Vaccines Against SARS-CoV-2

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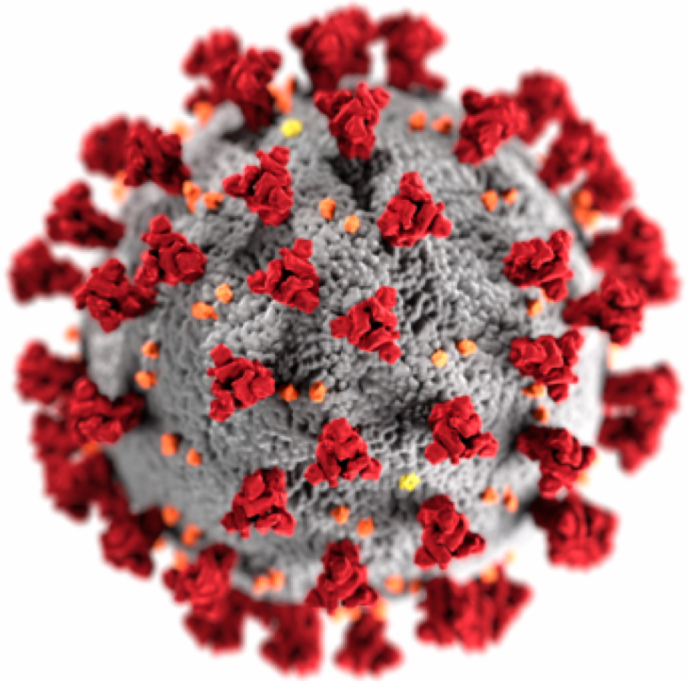
Disclosures

- Consultant for BMGF, Pfizer, Ellume, and Merck
- Research grants from Gates Ventures, NIH, CDC, BMGF, DARPA, Apple Inc., Sanofi-Pasteur, and Roche-Genentech
- Member of the NIH Maternal SARS-CoV-2 Vaccine Working Group and VTEU COVID-19 Scientific Advisory Group

Outline

- Basic principles to inform accelerated vaccine development in pandemics
  - Identification of pathogens with pandemic potential
  - Coronavirus phylogeny
  - Key antigenic targets
- Vaccines in Development
  - Vaccine development timeline
  - mRNA and adenovirus vectored vaccines
- Additional considerations
  - Target populations
  - Financing, delivery and duration of protection



Top Emerging Pathogens Likely to Cause Severe Outbreaks in the Near Future.*

Diseases to be urgently addressed under the WHO Research and Development Blueprint

Crimean Congo hemorrhagic fever virus
Filovirus diseases (Ebola and Marburg)
Highly pathogenic emerging coronaviruses relevant to humans (Middle East respiratory syndrome coronavirus [MERS-CoV], severe acute respiratory syndrome coronavirus [SARS-CoV])
Lassa fever virus
Nipah virus
Rift Valley fever virus
Any new severe infectious disease

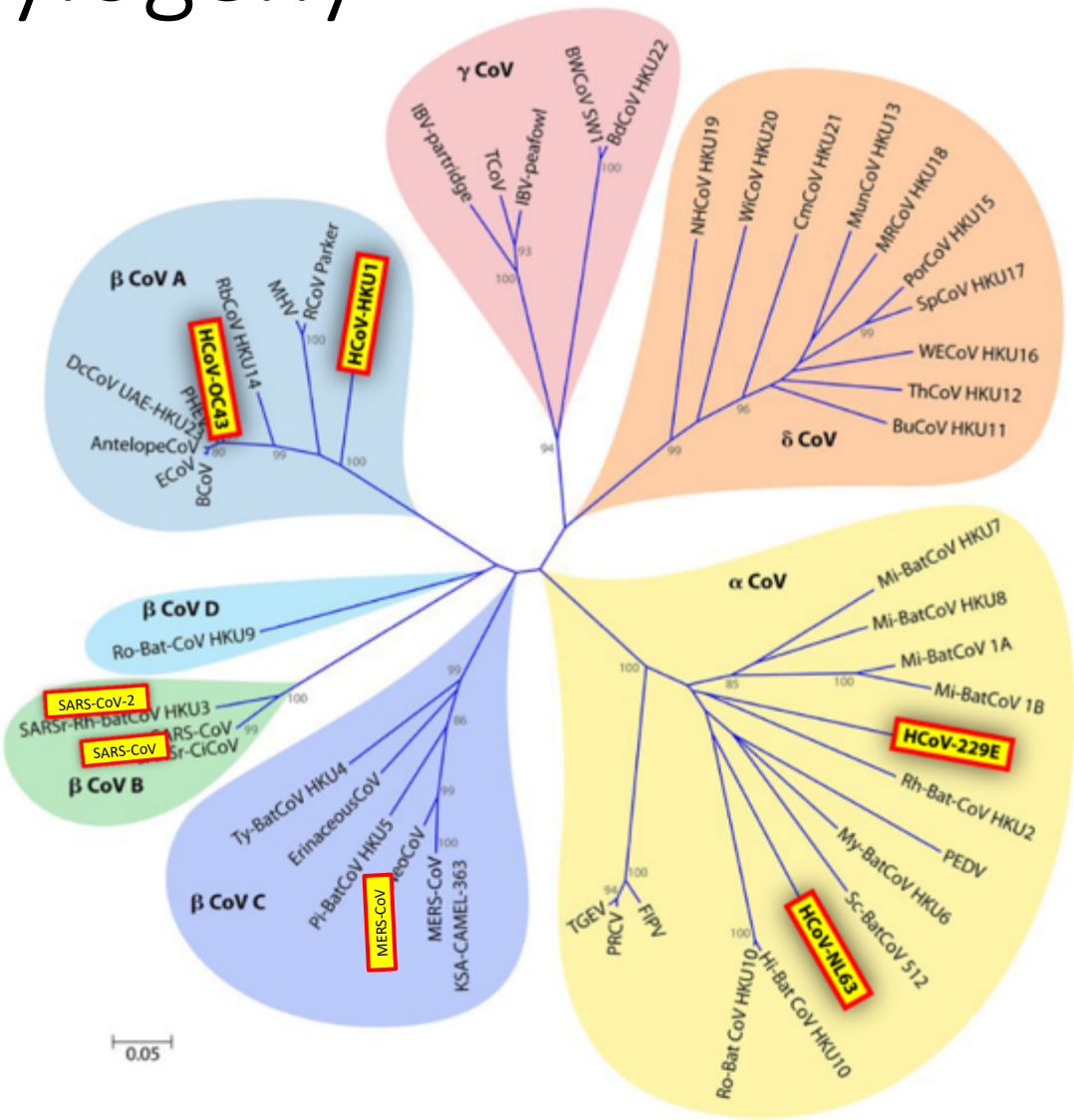
Serious diseases necessitating further action as soon as possible

Chikungunya
Severe fever with thrombocytopenia syndrome
Congenital abnormalities and other neurologic complications associated with Zika virus

Hammer headed fruit bat, Democratic Republic of the Congo, likely source of Ebola

