Episode 219 : Protection against MISC; therapeutic antibodies or soluble ACE-2 against omicron

Dear colleagues,

In today's episode:

- More arguments to vaccinate children: protection against MISC syndrome.
- Potential for beta Spike as a vaccine
- Several more potentially therapeutic monoclonal antibodies against omicrom
- Potential use of the soluble ACE-2 receptor as an entry blocker against omicron and other sarbecoviruses.

VACCINES

1) Protection of adolescents against Multisystem Inflammatory Syndrome in Children (MISC)

Ep 219-1: Clear protection in French adolescents: Of 33 hospitalizations Sept-Oct 2021 (Delta VOC), none had been fully vaccinated with Pfizer, 7 had received 1 dose and 26 were unvaccinated.

Ep 219-2: The US study is larger done between July–December 2021, a period of Delta variant. Amongst 102 MIS-C case-patients, five (5%) were fully vaccinated with 2 doses ≥28 days before hospitalization, and 97 (95%) were unvaccinated. **Vaccine efficacy was 91 %.** No fully vaccinated patients with MIS-C required respiratory or cardiovascular life support, as opposed to 39% of unvaccinated MIS-C patients.

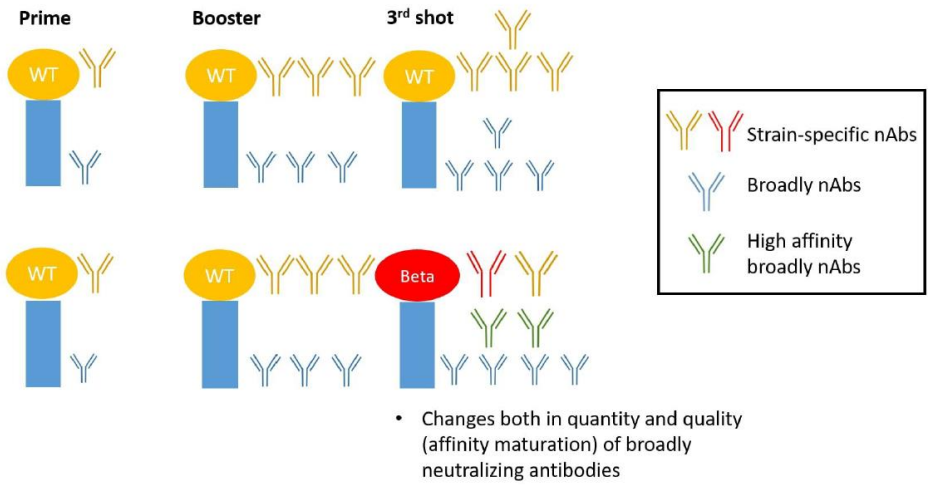
2) Combined Wuhan Wild Type (WT) + Beta Variant vaccine candidate:

Ep 219-3: MVC-COV1901 is a Taiwanese protein vaccine based on the **prefusion SARS-CoV-2 spike** protein (**S-2P**) and is adjuvanted with CpG 1018 and aluminum hydroxide (similar to the US Novavax and the Chinese Clover).

A vaccination scheme with 3 doses is proposed either 3 X wild type or 2 doses WT + one Beta S-2P:
Two doses of WT S-2P + 1 dose of Beta variant induced **highest neutralizing antibody titer**

- against live SARS-CoV-2 of all current variants of concern VoCs,
- and improved neutralization against Omicron variant pseudovirus

compared to three doses of wildtype S-P.
All vaccine regimens: **protected hamsters from SARS-CoV-2 Delta** variant challenge and resulted in reduced lung live virus titer and pathology.
The proposed mechanism is **immune refocusing:**

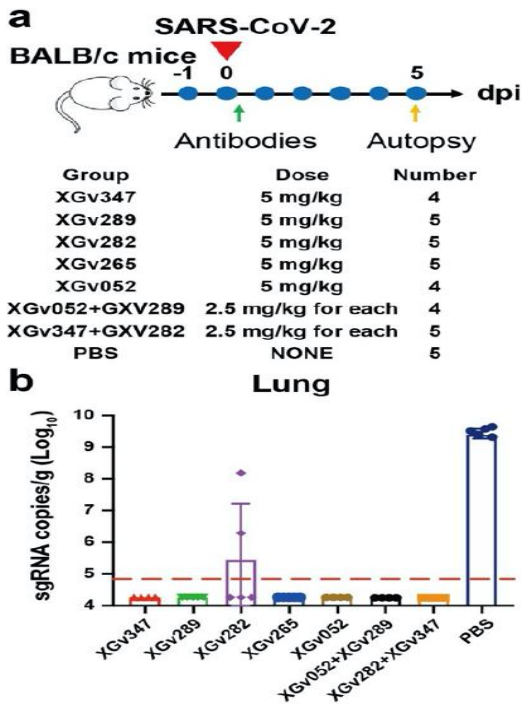


POTENTIALLY THERAPEUTIC ANTIBODIES

Ep 219-4: Kang Wang (China): A subset of **antibodies derived from memory B cells** of volunteers vaccinated with 3 doses of an inactivated SARS-CoV-2 vaccine work individually as well as synergistically **to keep variants, including Omicron, at bay**.

