Using no change against changes

– Development of pan-sarbecovirus vaccines

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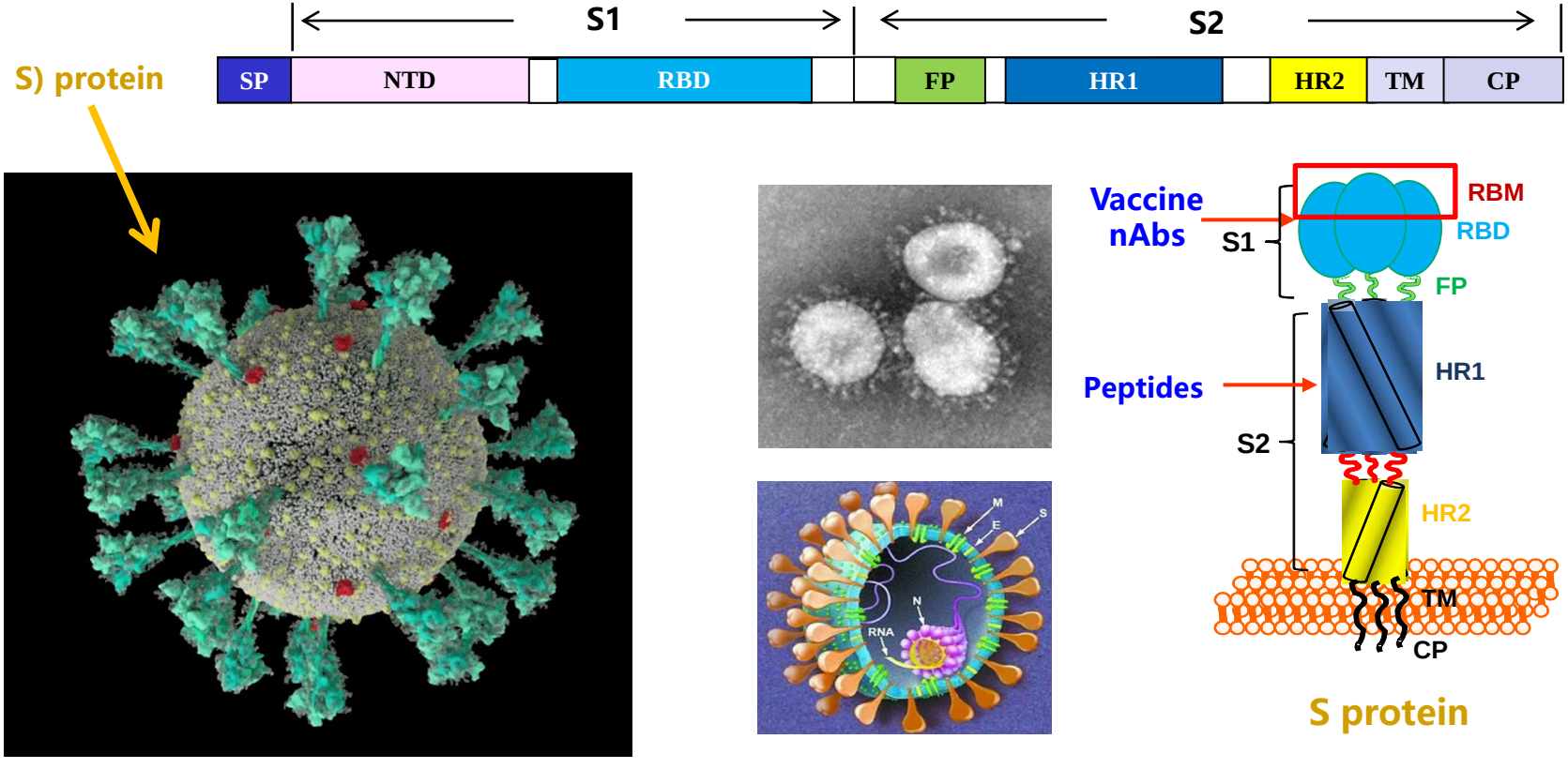
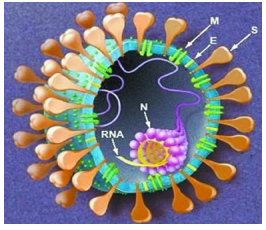
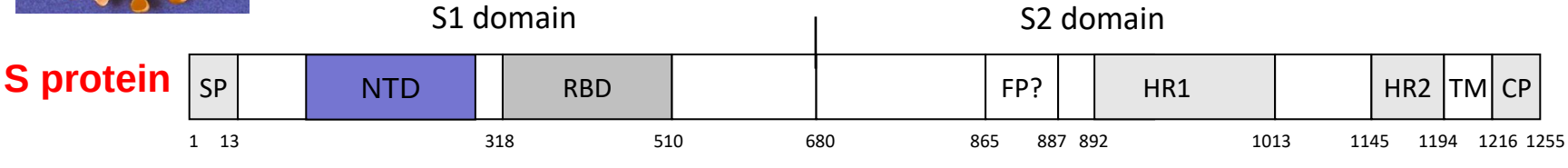
Coronavirus S protein



SARS vaccine design (2003)