Coronavirus Phylogeny

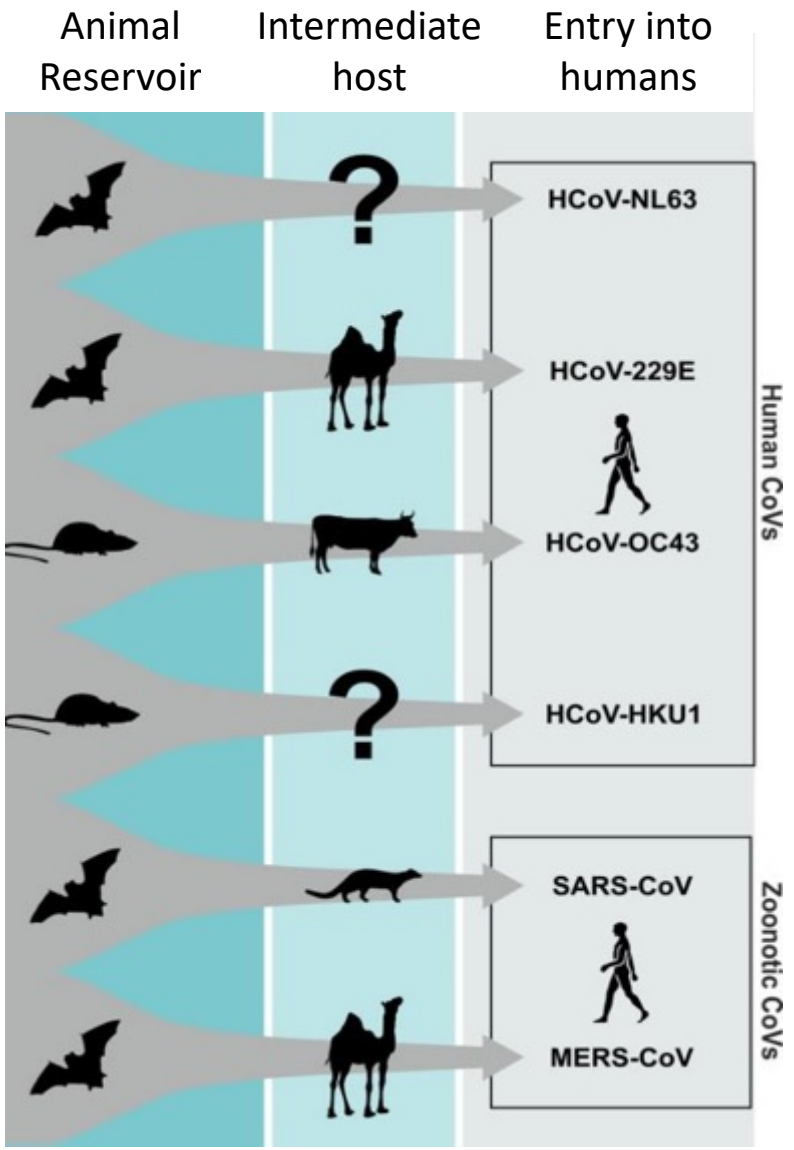
4 endemic coronaviruses (HCoV-229E, NL63, OC43, and HKU1) cause 15-30% of common colds



SARS-CoV-2
Betacoronavirus
Positive sense 30 kb genome

Source: Jasper FW Chan et al. *Clin. Microbiol. Rev.* 2015.