In this experiment mice were pretreated with selected monoclonal Ab and challenged with SARS-CoV-2 beta: clear protection againsty replicative virus in the lung (subgenomic RNA)

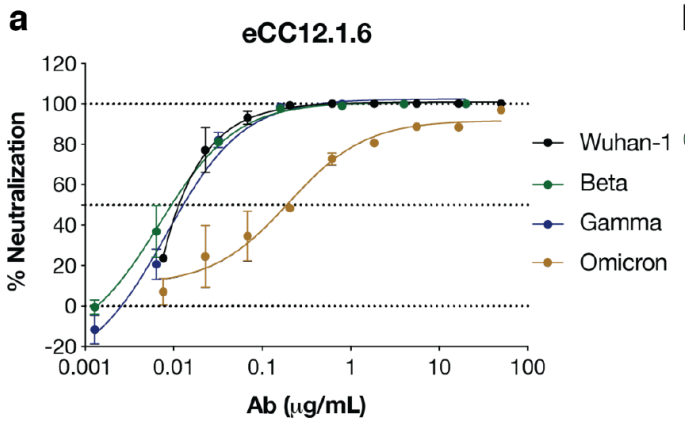
In vitro experiments also showed good activity against omicron.



Group	Dose	Number
XGv347	5 mg/kg	4
XGv289	5 mg/kg	5
XGv282	5 mg/kg	5
XGv265	5 mg/kg	5
XGv052	5 mg/kg	4
XGv052+GXV289	2.5 mg/kg for each	4
XGv347+GXV282	2.5 mg/kg for each	5
PBS	NONE	5

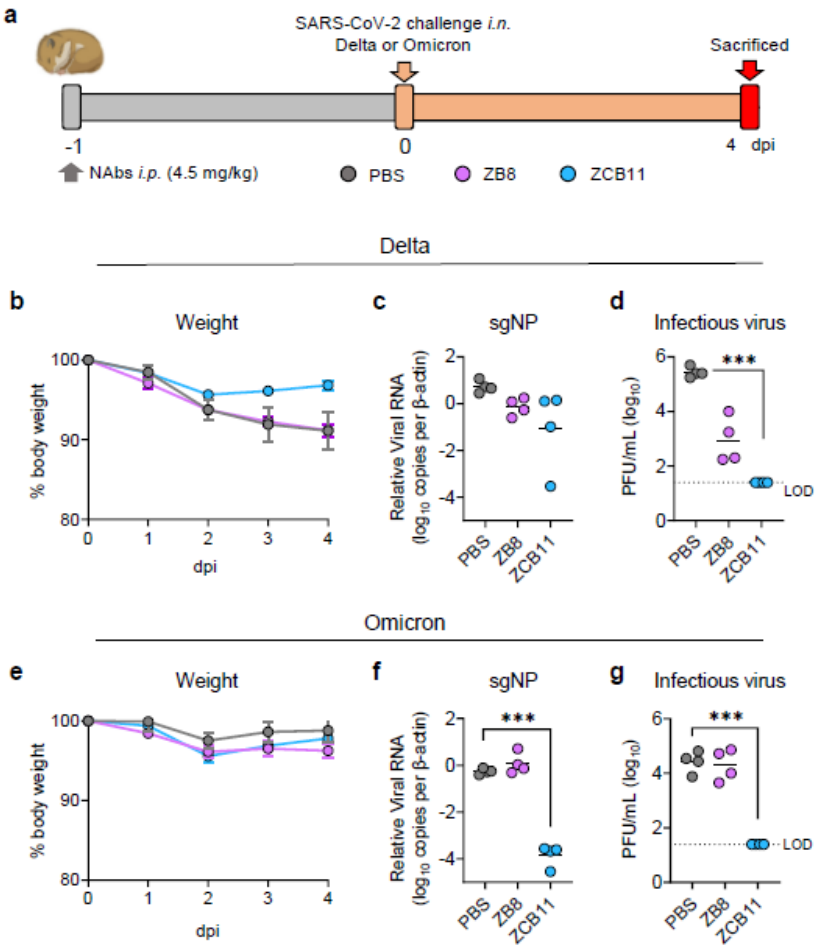
Ep 219-5: Westendorf (Eli Lilly Co) LY-CoV1404 is a human monoclonal against the receptor binding domain and potently neutralizes all variants, including omicron, in vitro.