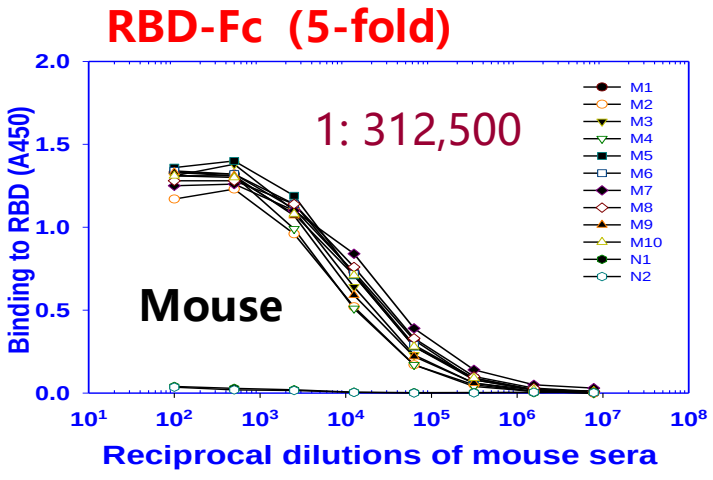


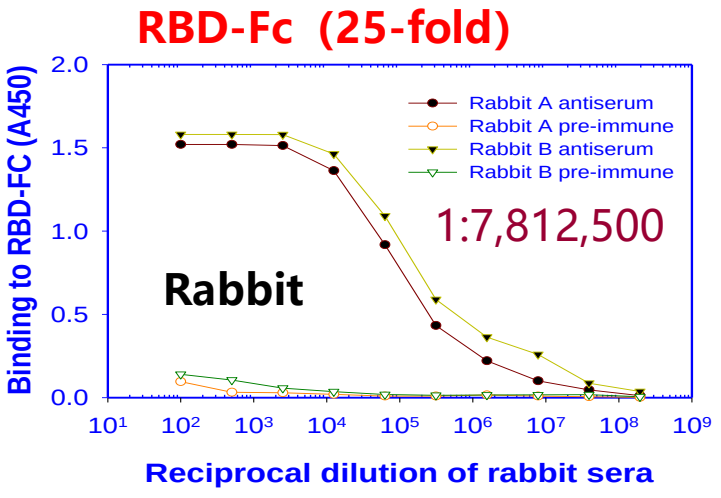


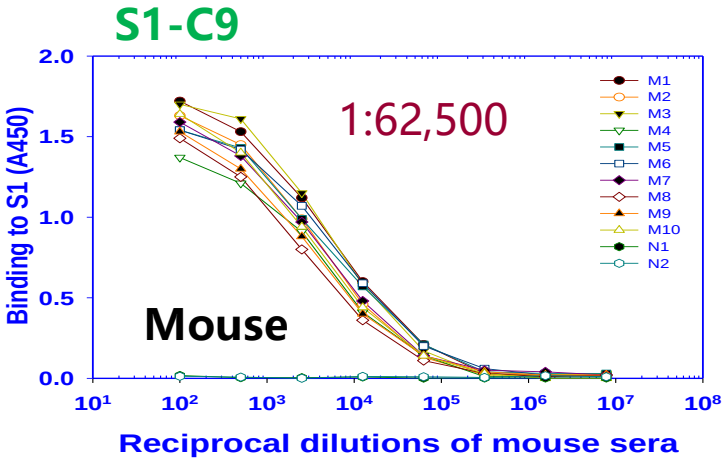
Why IgG Fc?

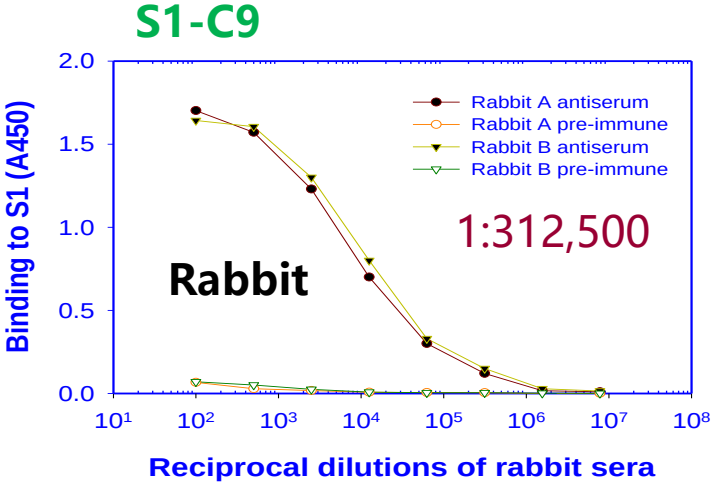
- Increase half-life
- Form dimer
- Adjuvant effect
- Easy for purification

