COVID-19 vaccine development using recombinant vesicular stomatitis virus (rVSV) vector system

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DDG of Science

International Vaccine Institute

ACCELERATING VACCINES FOR GLOBAL HEALTH

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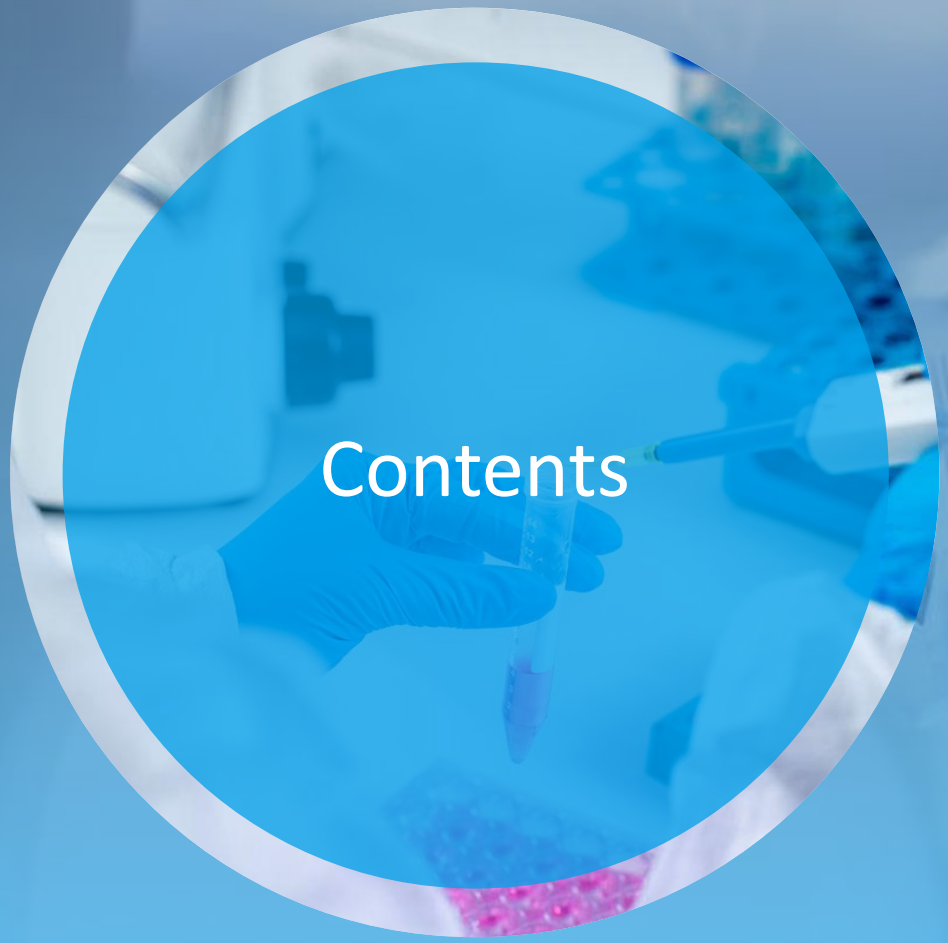
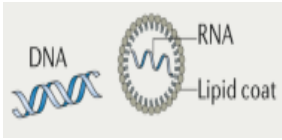
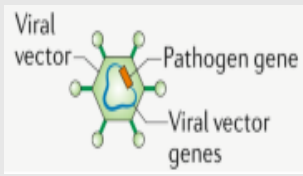


Contents

Recombinant Vesicular Stomatitis Virus (rVSV) vector-based vaccine platform

Different types of vaccine

Types of vaccine	How it works	Licensed vaccines using this technology
Live attenuated 	Weakened version of the actual pathogen	MMR, BCG, Yellow fever, Influenza, Rabies
Inactivated 	Whole pathogen after it has been killed by heat or chemicals	Polio, Japanese Encephalitis, Hep A
Subunit 	Piece of pathogen's surface to focus immune system on a single target	Pertussis, Influenza, Hep B, Pneumococcal, HPV
Nucleic acid 	DNA or RNA molecules to teach the immune system to target key pathogenic protein	COVID-19
Viral vector 	Uses harmless virus to deliver pathogenic genes to build immunity	Ebola, COVID-19

Nature Reviews Immunology, vol21, 83–100(2021), CDC report (2021)

Viral vectors for vaccine development

Poxviruses (Vaccinia)

Measles virus

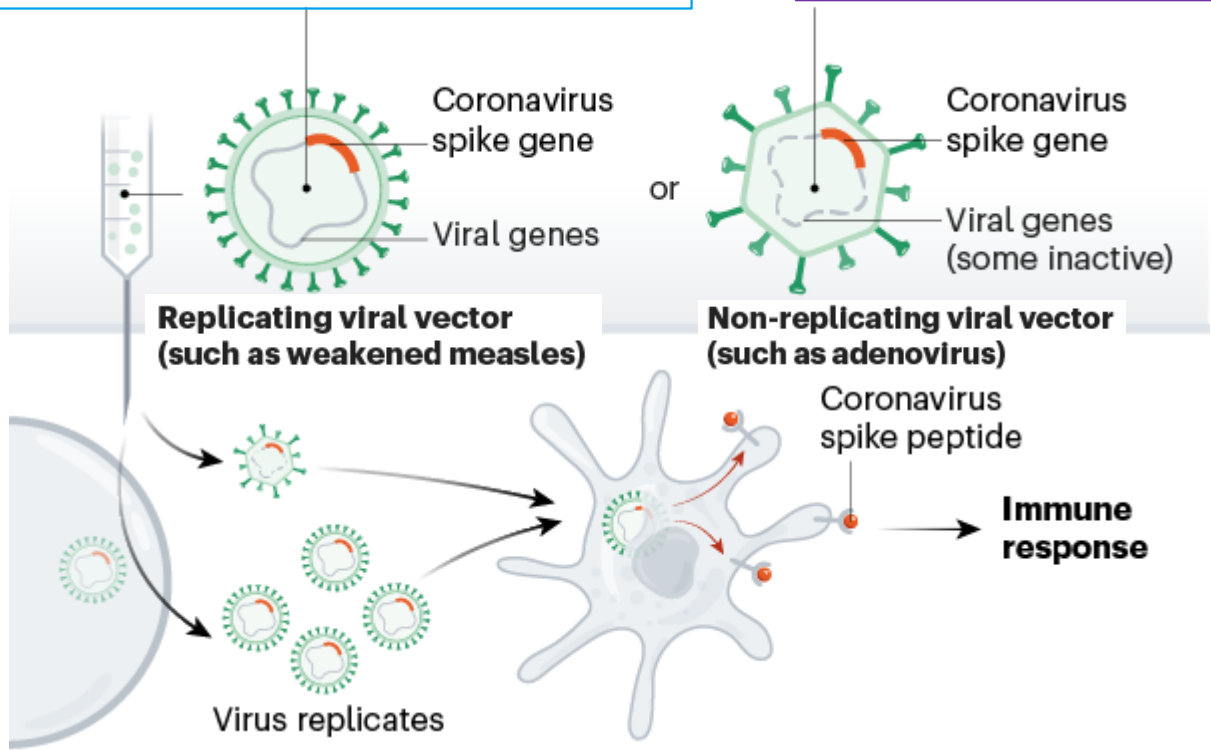
Rhabdoviruses
(VSV-based Platform Technology)