Origins and History of Human Coronaviruses



NL63 ~500-800 years

229E ~200-300 years

OC43 ~130 years

HKU1 >20 years

SARS-1 ~18 years

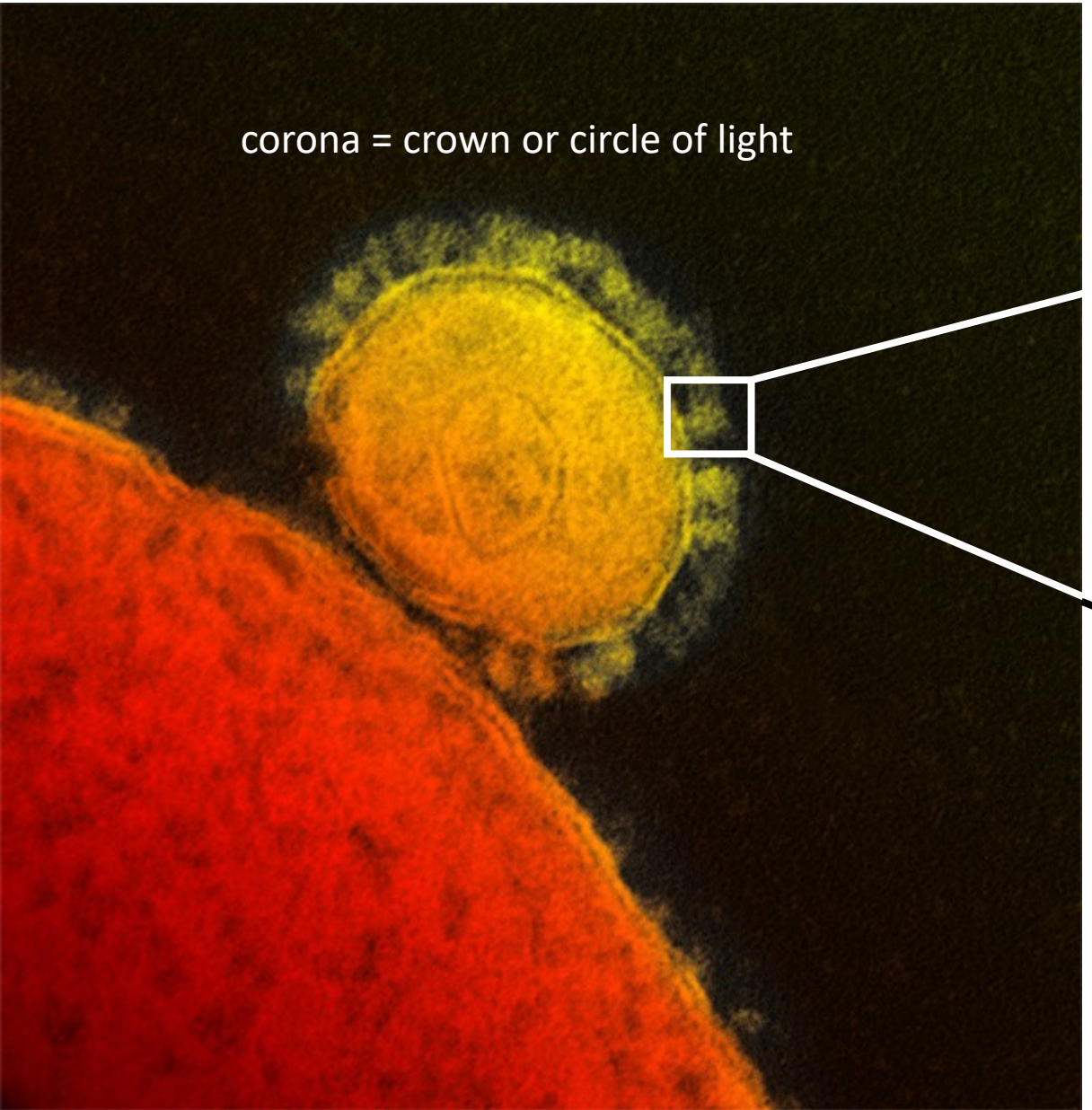
MERS ~8 years

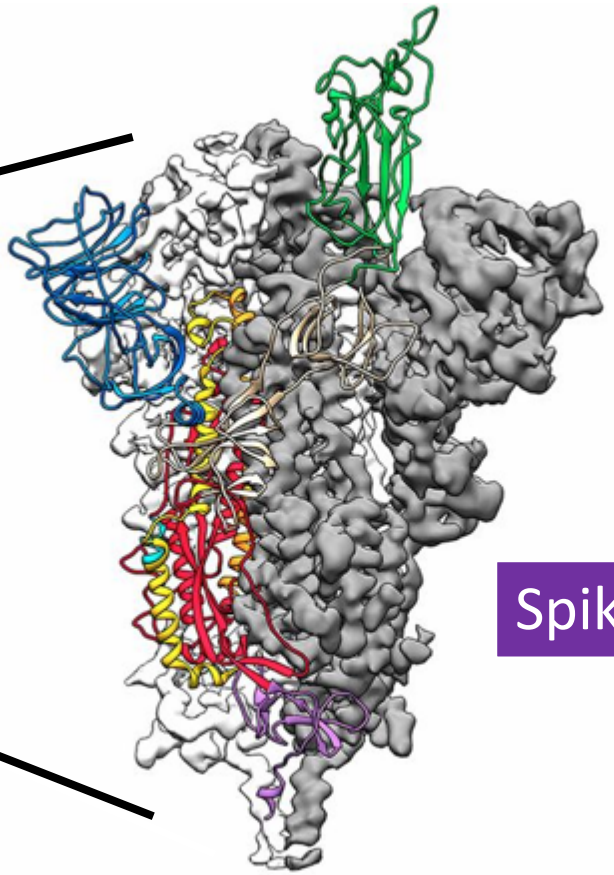
Drosten et al Adv Viral Research 2018
and adapted from Ralph Baric

Antigenic Structure Characterization

- We know from studies on SARS-CoV-1 and related MERS-CoV vaccines that the **S protein** on the surface of the virus is an ideal target for a vaccine.
- In SARS-CoV-1 and SARS-CoV-2, this protein interacts with the receptor **ACE2**, and antibodies targeting the spike can interfere with this binding, thereby neutralizing the virus

Coronavirus Biology and Nomenclature

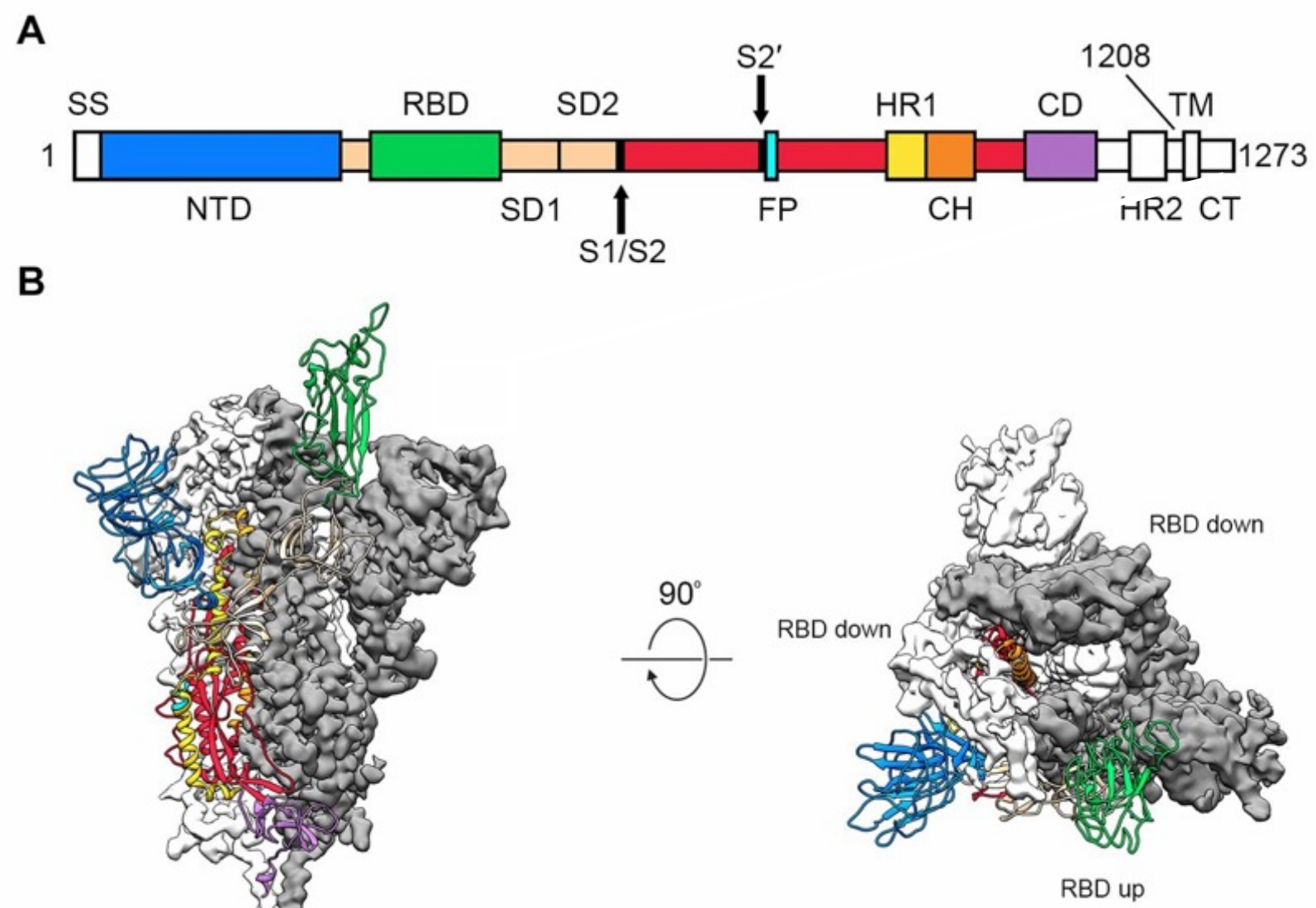




Spike Protein

Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, Graham BS, McLellan JS. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020 Feb 19:eabb2507. doi: 10.1126/science.abb2507.