RBD-Fc elicits antibody response about 5-～25-fold stronger than S1



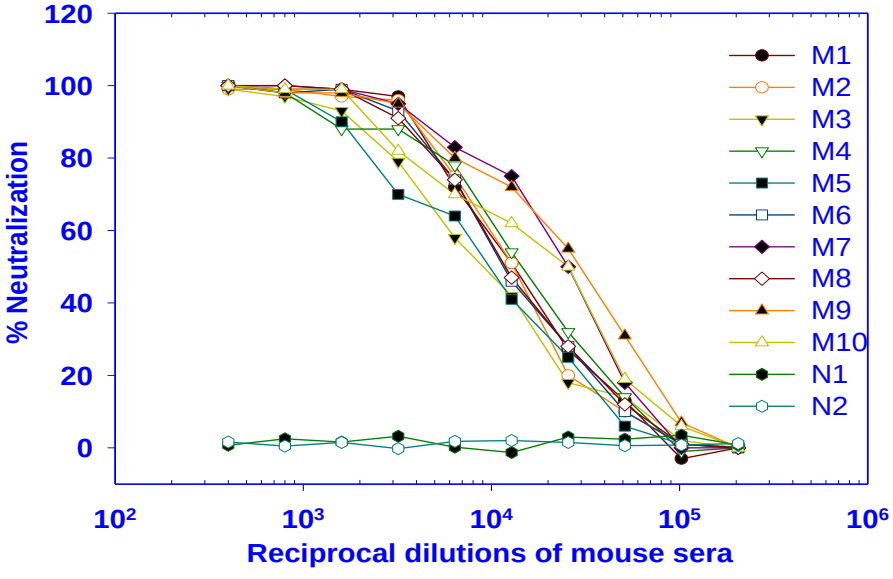






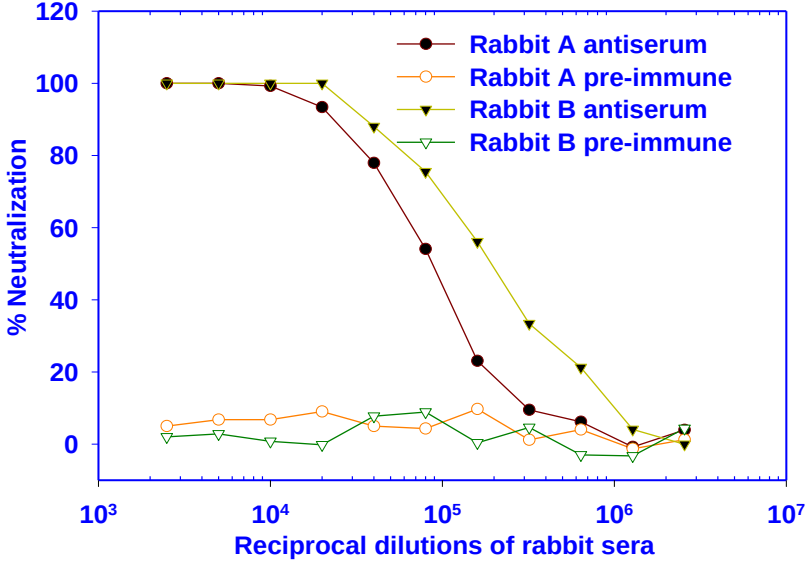
Neutralizing pseudotyped SARS-CoV

Mouse sera



Mean NT_{50}: 1: 13,636

Rabbit sera

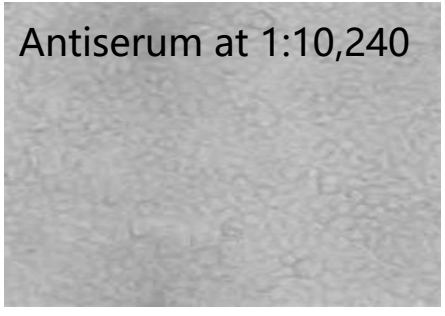


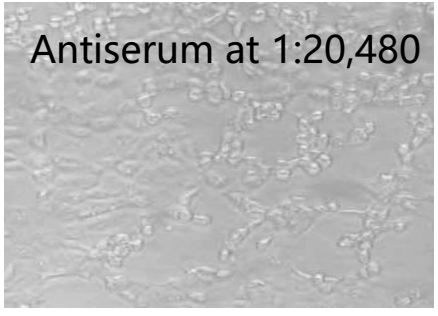
Mean NT_{50} : 1: 95,792

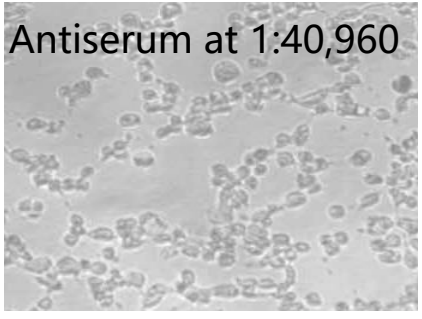
Neutralizing live SARS-CoV

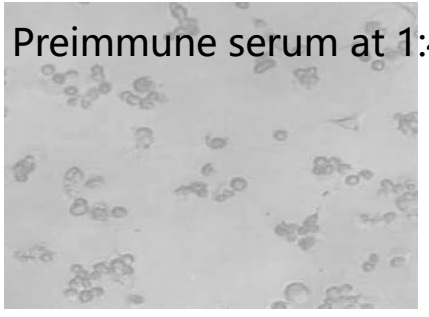
Mouse sera

Mean NT_{50} 1:10,862



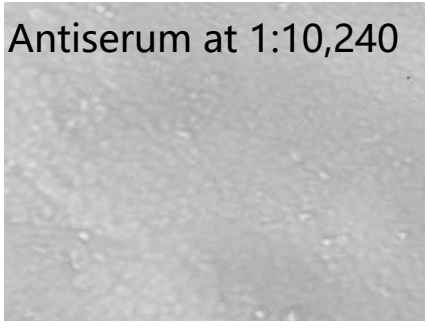


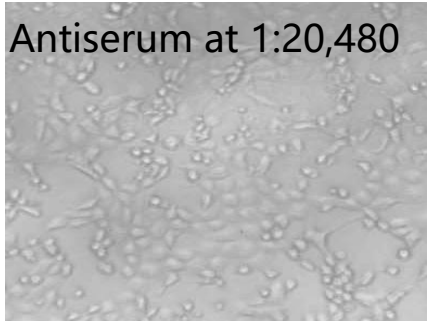


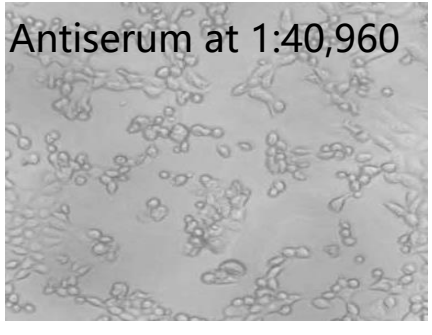


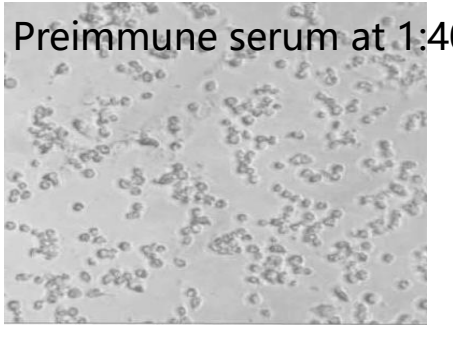
Rabbit sera

Mean NT_{50} 1:15,360









Development of SARS & MERS vaccines

BBRC 2004, JI 2004, JCM 2004, JI 2005, JV 2005, EID 2005, Virology 2005, JCM 2005, Vaccine 2005, JI 2006, Vaccine 2006, JV 2006, Vaccine 2007, JI 2008, JI 2009, JID 2013, JV 2013(x2), PNAS 2014, JV 2014, CID 2015, mBio 2015, JV 2015 (x3), EID 2016, Nat Commun 2016, CMI 2016, JV 2017, EMI 2017, EMI 2018, JV 2018, Crit Care Med 2018, CMI 2019, Nat Rev Microbiol 2009.