Alphaviruses

Herpes Viruses

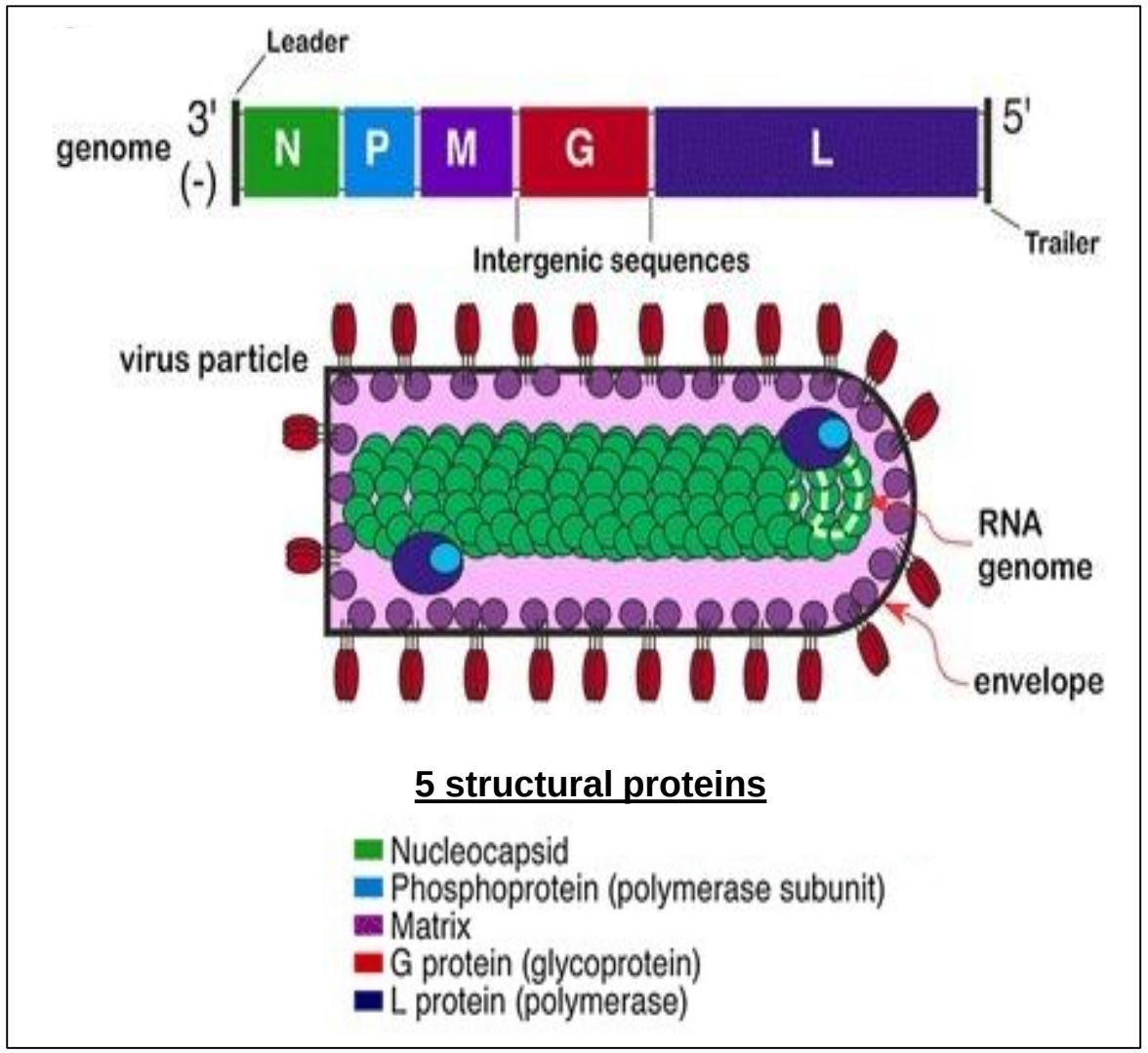
Retroviruses

Adenoviruses

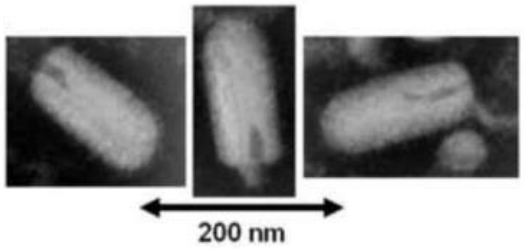


NEWS FEATURE 28 April 2020

Vesicular Stomatitis Virus (VSV)



- Negative strand RNA genome: ~12K nt
- **No pre-existing Ab in human**
- Wide host range, mild infection in human
- **High yield production**: 1 - 4 x 10^9 pfu/ml
- Accommodates up to 6 Kbp of foreign genes
- Two antigenically distinct serotypes
  : Indiana and New Jersey strain
- **M gene mutant: avirulent**



Open Forum Infect Dis. 2015 Sep; 2(3) ofv082, Trends in Mol. Med. 2004 10:210-216, J. Virol. Methods 2015 218:71-76, PNAS 2013 110:7306-7300

Current viral vector vaccine using rVSV

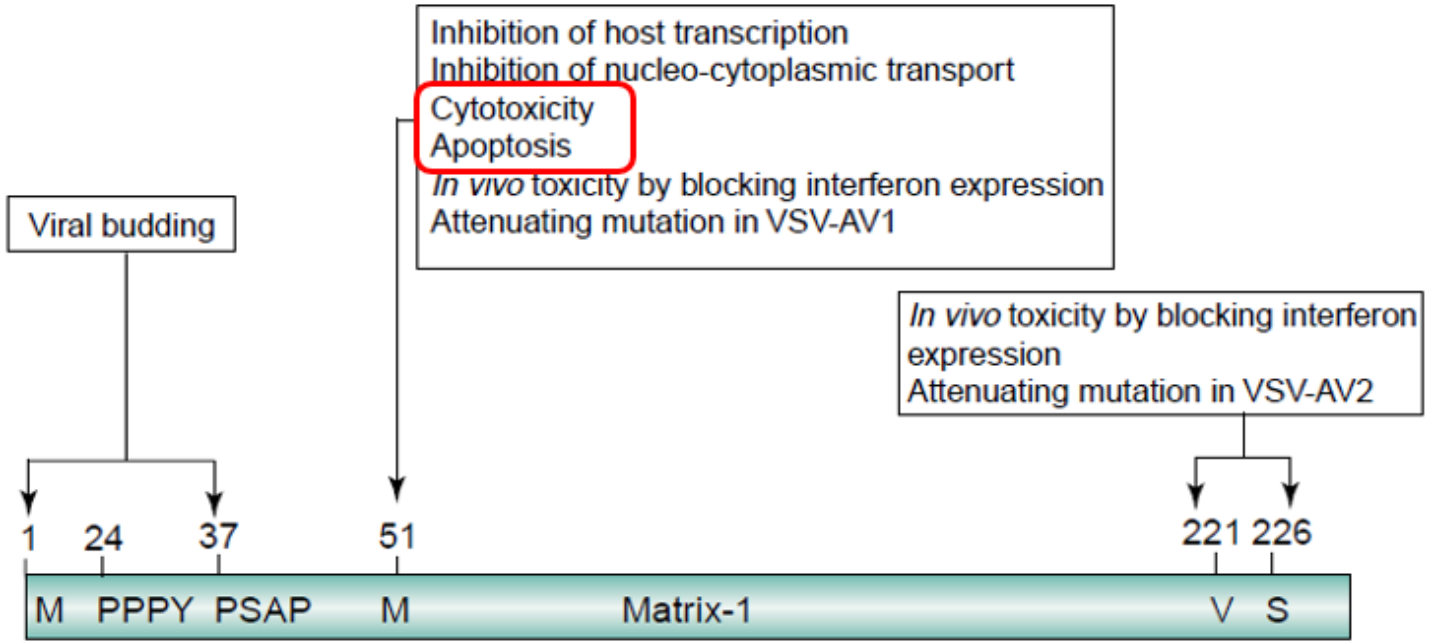
- Since 2011, rVSV vectors have been evaluated in four completed or ongoing clinical trials for HIV-1.
- Since 2014, Phase I, II and III clinical trials of an rVSV-Ebola vaccine have been conducted.

  : the most advanced vaccine candidate in the recent Ebola virus epidemic in West Africa

  : 12 candidate vaccines

: Merck's ERVEBO®(rVSVΔG-ZEBOV-GP) is approved in the U.S. and E.U.