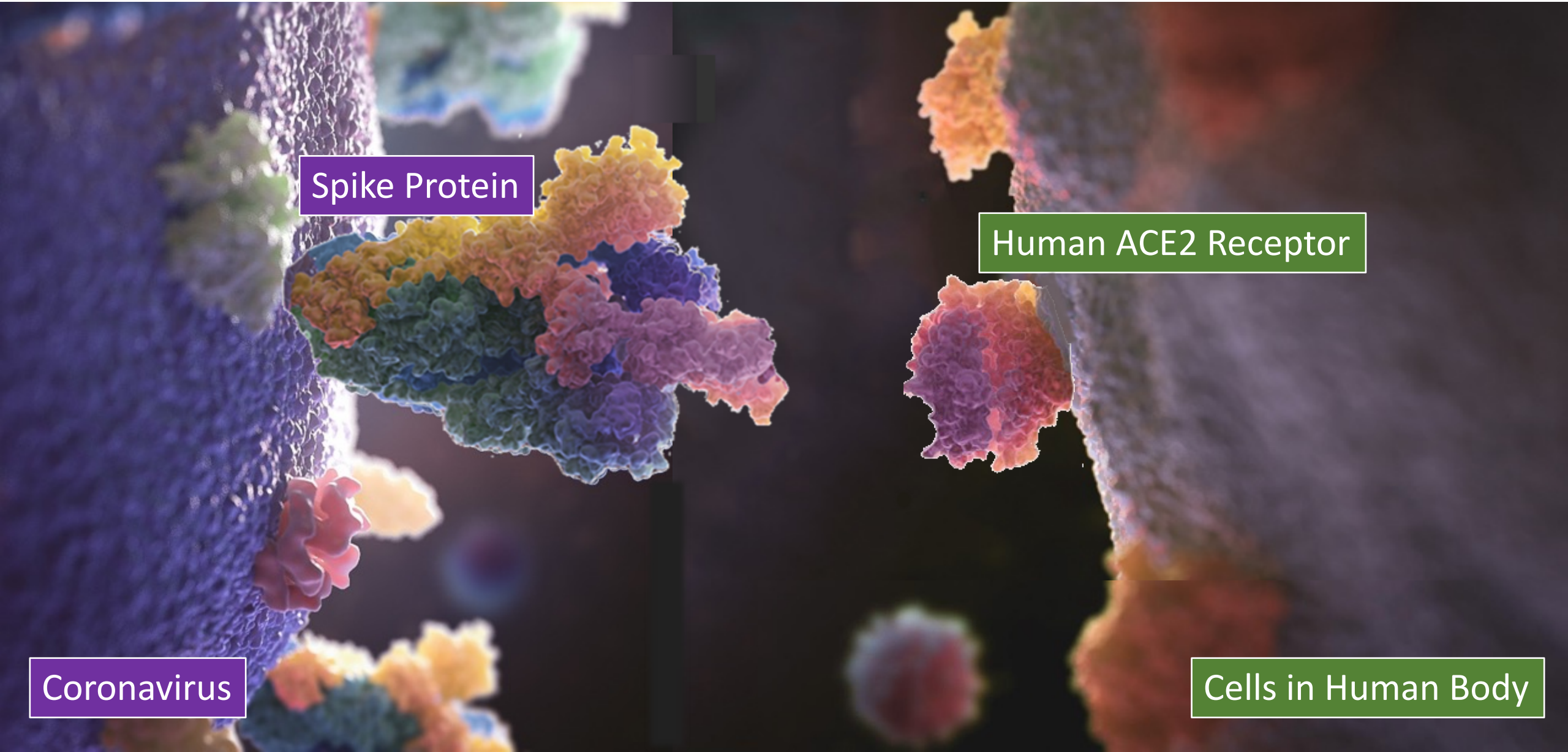
Coronavirus Biology and Nomenclature



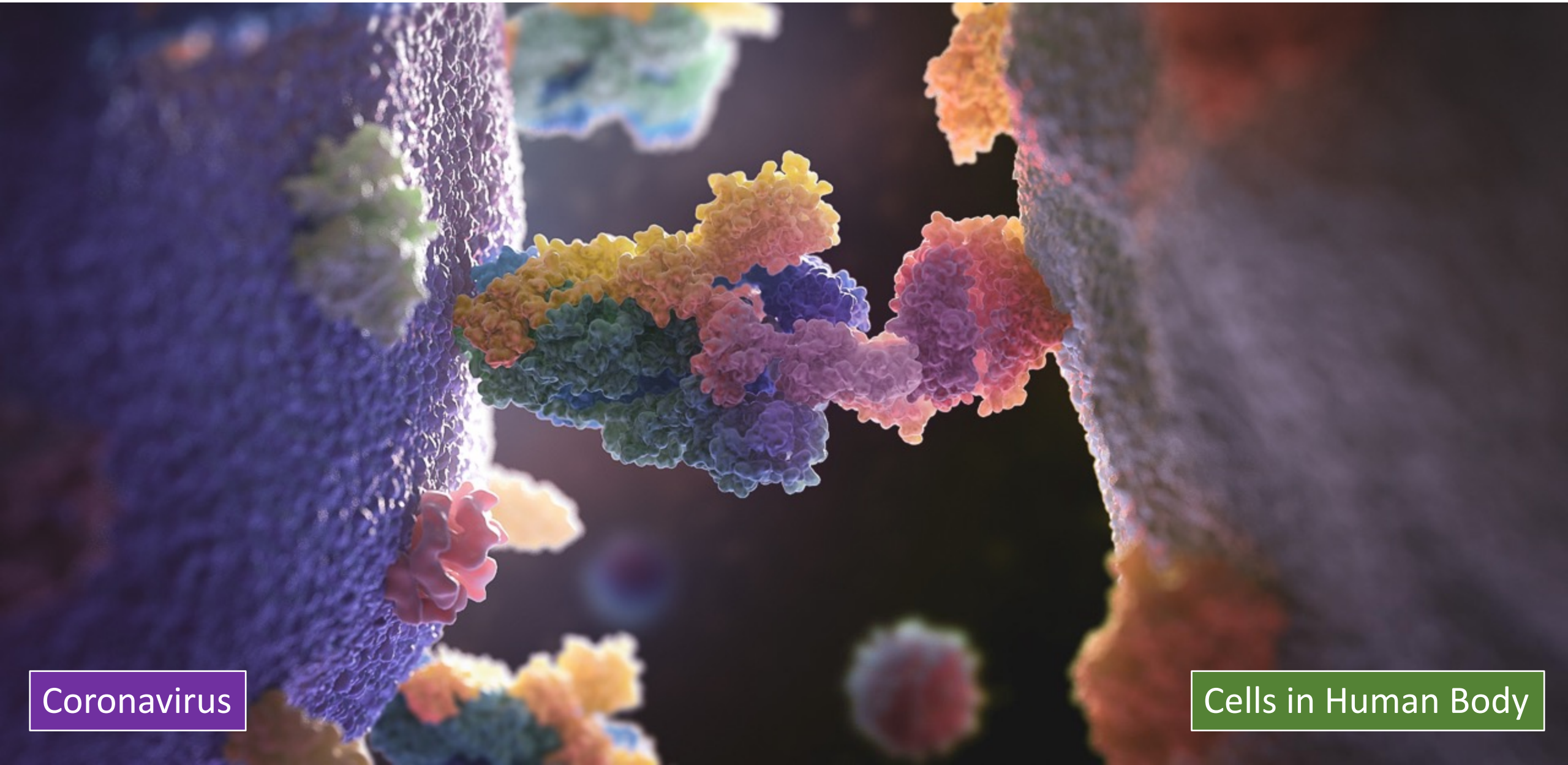
- Spike protein: fusion protein in a metastable conformation
- S1 and S2 subunits
- RBD is part of S1 subunit

Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, Graham BS, McLellan JS. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020 Feb 19:eabb2507. doi: 10.1126/science.abb2507.