Neutralizing immunogenicity:

RBD-Fc dimer > RBD trimer > RBD monomer > S1 > S > viral particles

First generation COVID-19 Vaccines (S or viral particles)

Type	name	developer	Neutralization antibody titer (NT_{50})				
			Mice LV*	NHP PsV	NHP LV	Human PsV	Human LV
Inactivated vaccine	BBIBP-CorV (Sinopharm)	Beijing Institute of Biological Products	~1,000 (3 immunes)	ND	215~256 (2 immunes)	ND	247 (2 immunes)
	PiCoVacc	Sinovac Biotech Ltd	1,500 (2 immunes)	ND	~50 (3 immunes)	ND	24~65
	Unnamed	Wuhan Institute of Biological Products	ND	ND	ND	ND	ND
Adnovirus-vectored vaccine	Ad5-nCoV	CanSino/Beijing Institute of Biotech	ND	ND	ND	ND	~20 (1 immune)
	ChAdOx1 (AZD1222)	University of Oxford	40-80 (1 immunes)	ND	5-40 (1 immunes)	~410 (CS: ~360) (2 immunes)	218 (2 immunes)
RNA vaccine	mRNA-1273	Moderna/NIAID	ND	ND	ND	ND	231 (CS: 158) (2 immunes)
	mRNA BNT162	BioNTech/Pfizer	ND	ND	ND	ND	267 (CS: 94) (2 immunes)
DNA vaccine	INO-4800	Inovio Pharmaceuticals	98-340	ND	ND	ND	ND

Mouse sera NT50: 40~1,500; Monkey and human sera NT50: 20~267

RBD-based COVID-19 vaccines

Type	Antigen	Developer	Stage	nAb titer (NT_{50})		
				Mice	Mice	NHP
				Pseudovirus	Live virus	PsV/Live virus
mRNA vaccine	RBD-mRNA	Abogen	Phase 1/2	7,079 (2 immunes)	5,704 (2 immunes)	6,482 (2 immunes)
	RBD-mRNA	New York Blood Center	–	~10,000 (2 immunes)	540 (2 immunes)	ND
Subunit vaccines	RBD dimer	Anhui Zhifei Longcom	Phase 1/2 /3	ND	512-4,096 (2 immunes)	ND
	RBD monomer	Sichuan University	Phase 1/2	~2,400 (2 immunes)	ND	ND
	RBD-Fc dimer	Shanghai Pasteur	–	12,764 (3 immunes)	>512 (3 immunes)	ND
	RBD-Fc dimer	Fudan University	–	>10,000 (3 immunes)	>10,000 (3 immunes)	>10,000 (2 immunes)
Nano vaccines	RBD polymer	Sun Yat-sen University	-	~14,000 (2 immunes)	~14,000 (2 immunes)	~4,200 (2 immunes)

Mouse sera NT50: 512~14,000; Monkey sera NT50: 4,200~10,000

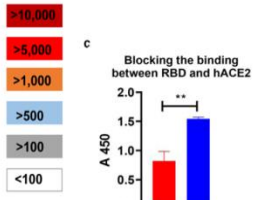
RBD-Fc based COVID-19 vaccine

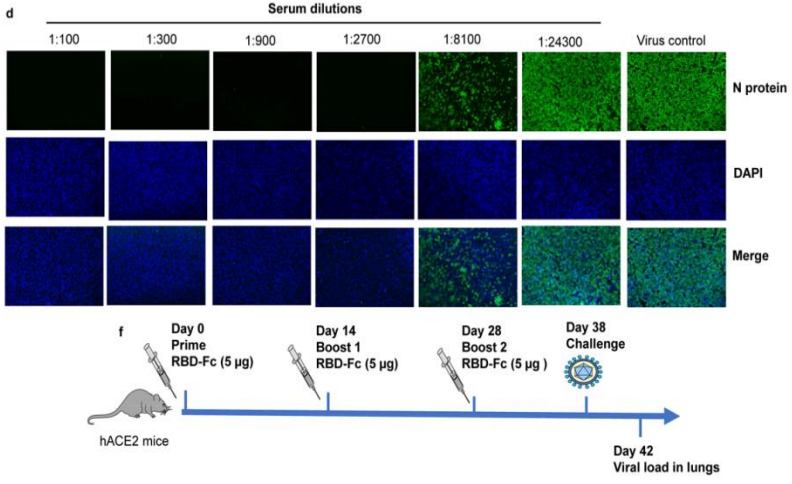
a

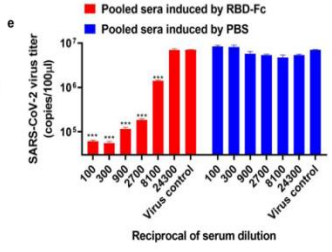
Neutralization activity (PsV assay)	Mouse 1 NT_{50}	Mouse 2 NT_{50}	Mouse 3 NT_{50}	Mouse 4 NT_{50}	Mouse 5 NT_{50}	Mouse 6 NT_{50}	Geometric mean NT_{50} (95% CI)
2.5 μg (21d)	2,413	690	276	1,147	1,298	608	864 (395-1889)
5 μg (21d)	4,353	892	1,421	755	2,784	620	1,389 (616-3135)
10 μg (21d)	9,490	404	7,935	2,479	1,096	405	1,795 (414-7785)
PBS (21d)	<100	<100	<100	<100	<100	<100	-

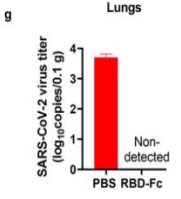
b

Neutralization activity (PsV assay)	Mouse 1 NT_{50}	Mouse 2 NT_{50}	Mouse 3 NT_{50}	Mouse 4 NT_{50}	Mouse 5 NT_{50}	Mouse 6 NT_{50}	Geometric mean NT_{50} (95% CI)
2.5 μg (35d)	1,469	780	602	3,121	6,007	4,450	1965 (729-5299)
5 μg (35d)	22,974	11,347	10,252	1,433	13,927	5,614	8179 (2962-22585)
10 μg (35d)	12,108	4,687	23,160	5,635	5,909	3,095	7166 (3347-15344)
PBS (35d)	<100	<100	<100	<100	<100	<100	-