The toxicity of wild-type VSV

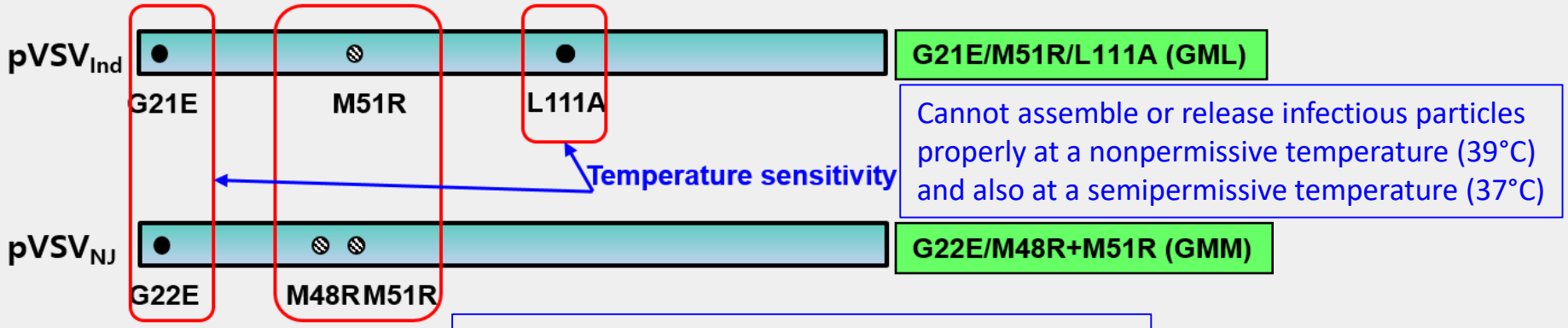


* Safety concerns have been raised to wild-type VSV

1. Neurovirulence shown in nonhuman primate after intracerebral or intranasal inoculation.
2. Vaccine-related headaches, arthralgia, and arthritis (including joint pain, tenderness or swelling) have been reported at high-dose injection.

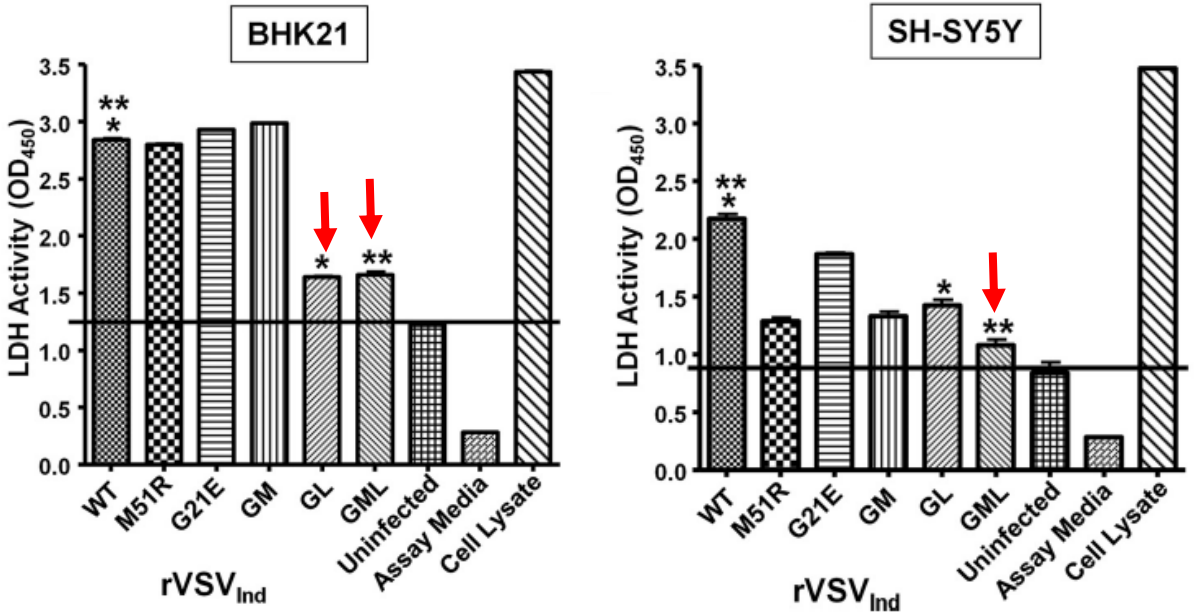
Trends in Mol. Med. 2004 10:210-216, J. Virol. 2015 89:6338, Virol., 2007 357:41

Attenuated rVSV vector - M gene mutant



Cannot assemble or release infectious particles properly at a nonpermissive temperature (39°C) and also at a semipermissive temperature (37°C)

Lost its neurovirulence in mice, as demonstrated by direct inoculation of the virus into the brain.



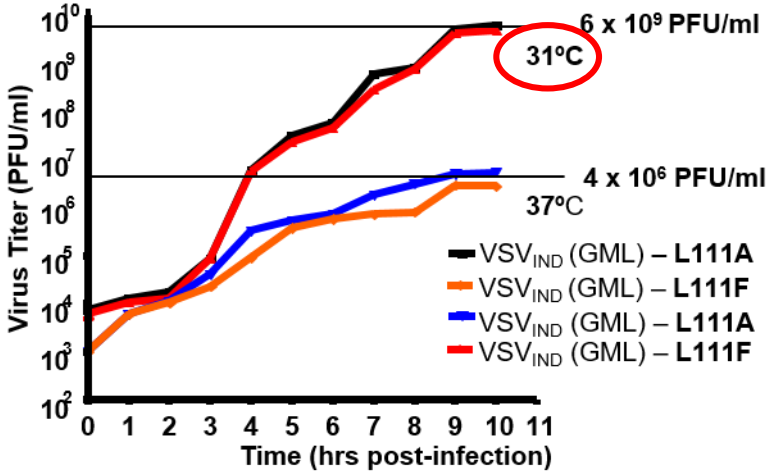
SH-SY5Y;Human neuroblastoma cells

- **The combined mutations in the *M* gene of rVSV reduced cytopathogenicity significantly in cells**

Trends in Mol. Med. 2004 10:210-216, J. Virol. 2015 89:6338, Virol., 2007 357:41

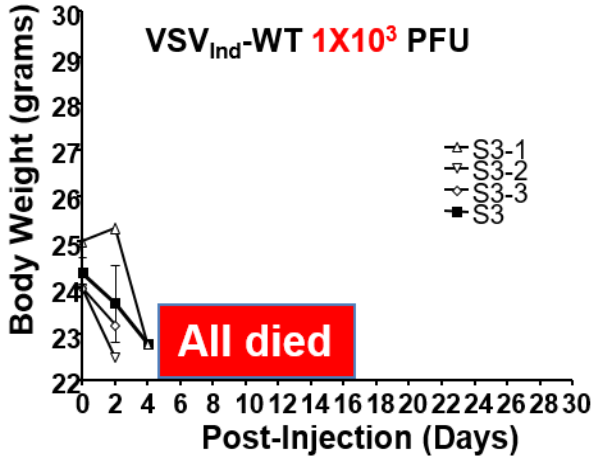
Attenuated rVSV vector - M gene mutant

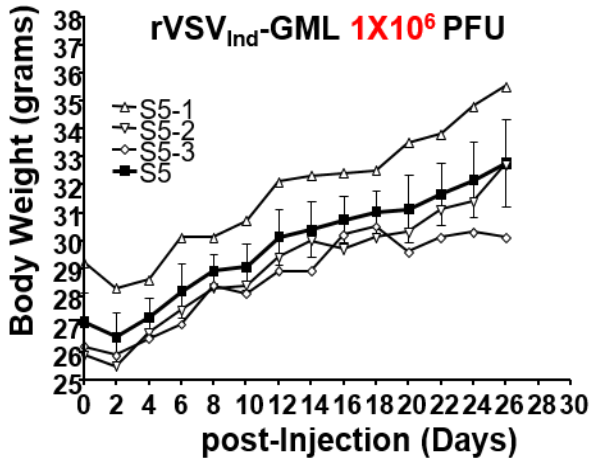
❖ **Growth kinetics**



- M gene mutation rVSV reduces replication efficiency at human body temperature.

