100)
Median age (range) (years)		40 (27–57)	34 (29–56)	44 (35–52)
Race or ethnic group, number (%)	African American	1 (14.3)	0	1 (20)
	Caucasian	4 (57.1)	5 (71.4)	3 (60)
	Hispanic	1 (14.3)	1 (14.3)	0
	Asian	1 (14.3)	1 (14.3)	0
	Mixed	0	0	1 (20)
Antiretroviral regimen, number (%)	NRTI	7 (100)	7 (100)	–
	NNRTI	1 (14.3)	0	–
	PI/INSTI	1 (14.3)	0	–
	INSTI	6 (85.7)	7 (100)	–
	PK	2 (28.6)	2 (28.6)	–
Inclusion criteria met[a], number (%)	Acute infection	5 (71.4)	2 (28.6)	–
	Early infection	2 (28.6)	5 (71.4)	–

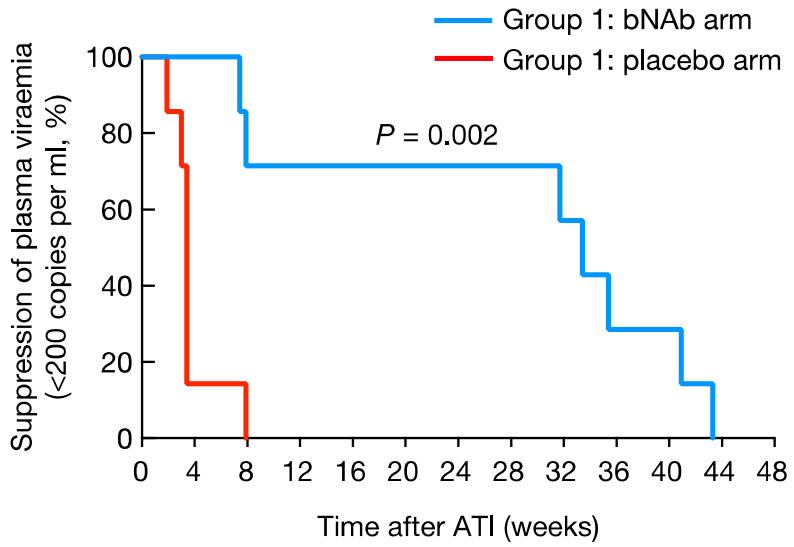
TOT = 19 study participants



Group 1: **14** participants in whom ART was initiated during the acute/early phase of infection and who subsequently underwent ATI (**randomized**)

Group 2: **5** individuals with viraemic control, naive for ART, and had baseline plasma viraemia of between 200–5,000 copies/mL (**open label**)





In group 2, 2 out of the 5 study participants whose baseline infectious HIV was sensitive to both antibodies maintained complete suppression of plasma viraemia for an average of 41.7 weeks

HIV is safe and well tolerated and, for those with antibody-sensitive virus, offers marked virological suppression without any significant or unforeseen immunologic and virological anomalies. As the next generation of bNAbs with increased breadth and prolonged half-lives (>60 days)[15,17,35] become available, there is a reason to believe that the infrequent administration (that is, twice a year) of such antibodies, possibly along with a long-acting injectable antiretroviral drug[12–14], could lead to ART-free HIV suppression for extended periods (years) in individuals with infection.

Conclusions

- mAbs offer the great advantage of plasticity toward different antigens, low side effects, and the possibility of interaction with the patient's immune system, which is not directly involved in the mechanism of action of antivirals
- Half-life and route of administration limits that can be overcome
- Cost and rapid development of resistance are major limitations to use in the prevention and treatment of infections such as HIV and SARS-CoV-2 infections
- Possibility of new therapeutic perspectives in other infections besides SARS-COV-2 and HIV infections