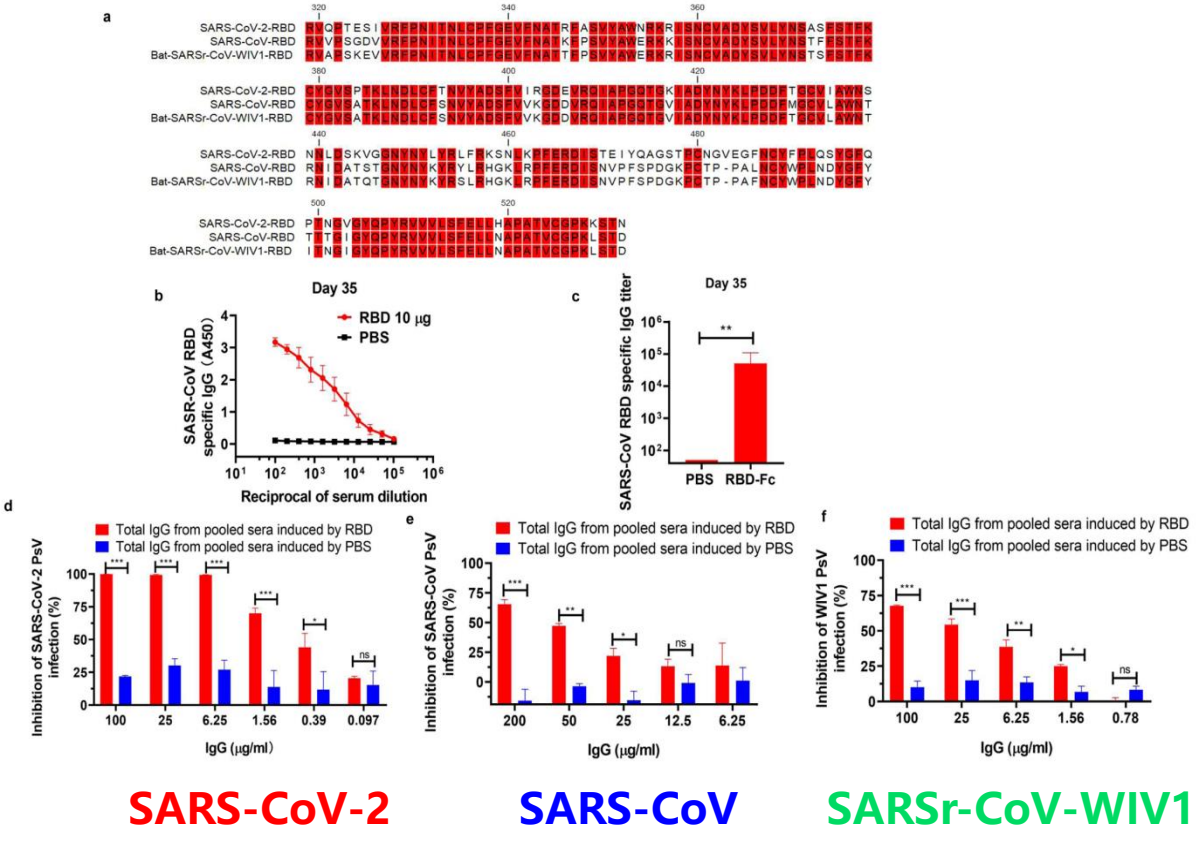




PsV NT50: ~8,000 Live virus NT50: ~8,000

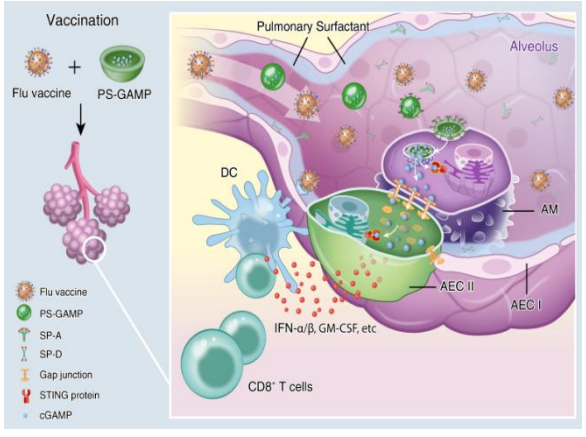
Liu Z, Jiang S et al. ***Signal Transduct Target Ther.*** 5:282, 2020