❖ **Neurovirulence studies in swiss webster mouse**





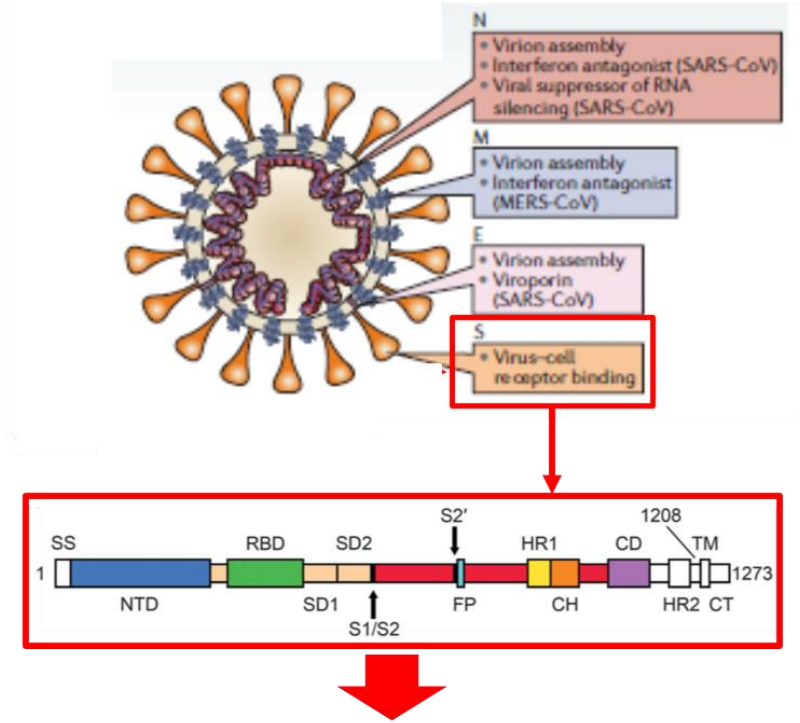
- The M gene mutation rVSV did not show toxicity even at 1000 times higher concentrations than wild type VSV.

➢ **Attenuated form of rVSV (M gene mutant) demonstrates safety and immunogenicity in animal experiments.**

rVSV-COVID-19 (Wu-hu-1) vaccine

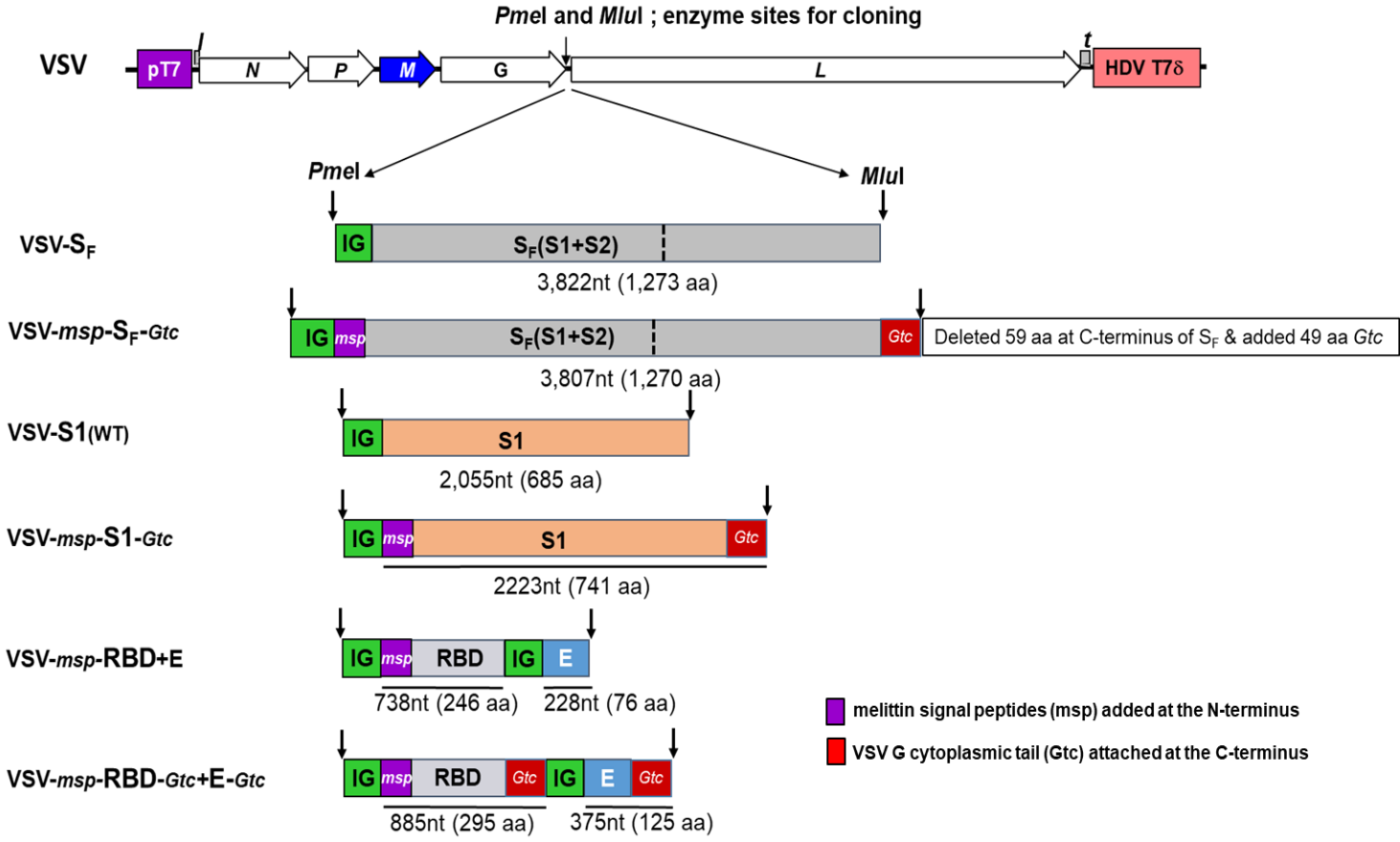
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