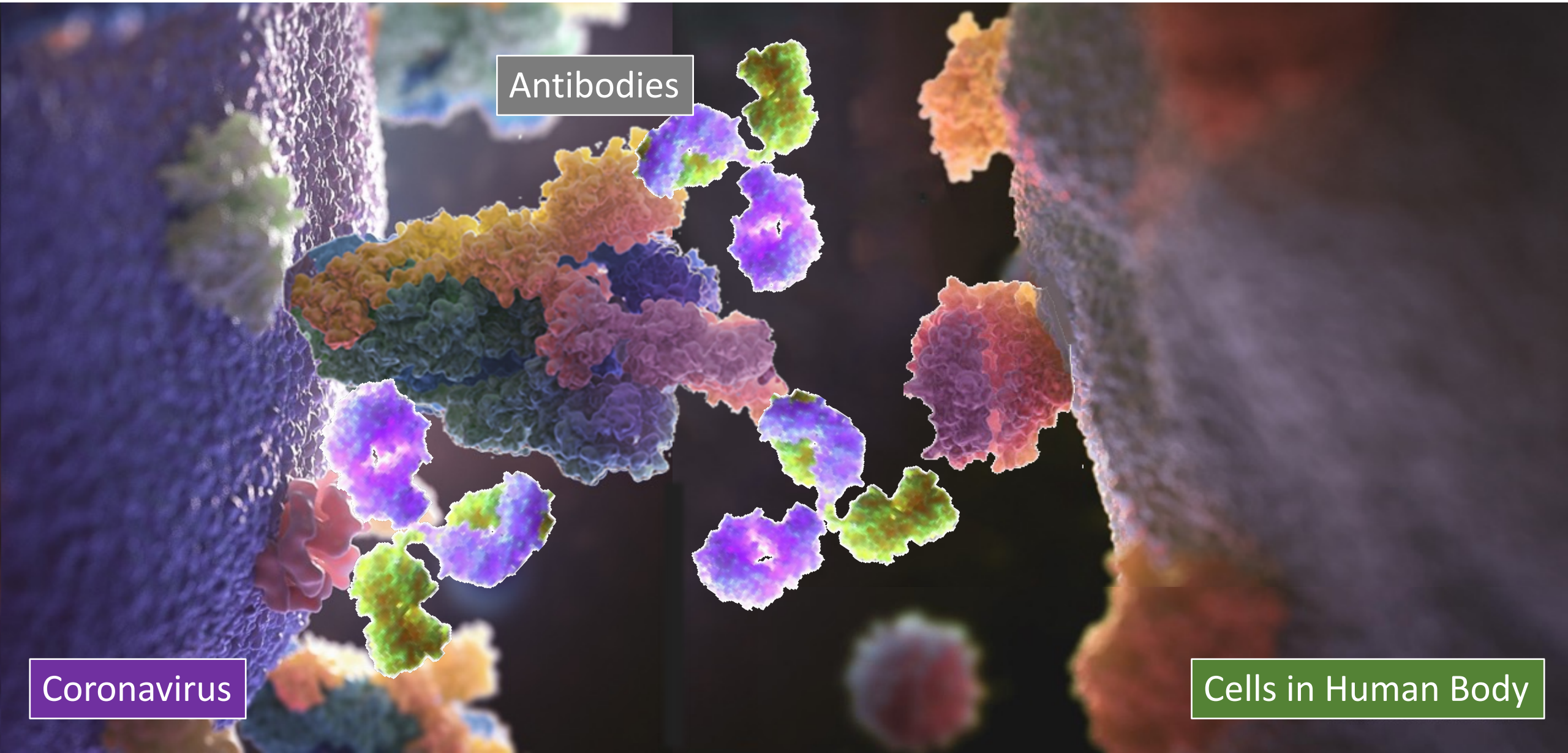
Coronavirus Spike Protein Mediates Entry



Coronavirus Spike RBD Flips Up for Attachment



CoV Spike is Primary Target for Neutralization



SARS-CoV-2 Vaccine Development

2013-2019 | 2020 | 2021

SARS-CoV-2 Outbreak

2013-2019
Extensive work on MERS and other CoV

Dec 31, 2019
1st report of respiratory virus outbreak in Wuhan, China

Jan 6, 2020
Wuhan outbreak may be CoV

Jan 10, 2020
2019-nCoV sequences published

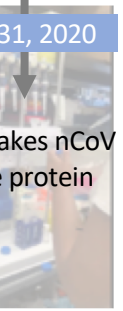
Jan 11, 2020
2019-nCoV constructs ordered

Jan 13, 2020
VRC decides on vaccine sequence with Moderna

Jan 14, 2020
Moderna receives sequence for GMP production

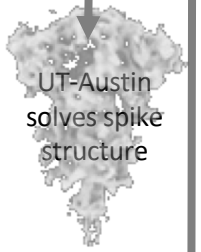
Jan 23, 2020
DMID initiates clinical and regulatory process

Jan 31, 2020
VRC makes nCoV spike protein



Feb 1, 2020
First nCoV spike ELISA for cross-reactivity

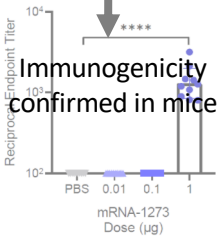
Feb 3, 2020
UT-Austin solves spike structure



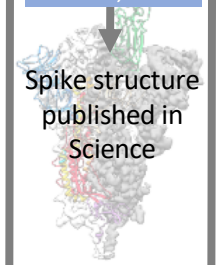
Feb 4 2020
VRC vaccinates mice

Feb 4, 2020
Moderna vials vaccine

Feb 18, 2020
Immunogenicity confirmed in mice



Feb 19, 2020
Spike structure published in Science



Feb 20, 2020
DMID submits IND

Feb 21, 2020
Moderna ships vaccine to DMID

Mar 2, 2020
FDA safe-to-proceed

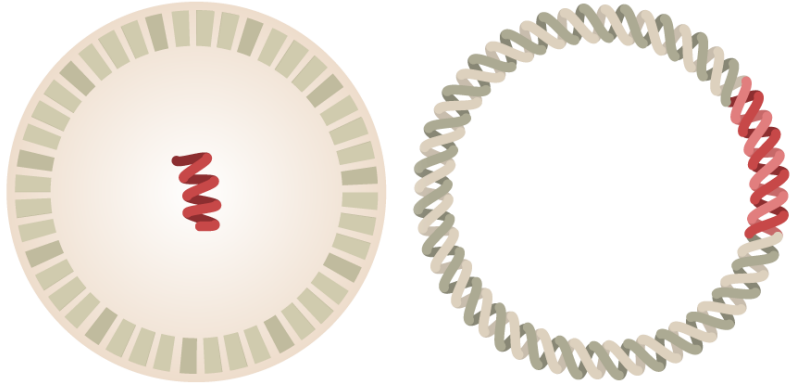
March 16, 2020
Phase 1 Clinical trial Starts