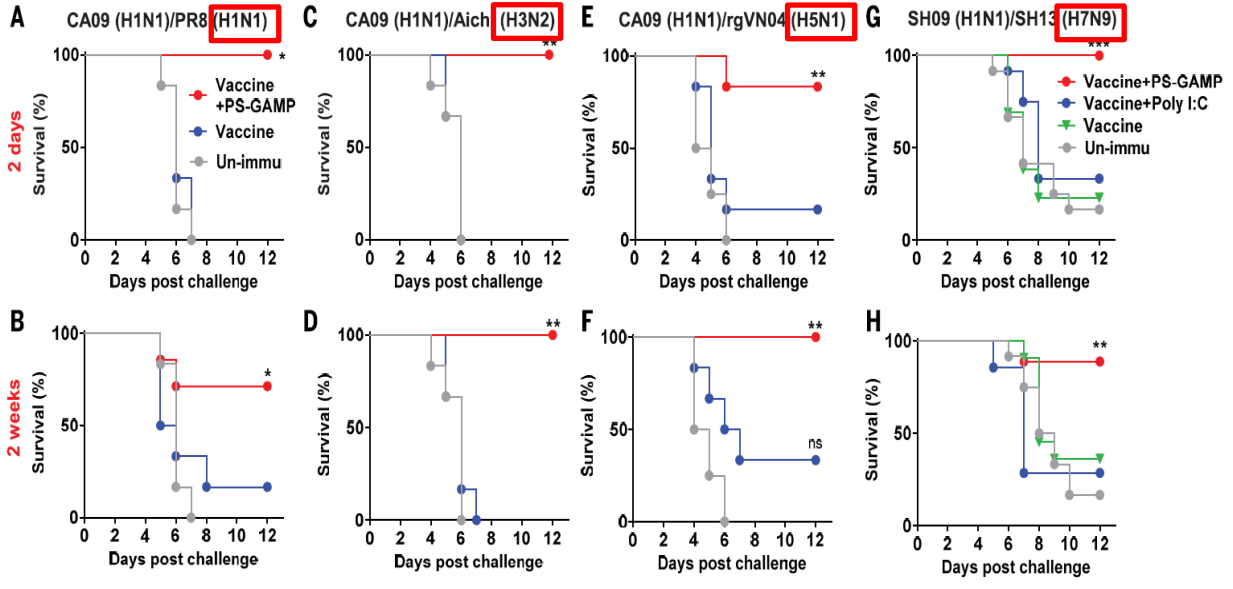
RBD-Fc-based COVID-19 vaccine



Liu Z, Jiang S et al. ***Signal Transduct Target Ther.*** 5:282, 2020

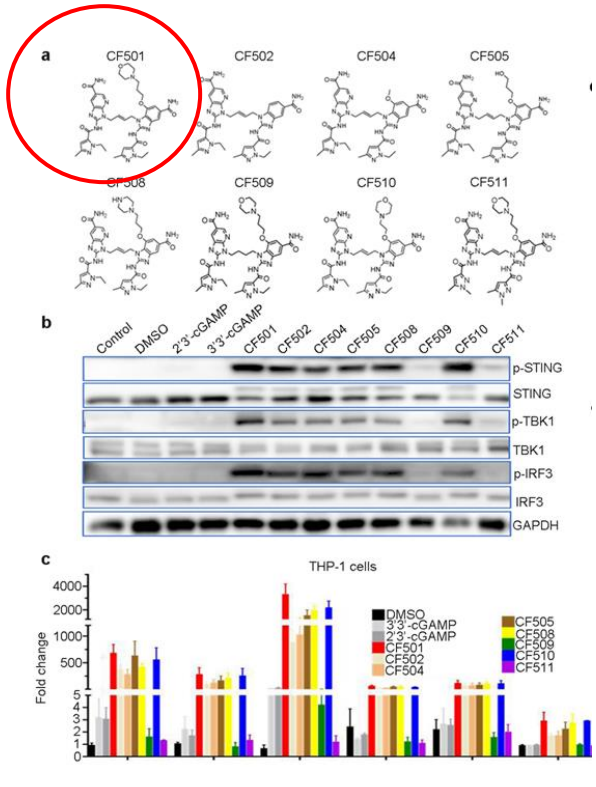
PS-GAMP as an adjuvant for broad-spectrum flu vaccines