- *Coronaviridae* family, single-stranded RNA virus, cause of COVID-19

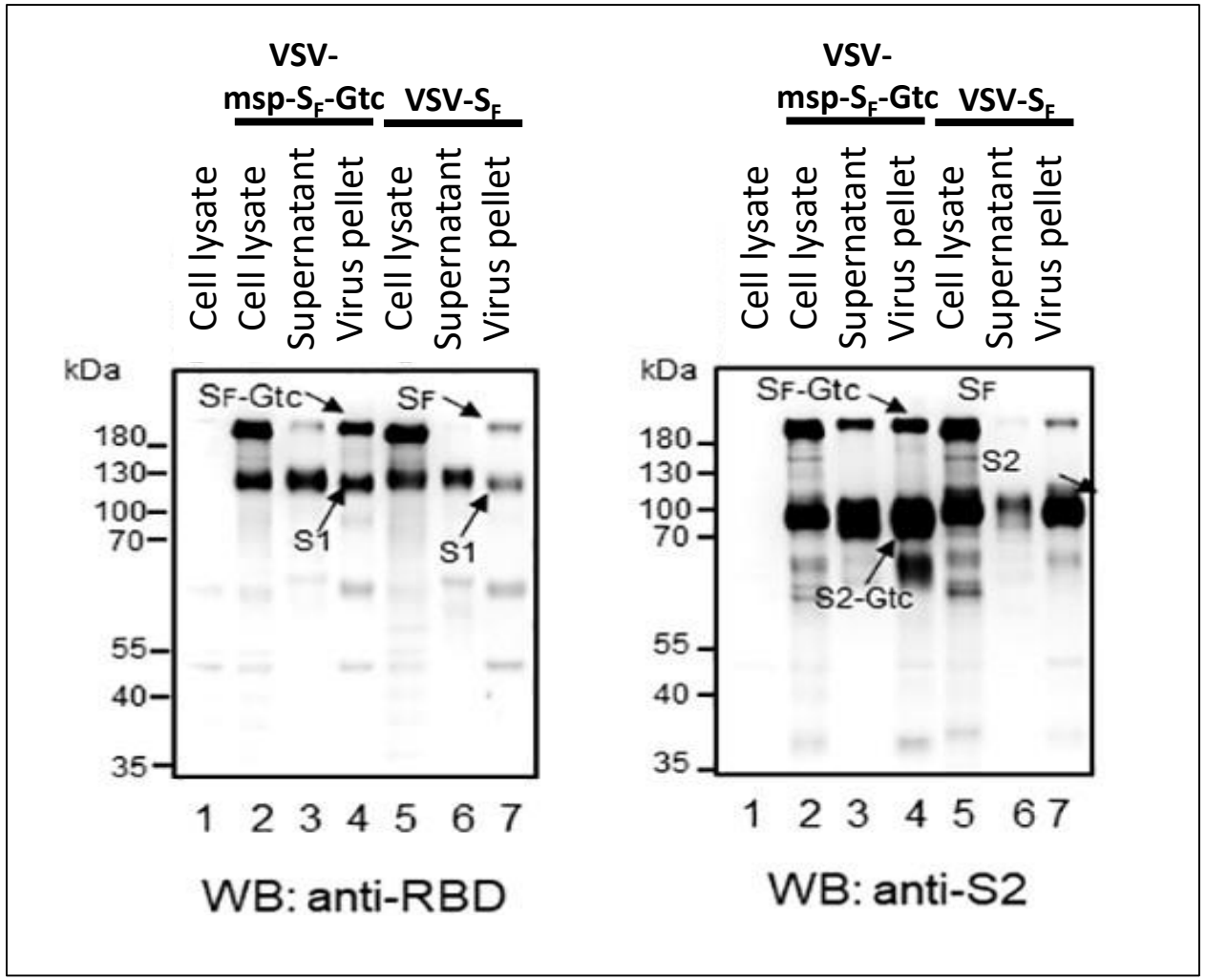


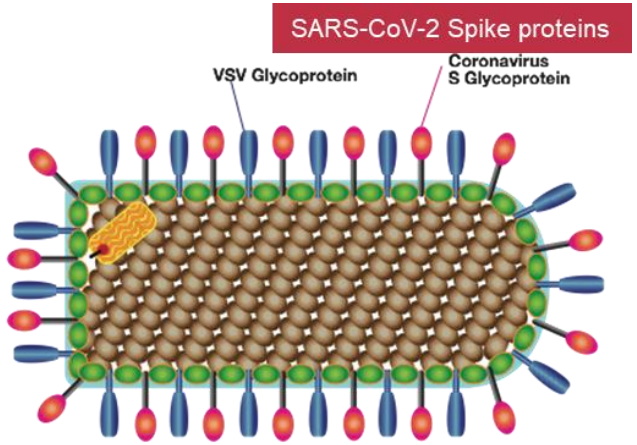
Spike (S) protein binds to the ACE2 receptor, responsible for host cell entry, and is considered as a vaccine target

- Construction of rVSV-COVID-19 candidates



Expression of SARS-CoV-2 proteins from rVSV-COVID-19





Depicted model of pseudotype rVSV virions with SARS-CoV-2 spike proteins

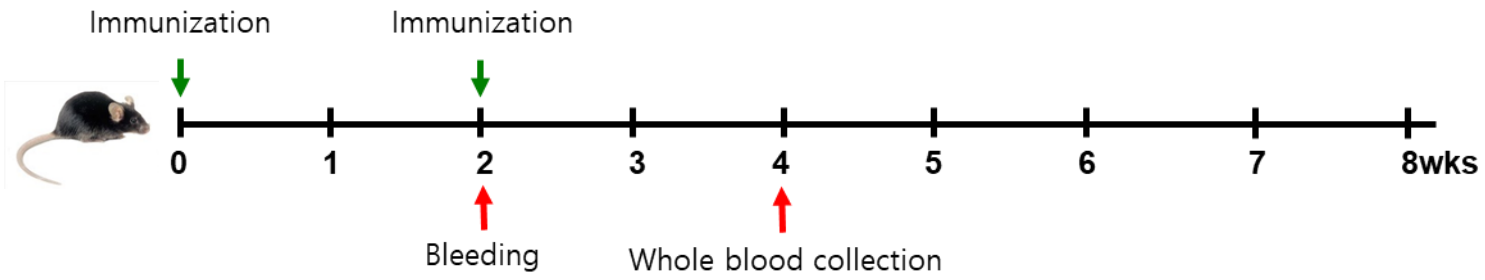
- **Secretion and incorporation into viral particles of SARS-CoV-2 protein are enhanced by the addition of msp and Gtc.**

Plos phathogen, 2021, 17(12): e1010092

Vaccine efficacy evaluation of rVSV-COVID-19 vaccine candidates

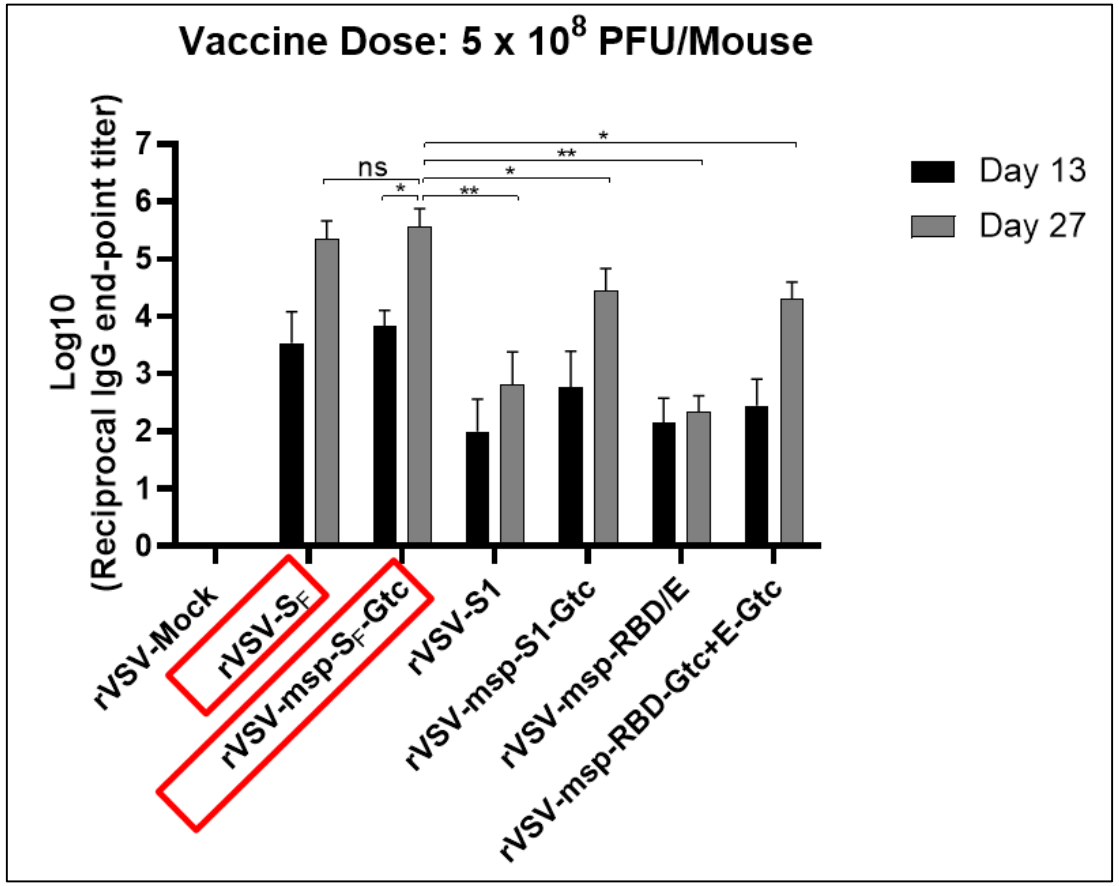
❖ Experimental scheme

Group	Priming	Boosting	Interval	Mouse	Route
1	$rVSV_{IND}$-Mock ($5x10^8$ pfu)	$rVSV_{IND}$-Mock ($5x10^8$ pfu)	2 wks	C57BL/6	i.m.
2	rVSV-S_F ($5x10^8$ PFU)	rVSV-S_F ($5x10^8$ PFU)			
3	rVSV-msp-S_F-Gtc ($5x10^8$ PFU)	rVSV-msp-S_F-Gtc ($5x10^8$ PFU)			
4	rVSV-S1 ($5x10^8$ PFU)	rVSV-S1 ($5x10^8$ PFU)			
5	rVSV-msp-S1-Gtc ($5x10^8$ PFU)	rVSV-msp-S1-Gtc ($5x10^8$ PFU)			
6	rVSV-msp-RBD/E ($5x10^8$ PFU)	rVSV-msp-RBD/E ($5x10^8$ PFU)			
7	rVSV-msp-RBD-Gtc+E-Gtc ($5x10^8$ PFU)	rVSV-msp-RBD-Gtc+E-Gtc ($5x10^8$ PFU)			