Previous fastest timeline
ZIKV DNA vaccine

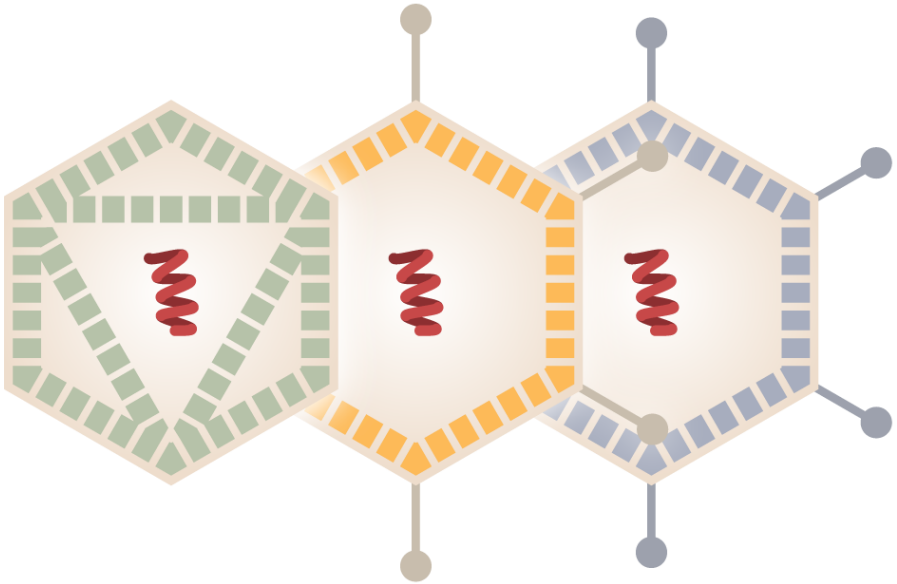
3 days | 38 days | 24 days

90 days | 100 days

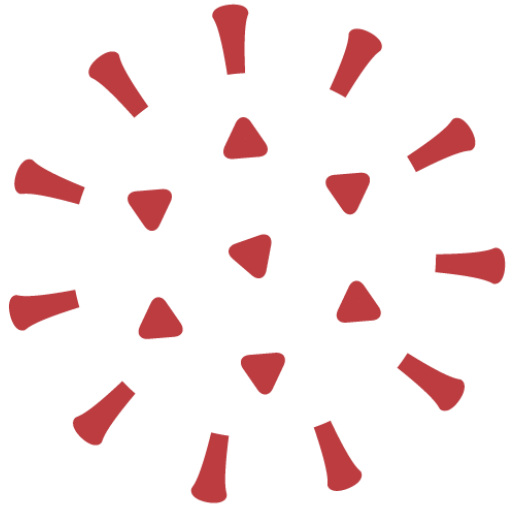
Genetic vaccines (mRNA or DNA)



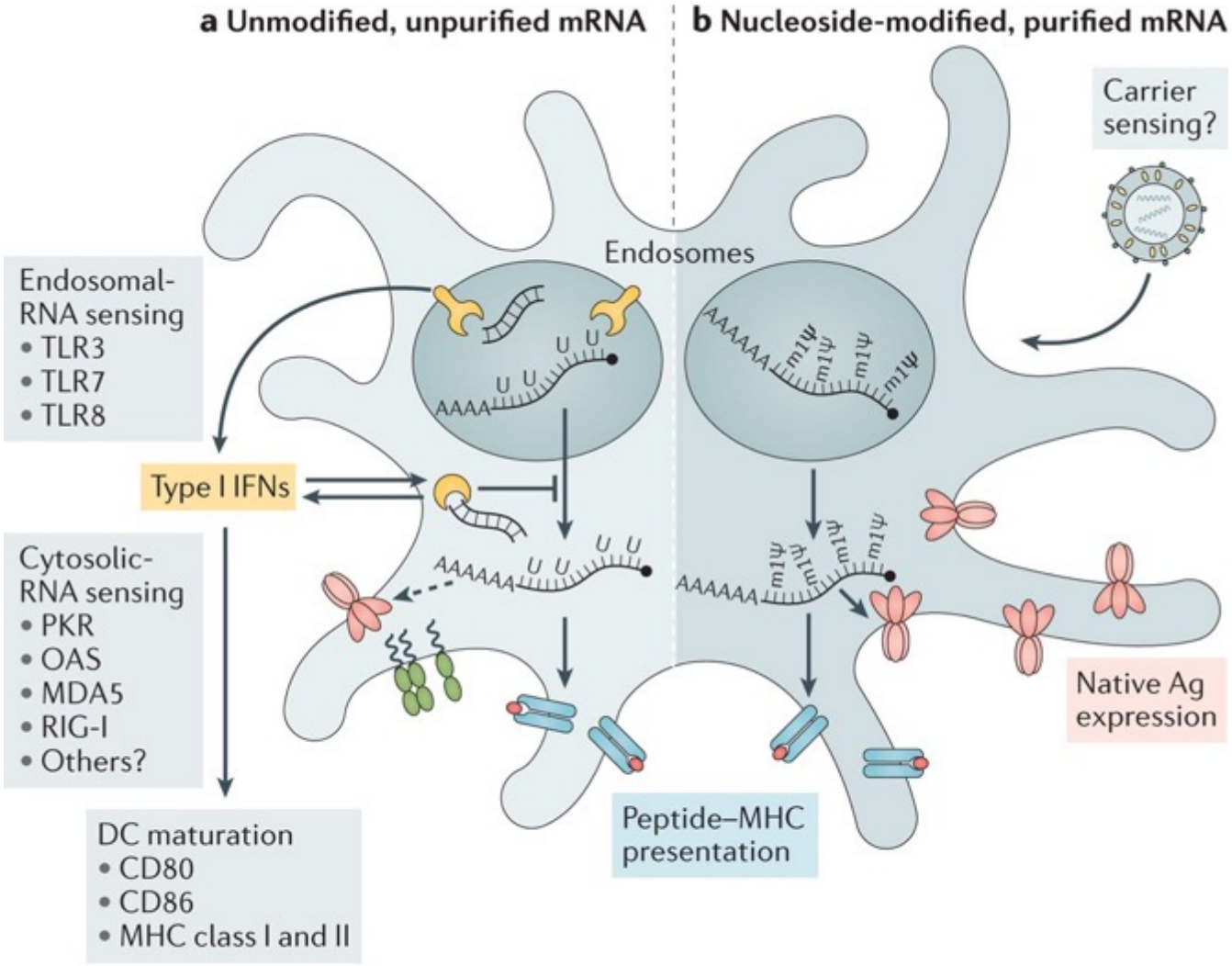
Viral-vectored vaccines (AdV)



Protein subunit vaccines



mRNA vaccines



mRNA is the intermediate step between the translation of protein-encoding DNA and the translation of proteins by ribosomes in the cytoplasm

Pardi, 2018

Clinical-Phase Vaccine/Antibody Candidates for SARS-CoV-2

Candidate	Vaccine characteristics	Lead developer	Status
mRNA-1273	LNP-encapsulated mRNA vaccine encoding S protein	Moderna/NIH	Phase III (NCT04283461)
ChAdOx1 nCoV-19	Chimp Adenovirus vector with S protein	Astra-Zeneca/Oxford	Phase III (NCT04456595)
Ad5-nCoV	Adenovirus type 5 vector that expresses S protein	CanSino Biologicals	Phase III (NCT04313127)
REGN-COV2	Antibody against spike (cocktail)	Regeneron	Phase I/II/III (NCT04425629, NCT04426695, NCT04452318)
LY-CoV555	Antibody against spike	Abcellera Biologics/Eli Lilly/VRC-NIAID Institute of Microbiology CAS/Junshi Biosciences/Eli Lilly	Phase I/II (NCT04411628 and NCT04427501)