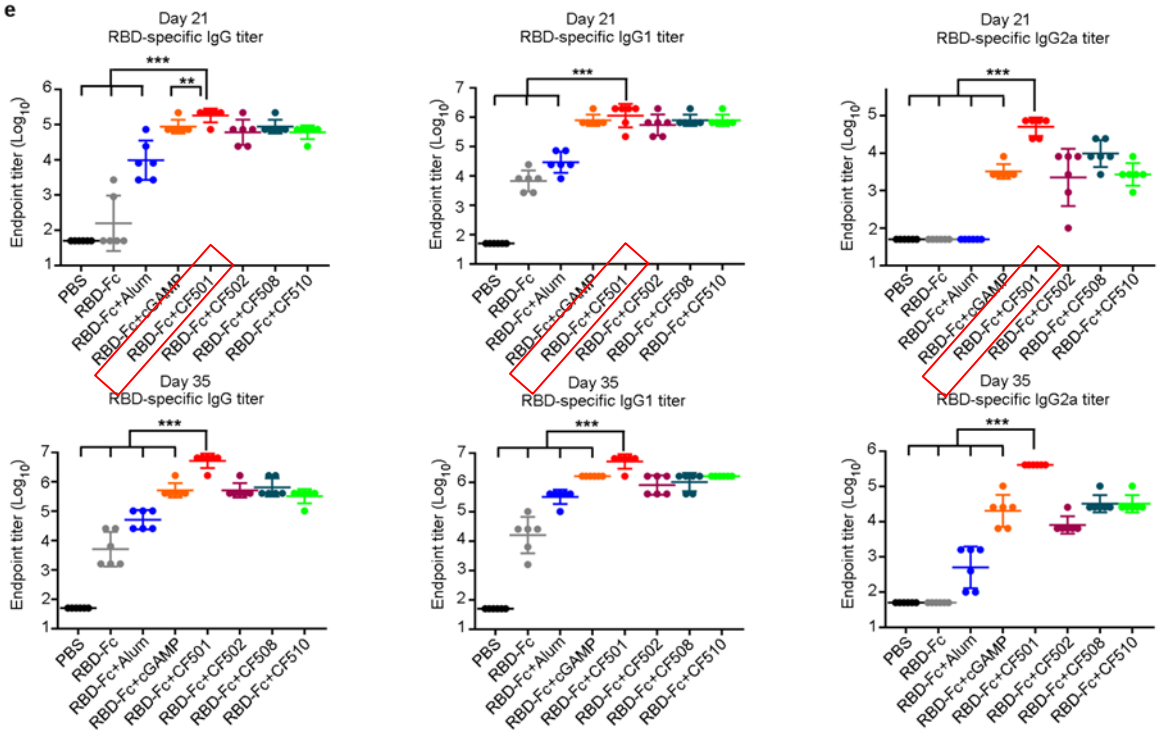




Wang J,…… Jiang S, Lu L, Wu MX, et al. ***Science.*** 367(6480): eaau0810, 2020

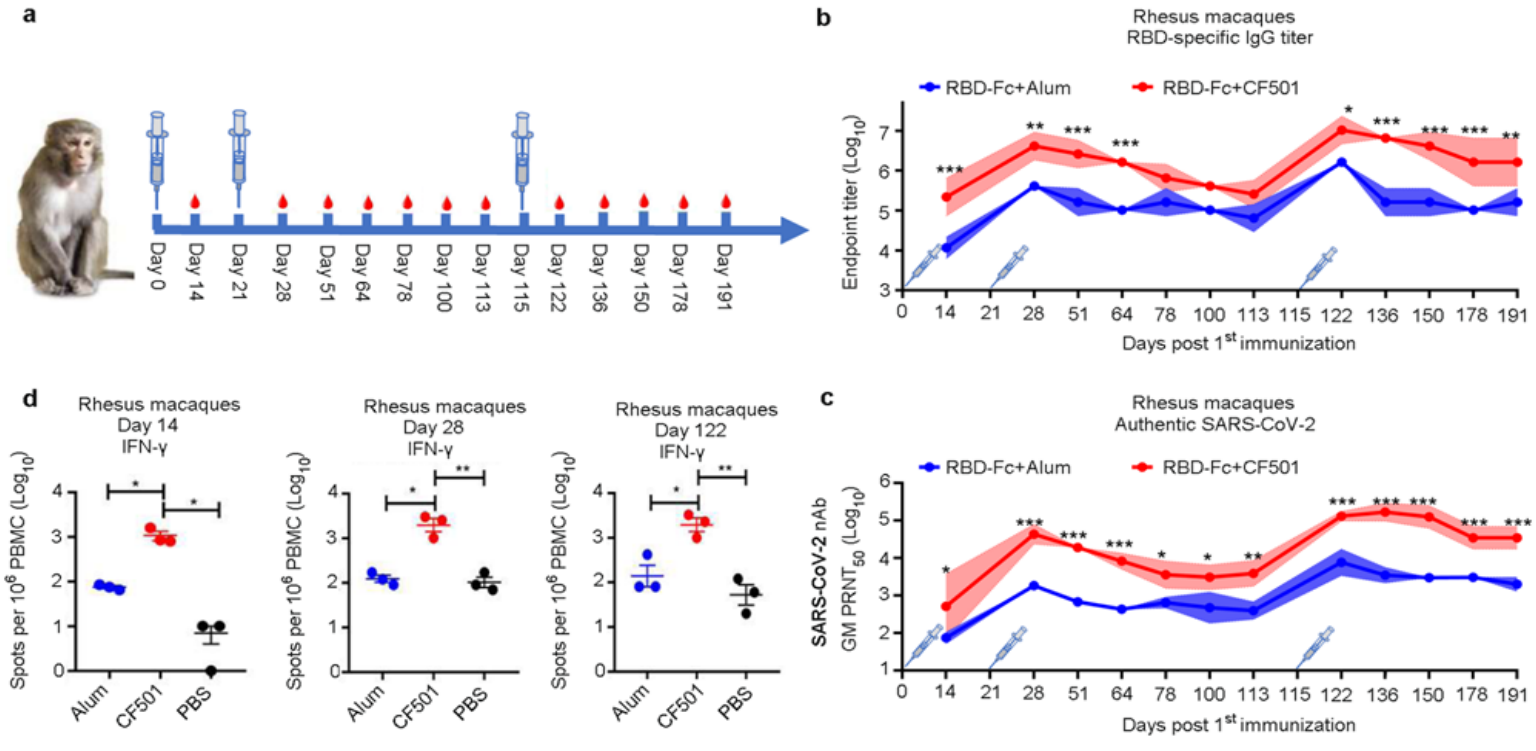
Identification of STING antagonist CF-501 as an adjuvant





Liu Z et al. ***Cell Res.*** 32(3):269-287 (2022)

CF501/RBD-Fc-based pan-sarbecovirus vaccine



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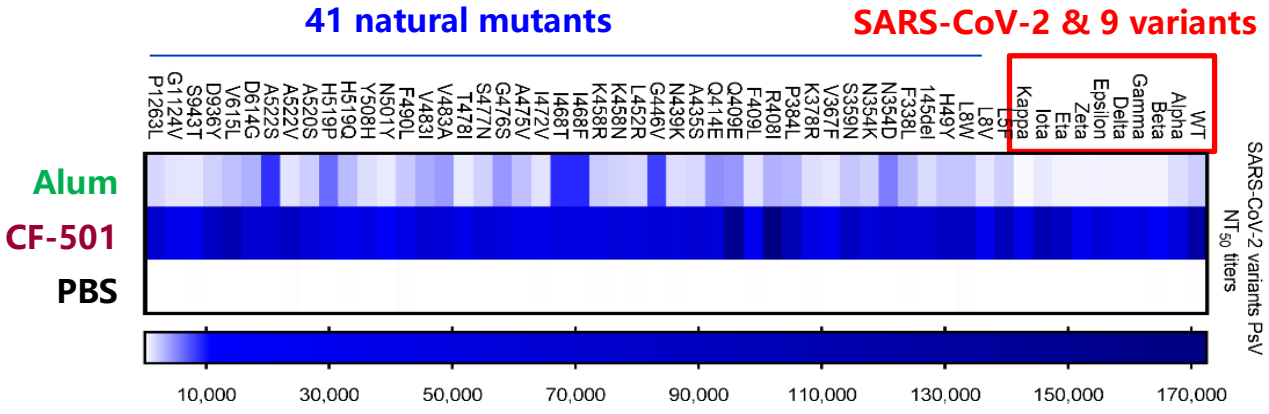