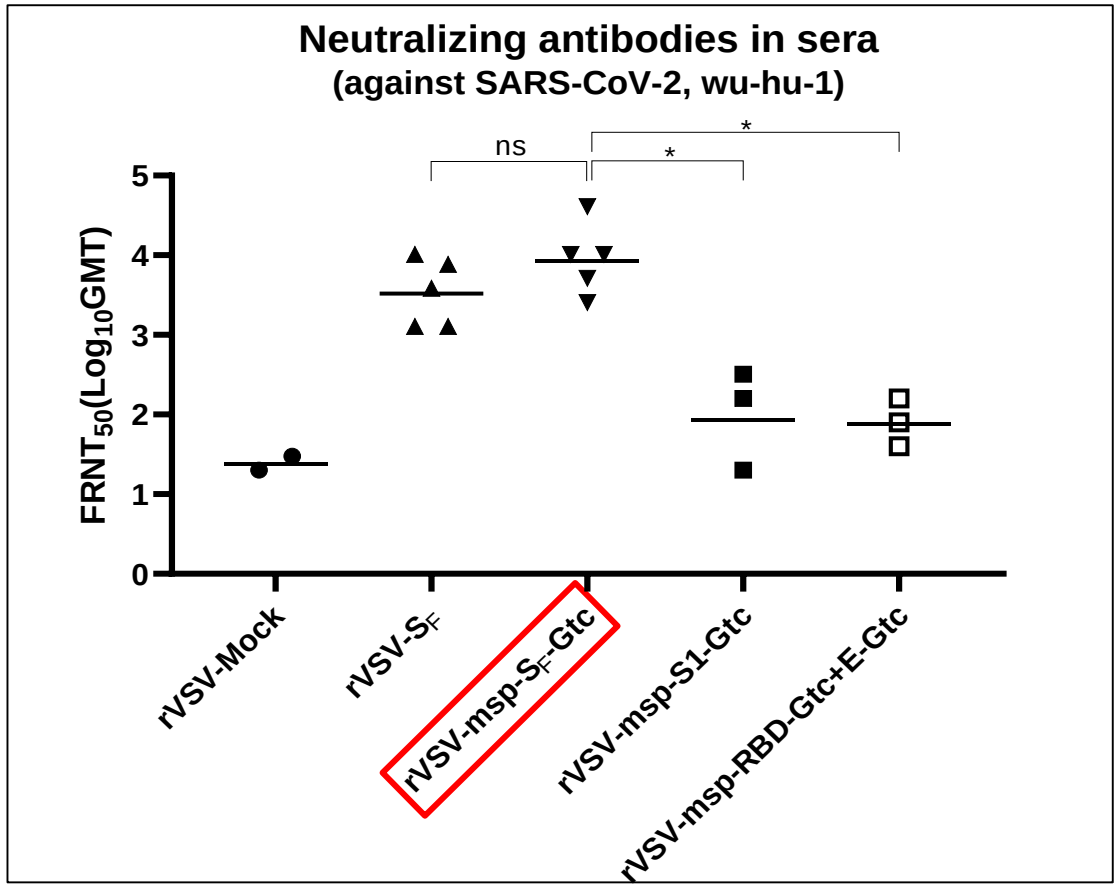


Vaccine efficacy evaluation of rVSV-COVID-19 vaccine candidates

❖ **The IgG antibody titers**



❖ **The neutralizing antibody titers**



➢ **Mice immunized with rVSV-msp-S_F-Gtc showed the highest spike protein-specific antibody titers and neutralizing antibody titers.**

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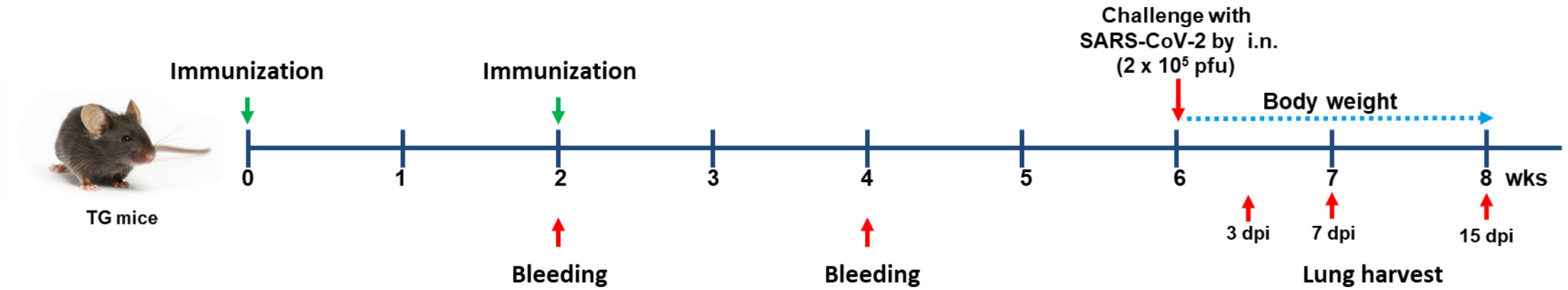
Protective effect of rVSV-COVID-19 vaccine in K18/hACE2 transgenic mouse