Ep 219-6: Fangzhu Zoa (La Jolla Ca): another example of a broad neutralizing candidate



Ep 219-7: Biao Zhou (China):

- ZCB11 is a public broadly neutralizing Ab isolated from an “elite vaccinee” (after 2 X Pfizer).
- ZCB11 administration **protected against lung infection by both Delta and Omicron** variants in golden Syrian hamsters.

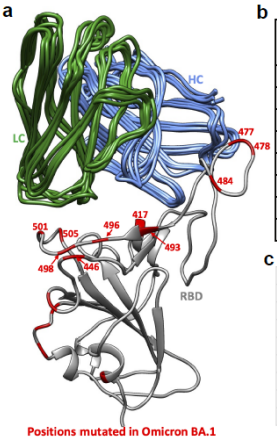


Ep 219-8: Daniel Steward: Structural basis of Omicron neutralization by **affinity-matured public antibodies**

- Starting from a public class of IGHV3-53-using SARS-CoV-2 neutralizing antibodies, which typically fails to neutralize variants carrying mutations in the RBD, including Omicron.
- Nevertheless from an individual seven months after infection several of these IGHV3 antibodies were capable of broad and potent neutralization, including Omicron.
- The “hypermutations” needed for this transition from weak to broad neut were identified.

breadth.

a



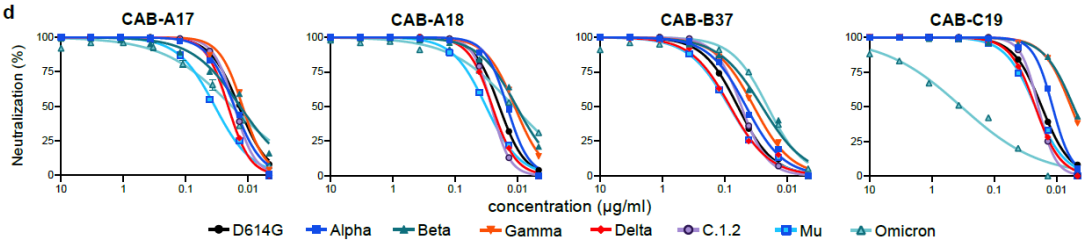
b

ID	VH gene	VD gene	VJ gene	%V SHM (nt)	%V SHM (aa)	HCDR3	VL gene	VJ gene	%V SHM (nt)	%V SHM (aa)	LCDR3
CAB-A17	IGHV3-53*01	IGHD3-10*01	IGHJ4*02	8.9	12.6	ARDYGDFYFDY	IGKV3-20*01	IGKJ1*01	3.8	7.3	QQYGSSPRT
CAB-A18	IGHV3-53*01	IGHD3-10*01	IGHJ4*02	4.4	10.5	ARDFGEFYFDY	IGKV3-20*01	IGKJ1*01	5.5	8.3	QQYGSSPRT
CAB-A49	IGHV3-53*01	IGHD3-10*01	IGHJ4*02	4.4	6.3	ARDFGEFYFDF	IGKV3-20*01	IGKJ1*01	2.8	5.2	QQYGSSPRT
CAB-B37	IGHV3-53*01	IGHD3-9*01	IGHJ6*02	6.9	13.7	ARLPYGTDV	IGKV1-33*01	IGKJ5*01	3.9	7.4	QQYDNLPIT
CAB-C19	IGHV3-53*01	IGHD6-19*01	IGHJ3*02	4.1	6.3	ARVLPVAGDSFDF	IGKV1-33*01	IGKJ1*01	6.4	14.7	QHYNNFLVTWT
CAB-D16	IGHV3-53*01	IGHD3-9*01	IGHJ6*02	9.2	11.6	AREVYALDV	IGKV1-9*01	IGKJ4*01	5.6	13.7	QRVNHPPA
CAB-E24	IGHV3-53*01	IGHD2-8*01	IGHJ3*02	6.1	12.6	ARDRGNGAFDI	IGKV1-9*01	IGKJ2*01	1.8	2.1	QQLNSYPGDT
CAB-E30	IGHV3-53*01	IGHD3-10*01	IGHJ3*02	6.8	13.7	ARDRGNAAFDF	IGKV1-9*01	IGKJ2*01	3.5	8.4	QQLDTYPGDT

c

	D614G	Alpha	Beta	Gamma	Delta	C.1.2	Mu	Omicron
CAB-A17	0.014	0.016	0.013	0.012	0.021	0.016	0.034	0.015
CAB-A18	0.020	0.015	0.010	0.011	0.025	0.026	0.032	0.012
CAB-A49	0.015	0.013	>1	>1	0.015	0.008	0.028	>10
CAB-B37	0.063	0.046	0.025	0.034	0.082	0.054	0.085	0.020
CAB-C19	0.017	0.011	0.005	0.006	0.022	0.020	0.022	0.225
CAB-D16	0.011	0.009	0.027	0.010	0.016	0.008	0.012	>10
CAB-E24	0.013	0.010	0.209	0.117	0.020	0.008	0.020	6.380
CAB-E30	0.013	0.010	0.172	0.076	0.020	0.007	0.025	>10