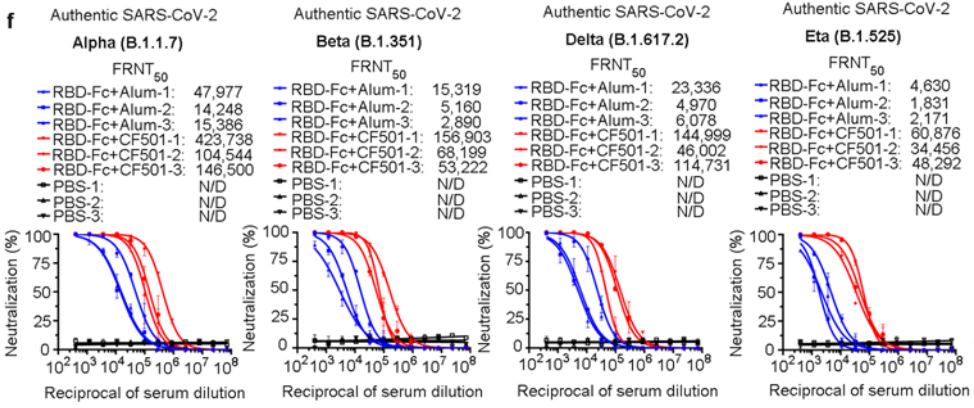

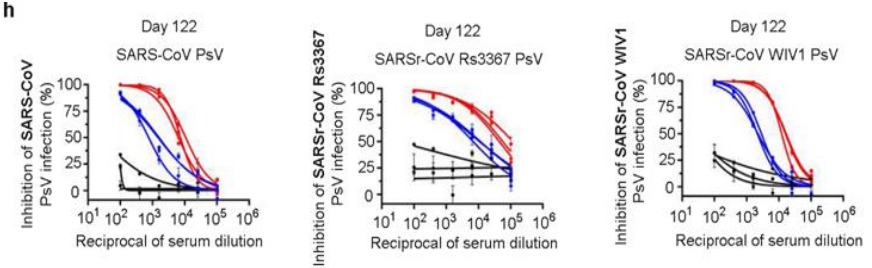

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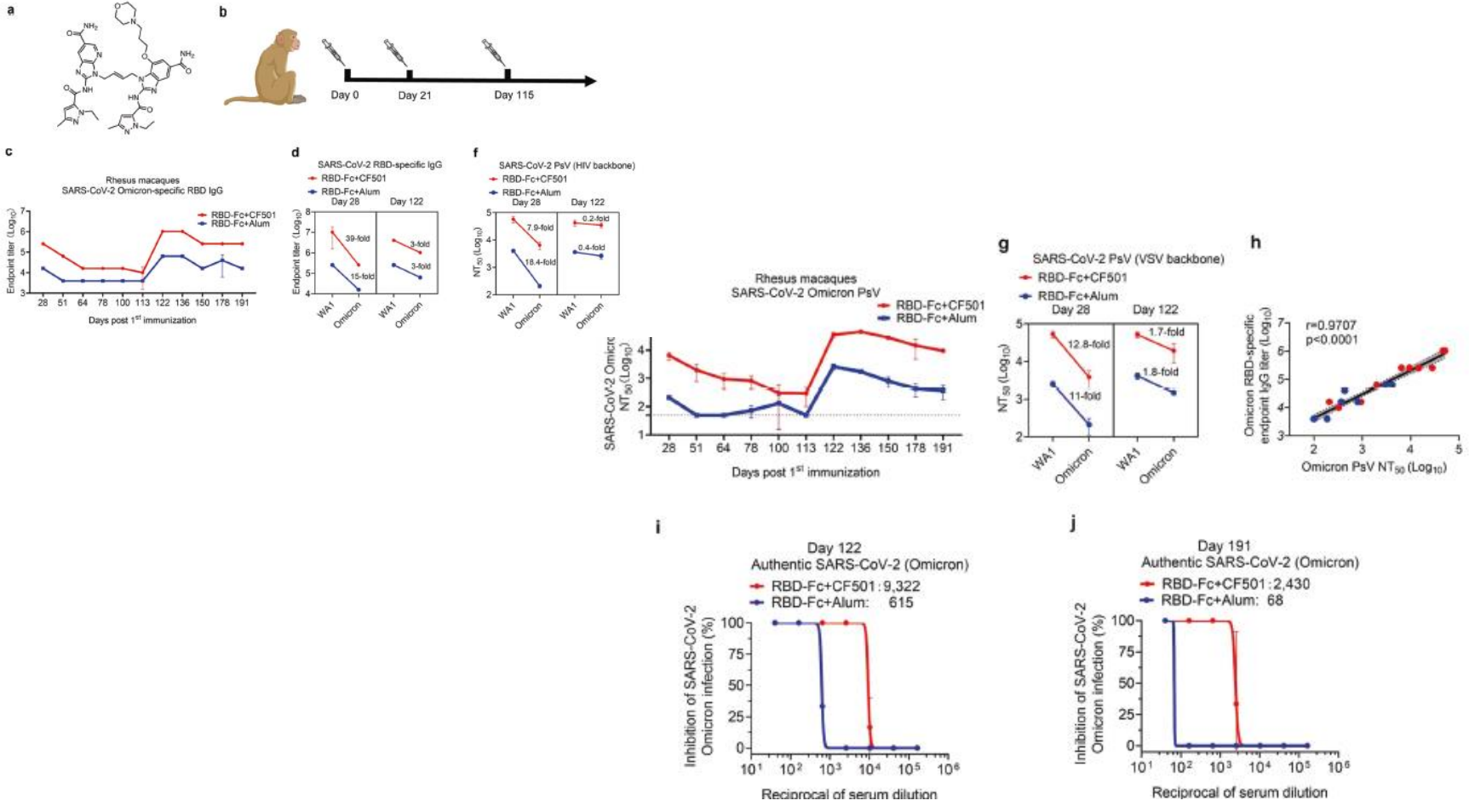

Liu Z et al. ***Cell Res.*** https://doi.org/10.1038/s41422-022-00631-z (2022)

Summary

CF-501/RBD-Fc-based pan-sarbecovirus vaccine is more than 20-fold more potent than alum/RBD-Fc-based vaccine. It is effective against:

1) SARS-CoV-2 and its variants (e,g, Alpha, Beta, Gamma, Delta, and Omicron);

2) SARS-CoV and its variants;

3) Bat SARSr-CoVs (e.g., WIV1, Rs3367, and RsSHC014).

Thanks !