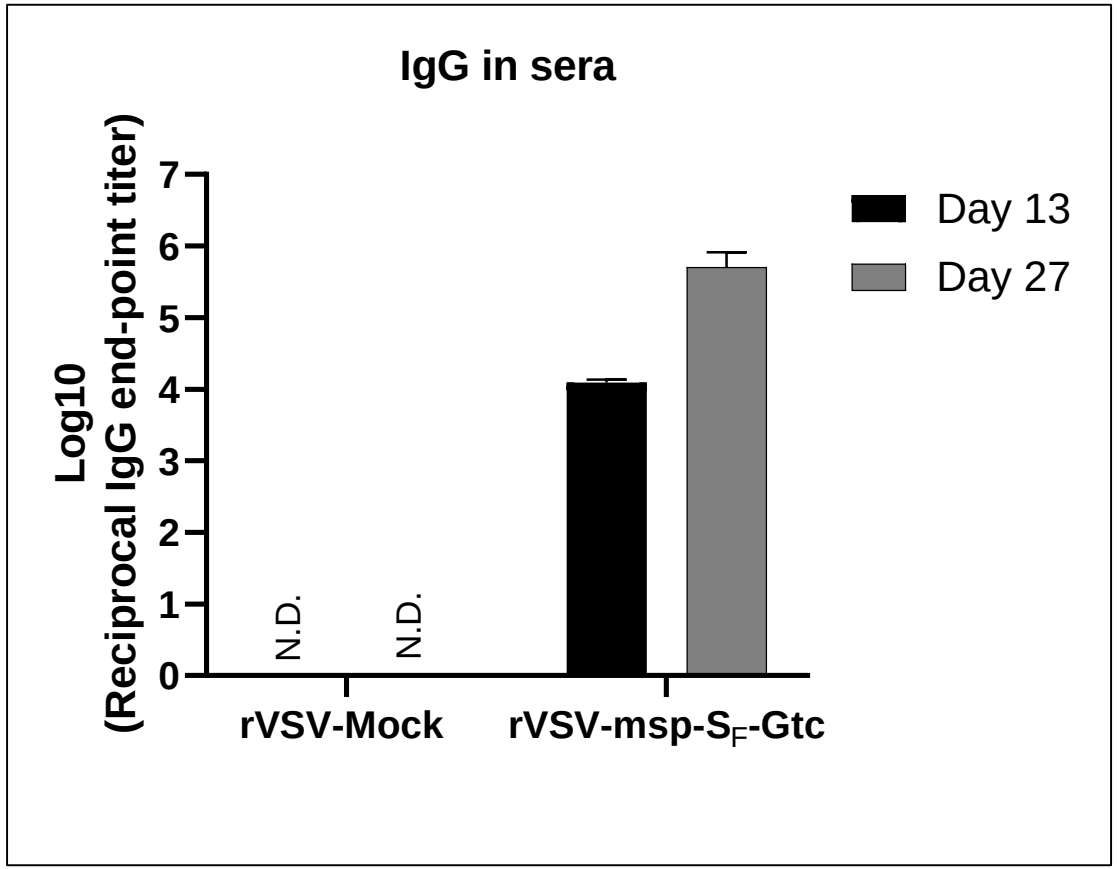
❖ Experimental scheme

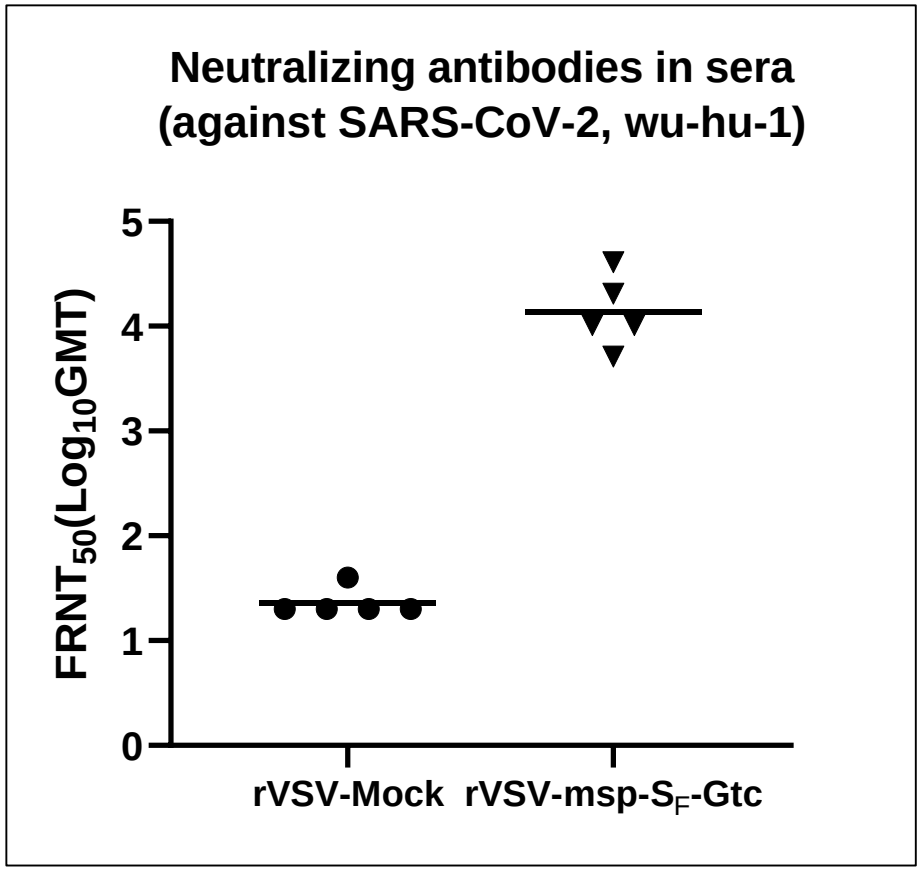


Group	Immunization	Route	Virus harvest & serum collection	Body weight
1	PBS (No infection)	i.m.	3 Dpi (n=3)	15 days (n=5)
			7 Dpi (n=2)	
2	rVSV-Mock ($5x10^8$ PFU)	i.m.	3 Dpi (n=3)	15 days (n=5)
			7 Dpi (n=2)	
3	rVSV-msp-S_F-Gtc ($5x10^8$ PFU)	i.m.	3 Dpi (n=3)	15 days (n=5)
			7 Dpi (n=2)	

Protective effect of rVSV-COVID-19 vaccine in K18/hACE2 transgenic mouse

❖ **The IgG and neutralizing antibody titers before virus challenge**





➢ **Mice immunized with rVSV-msp-S$_F$-Gtc had substantially high levels of binding and neutralizing antibody titers.**

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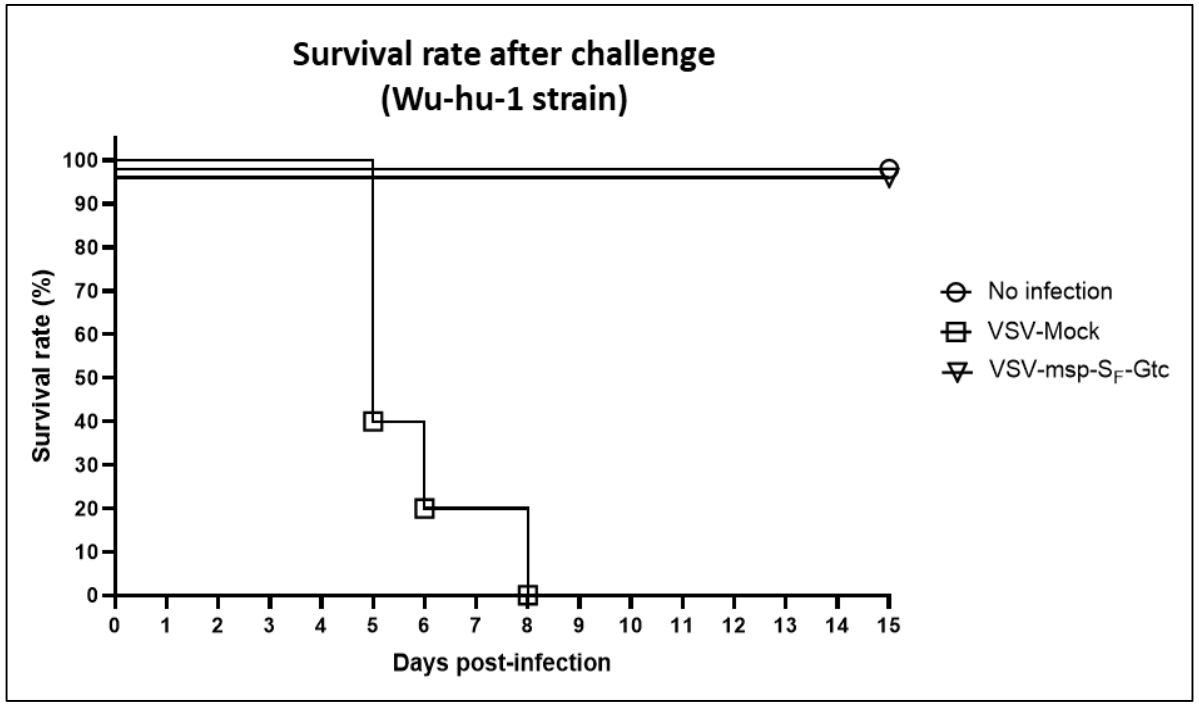
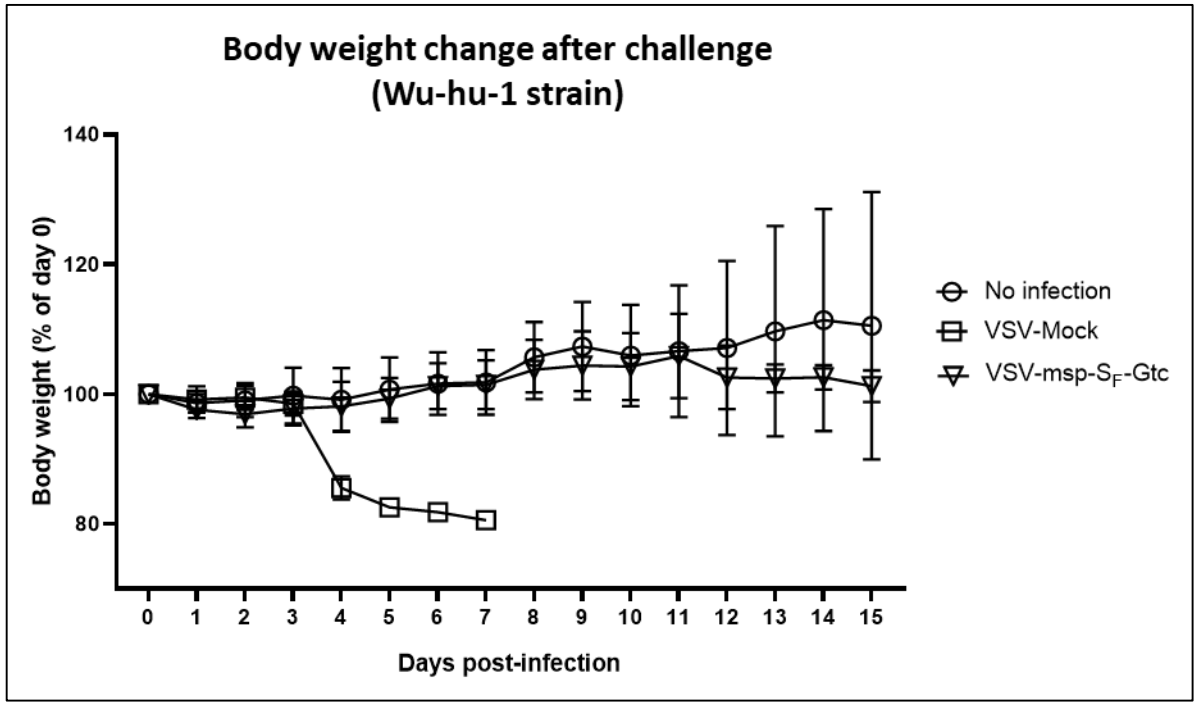
Protective effect of rVSV-COVID-19 vaccine in K18/hACE2 transgenic mouse

❖ **The survival rate and the body weight change after virus challenge**





→ All vaccinated hACE2 transgenic mice survived and no significant weight loss was observed.