mRNA vaccines

Advantages

Induces robust immune response – both humoral and cellular

High production capacity: grow up quickly, and purification is simpler

Stable: no refrigeration needed

Disadvantages

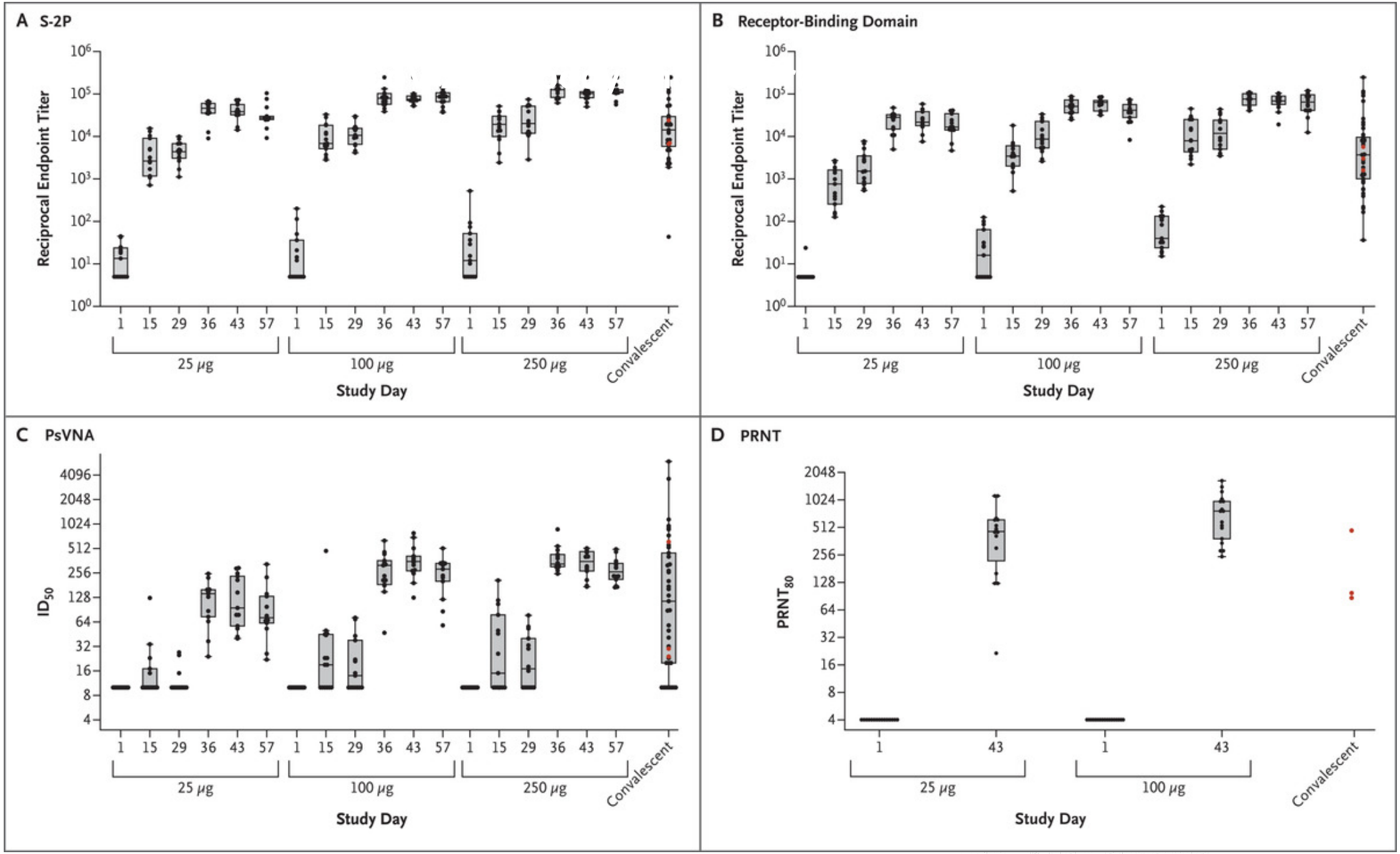
Never been approved for human use: UNPROVEN

Thought to be poorly immunogenic in humans

Moderna Therapeutics/NIH: mRNA-1273

- mRNA-based vaccine
- Lipid nanoparticle (LNP) –encapsulated
- Encodes for full-length prefusion-stabilized spike (S) protein
- Phase 1: Evaluation of 2-dose schedule (IM-injection on Days 1 and 29) in 45 participants
  - 3 study arms with broad dosing range: 25µg, 100µg, and 250µg
- Results: Immunogenicity good, comparable to convalescent sera; 3 individuals (21%) experienced SAEs after 2nd dose of 250 ug dose
- Phase 3 started July 27: enroll 30,000; should reach primary endpoints by end of 2020, beginning of 2021

LA Jackson et al. N Engl J Med 2020. DOI: 10.1056/NEJMoa2022483



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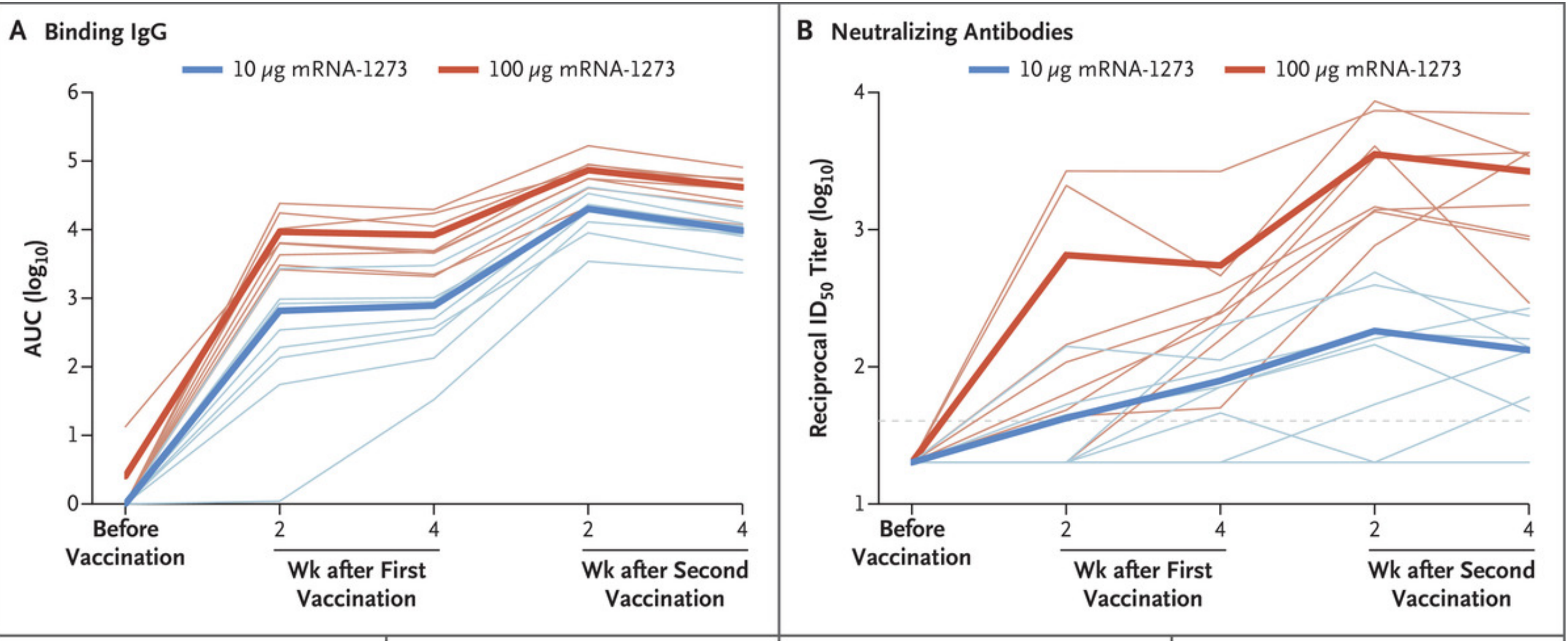
Antibody Responses after mRNA-1273 Vaccination in Rhesus Macaques.