d

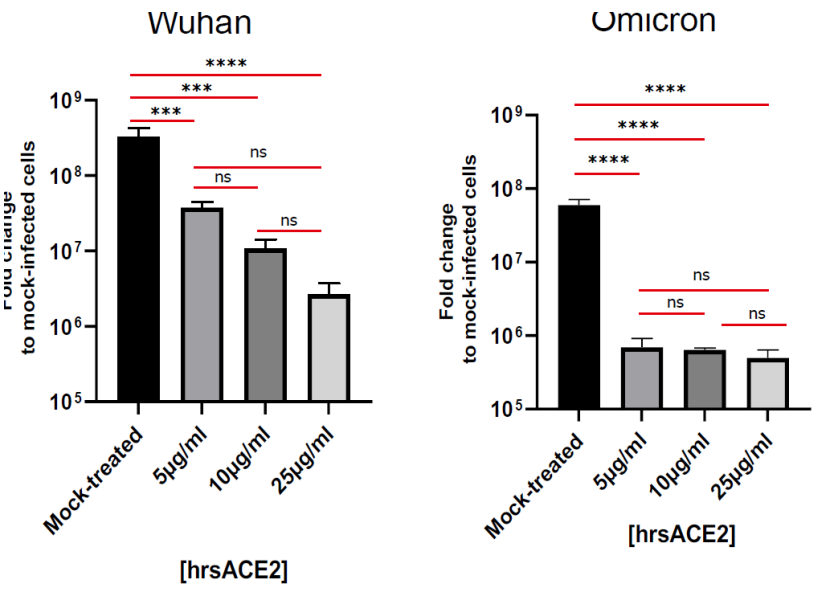


Ep 219-9: Tom Yuan (Twist Biopharma USA): **A synthetic bispecific antibody capable of neutralizing SARS-CoV-2 Delta and Omicron**

This brief report highlights RBT-0813 (also known as TB493-04), a synthetic, humanized, receptor-binding domain (RBD)-targeted bispecific antibody that retains picomolar affinity to the Spike (S) trimers of all major variants of concern and neutralizes both SARS-CoV-2 Delta and Omicron *in vitro*.

SOLUBLE ACE-2 as a THERAPEUTIC?

Ep 219-10: Vanessa Monteil: **Clinical grade ACE2 inhibits SARS-CoV-2 Omicron 1 infections**
Nice in vitro results:



Ep 219-11: Like previous SARS-CoV-2 variants, Omicron and some other sarbecoviruses showed high sensitivity against engineered ACE2, confirming the therapeutic value against diverse variants, including those that are yet to emerge.

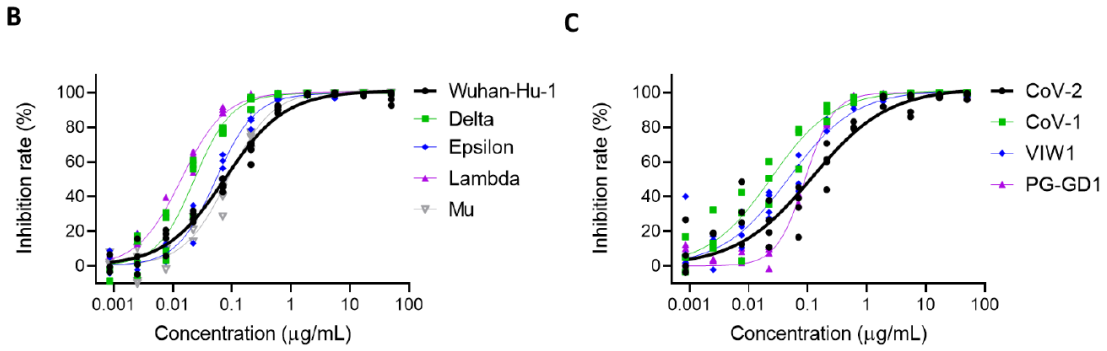


Fig. 4. Neutralization assay for ACE2 decoy with pseudovirus of SARS-CoV-2 variants and sarbecoviruses. (**A**) Alignment of amino acid sequences of sarbecovirus RBDs used in this study. ACE2 contacts are highlighted by green based on the crystal structure 6M0J. (**B** and **C**) Neutralization efficacy of the engineered ACE2(3N39v4) against previous SARS-CoV-2 variants (B), SARS-CoV-1 and other sarbecovirus (C) in 293T/ACE2 cells. n = 4 technical replicates.

Clearly, we are not harmless against omicron, but time is not on our side….

Best wishes,

Guido