➢ **The rVSV-COVID-19 vaccine candidate (msp-S$_F$-Gtc) showed protective effect against SARS-CoV-2 Wu-Hu-1 strain infection.**

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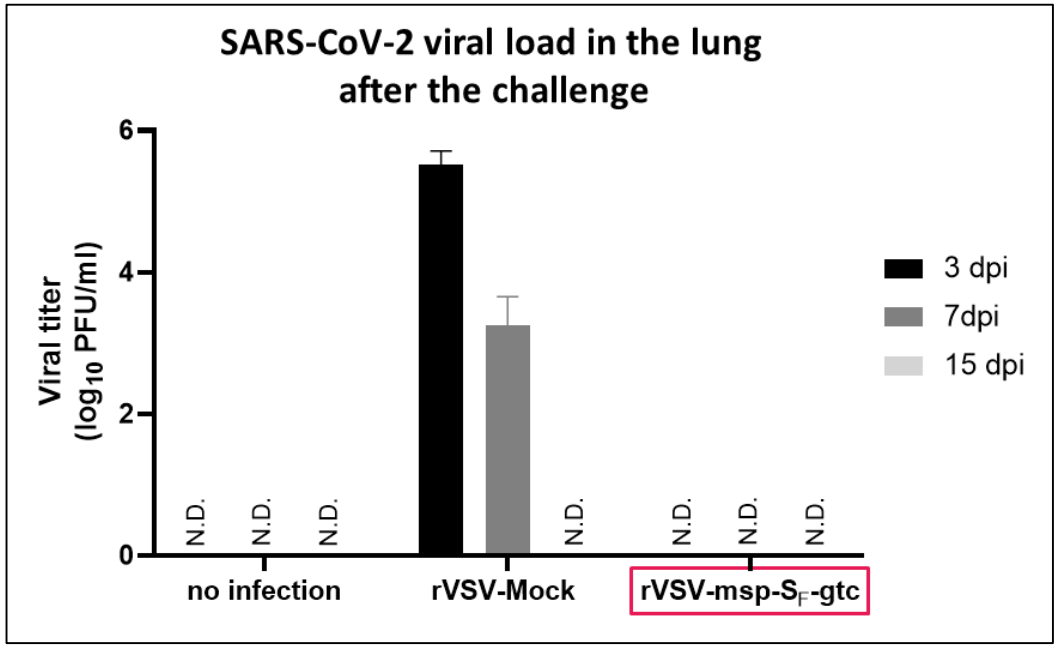
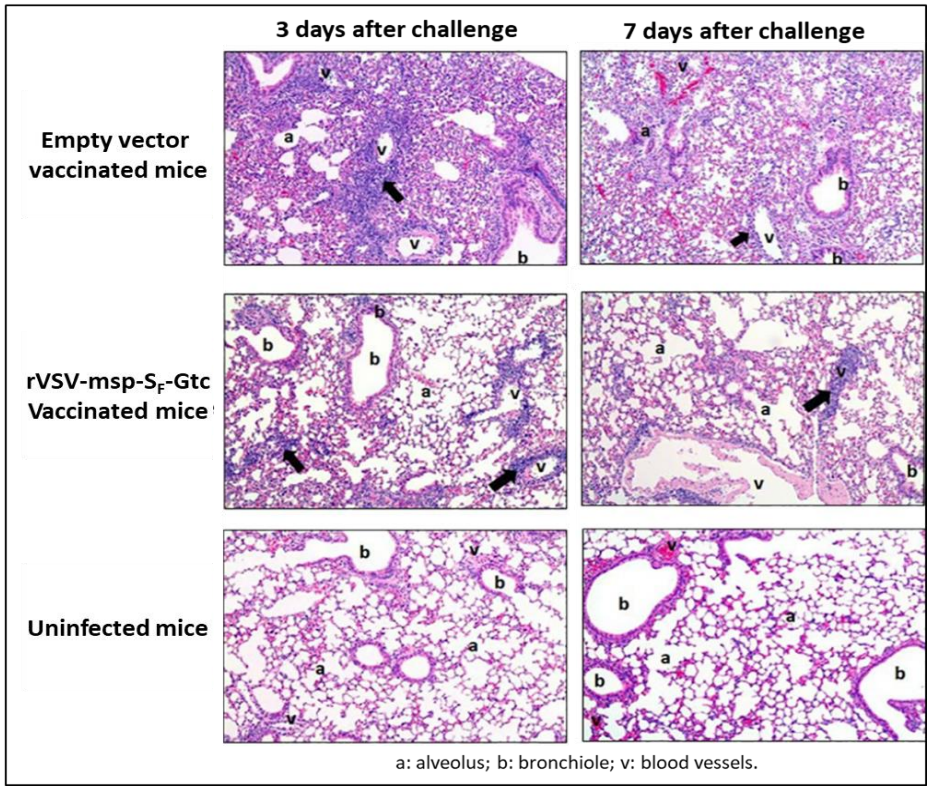
Protective effect of rVSV-COVID-19 vaccine in K18/hACE2 transgenic mouse

❖ The viral load in the lungs after virus challenge



❖ The histopathology of lung after virus challenge



➢ **rVSV-COVID-19-msp-S_F-Gtc vaccine protected animals from a lethal dose of SARS-CoV-2. (no viral load in the lung and lung damage)**

Inflammation score

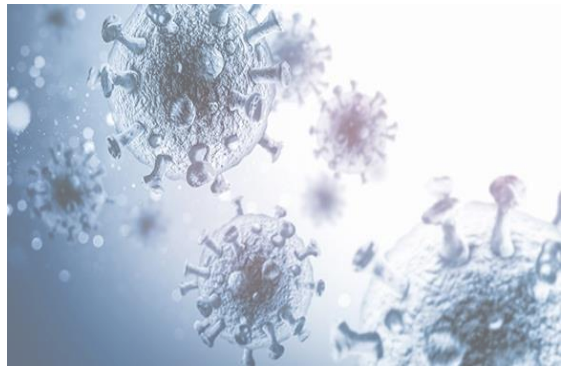
Groups \ Days	3 days after challenge	7 days after challenge
Empty vector vaccinated mice (n=3)	2	1
rVSV-msp-S_F-Gtc vaccinated mice (n=3)	0	0
Uninfected mice (n=3)	0	0

Plos phathogen, 2021, 17(12): e1010092

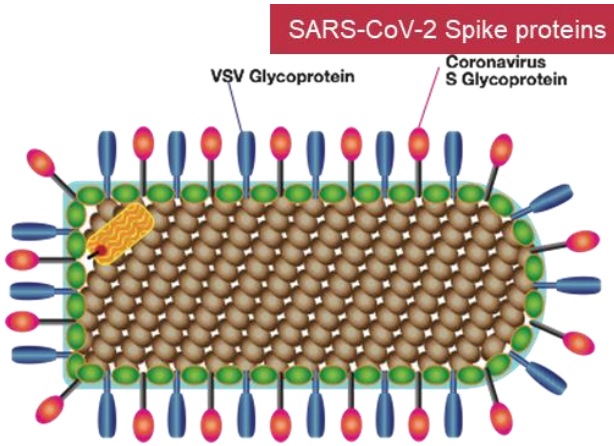
rVSV-COVID-19 (Omicron variant) vaccine

Summary of rVSV-COVID-19 vaccine

- **rVSV-COVID-19 vaccine (Wu-hu-1 strain)**
  - The immunogenicity and toxicology studies of rVSV-COVID-19 (Wu-hu-1) in mice and monkey have been evaluated.
  - Investigational New Drug (IND) application for Phase I clinical trial has been submitted.



- **rVSV-COVID-19 Omicron variant vaccines for variant viruses**



rVSV-msp-S-Gtc vaccine

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Q&A

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