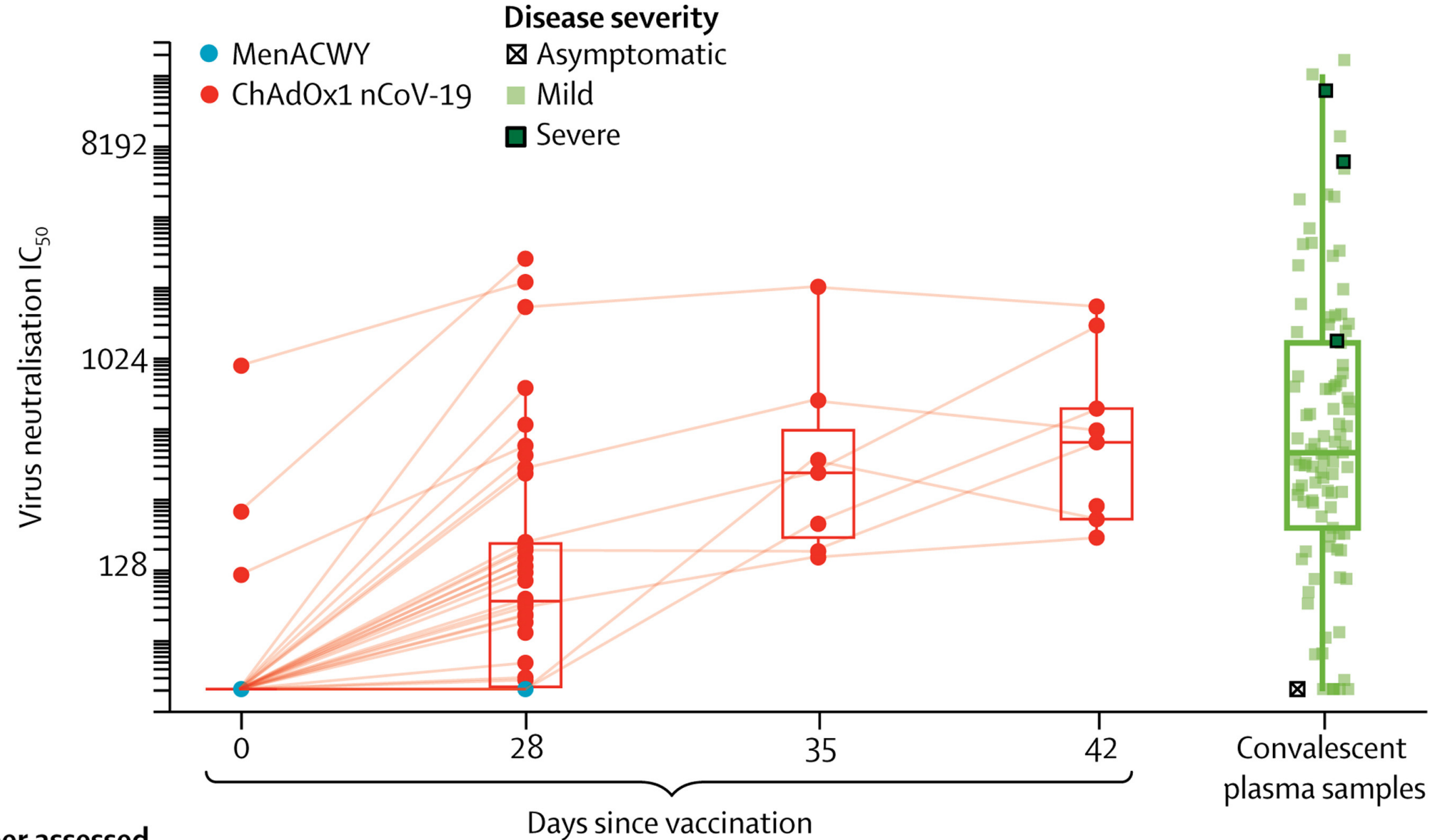


KS Corbett et al. N Engl J Med 2020. DOI: 10.1056/NEJMoa2024671

University of Oxford: ChAdOx1 nCoV-19

AstraZeneca

- Viral-vectored with chimp adenovirus
- Encodes for full-length prefusion-stabilized spike (S) protein
- Previously shown strong immune responses against MERS
- Phase 1/2: Randomly assigned (1:1) to receive ChAdOx1 nCoV-19 at a dose of 5×10^{10} viral particles or MenACWY as a single intramuscular injection
- Subjects: N=1000, age 18-55, 90% White
- No SAEs, some AEs
- Non-randomly selected subset got a 2nd dose, some got Tylenol pre-dose
- Good neut ab titers, T-cell response



Number assessed				
ChAdOx1 nCoV-19	39	38	10	9
MenACWY	30	30	0	0

Folegatti, Lancet 2020

Safety Review Underway of AstraZeneca's Vaccine Trial

A participant in the company's late-stage coronavirus vaccine trial reportedly developed severe neurological symptoms. Now experts must assess whether the vaccine was responsible.

CanSino Biologics

- Viral-vectored with adenovirus 5
- Adenovirus vector expresses full-length spike (S) protein
- Previously shown strong immune responses against MERS
- Phase 2: One dose, vaccine formulation at two concentrations (ie, 1×10^{11} or 5×10^{10} viral particles per mL) were tested against placebo
- Subjects: N=500, age 18-83, all Chinese
- Some AEs, no SAEs
- 96% seroconversion; Lower humoral immune response in older than 55 and those with preexisting immunity to Ad5, but all mounted good neutralizing antibody
- Approved for limited use in the Chinese military, continues ongoing phase 3 trials

Zhu, Lancet 2020

Other Vaccines

- Sinovac – inactivated vaccine, currently in phase 3, approved for limited use in China
- Wuhan Institute of Biological Sciences, Beijing Institute of Biological sciences (all produced by Sinopharm) – inactivated vaccine, currently in phase 3, approved for limited use in China
- Sputnik – Russian vaccine, approved for use in Russia

Other Considerations

- Cost to finance vaccine development - $1 billion dollars
- Studies needed in elderly (may need higher dose) and in pregnant women (make up large pool of essential workers)
- Duration of immunity? Booster shots?
- Harmonization of assays for comparisons across vaccines
- Vaccine refusal/hesitancy

Conclusions

- Novel coronaviruses were predicted to be a cause of a worldwide pandemic
- Coronavirus spike protein is the target of neutralization
- Multiple vaccine candidates, several in phase III, as well as monoclonals are in the pipeline
- Reliance on novel vaccine strategies in design, delivery, and rollout

Additional Resources

- https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html