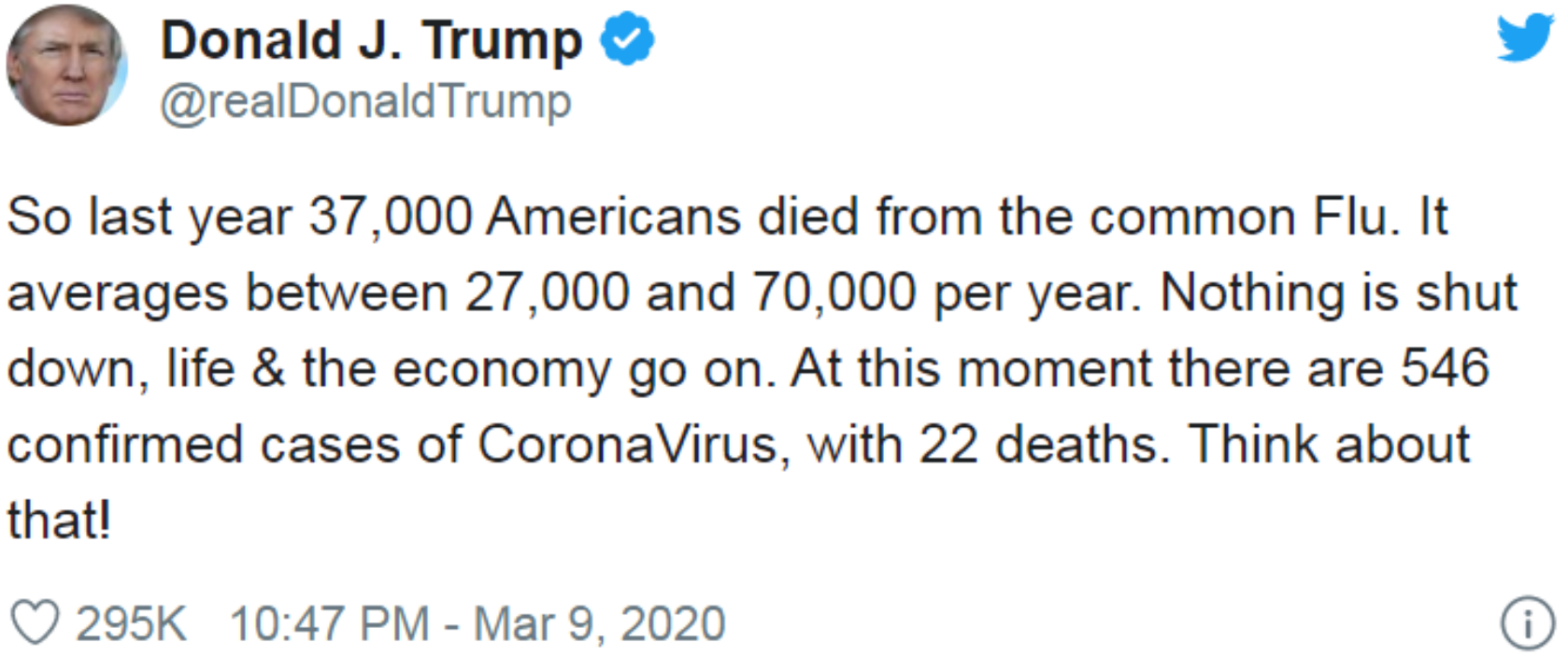
Development of SARS-CoV-2 vaccines

Contents

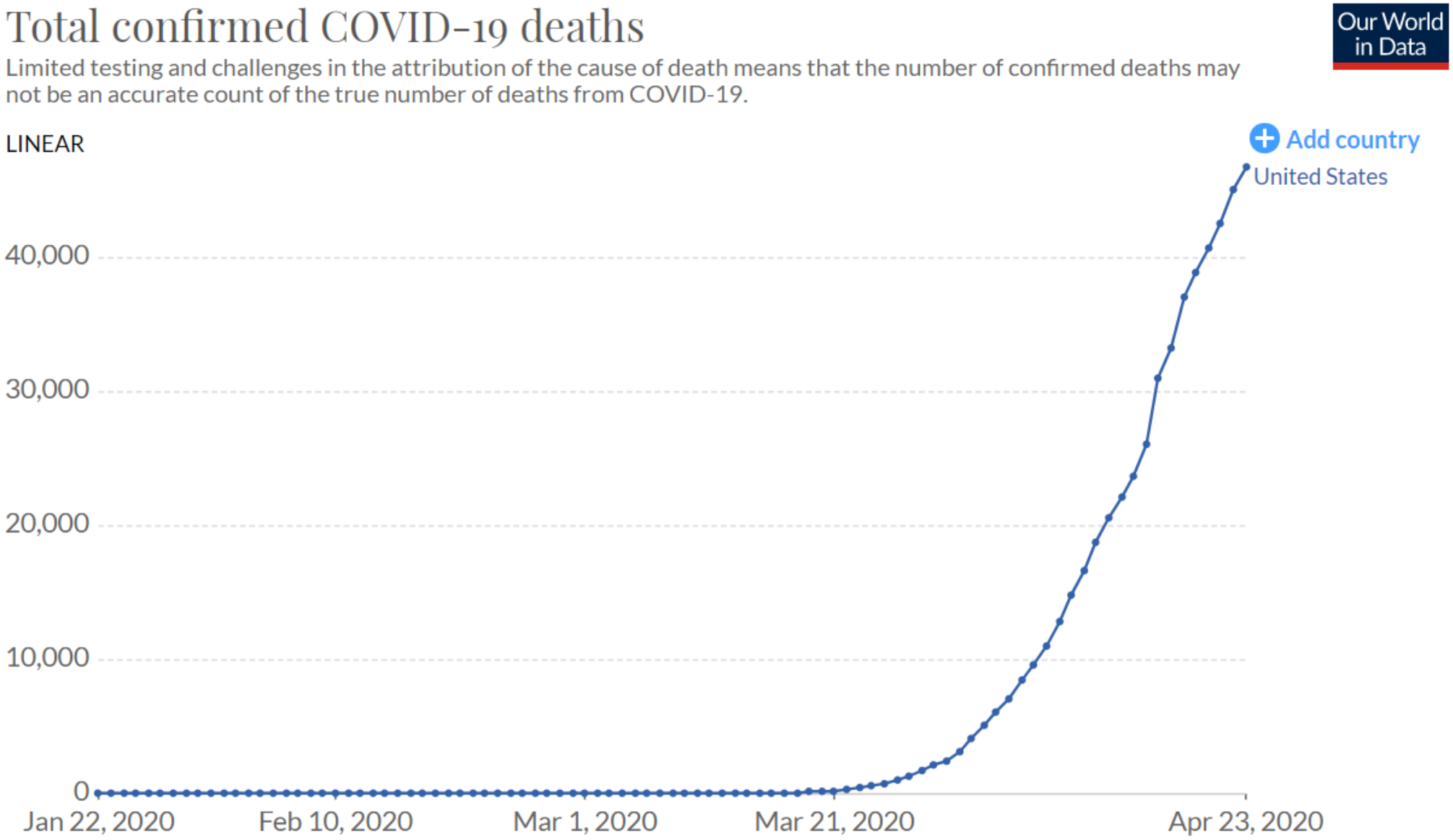
- COVID-19: not just a flu
- SARS-CoV-2 vaccines
- MVC’s SARS-CoV-2 vaccine development
- MVC’s competitive edge

COVID-19: not just a flu

The myth: COVID-19 is no worse than flu



The reality: COVID-19 has resulted in over 46,000 deaths in the US



COVID-19 is NOT just a flu!

Disease	Estimated case fatality rate (CFR)
COVID-19	~6-7% global estimate
SARS-CoV	10% Venkatesh and Memish (2004) Munster et al. (2020)
MERS-CoV	34% Munster et al. (2020)
Seasonal flu (US)	0.1-0.2% US CDC
Ebola	50% 40% in the 2013-16 outbreak WHO (2020) Shultz et al. (2016)

COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopki...

Total Confirmed
2,627,630

Confirmed Cases by Country/Region/Sovereignty

- 841,556 US
- 208,389 Spain
- 187,327 Italy
- 157,135 France
- 150,648 Germany
- 134,638 United Kingdom
- 98,674 Turkey
- 85,996 Iran
- 83,876 China
- 57,999 Russia
- 46,182 Brazil

Admin0

Last Updated at (M/D/YYYY)
4/23/2020, 11:29:09 AM

We need a vaccine!

Cumulative Confirmed Cases

185
countries/regions

Lancet Inf Dis Article: Here. Mobile Version: Here.
Lead by JHU CSSE. Automation Support: Esri Living Atlas team and JHU APL. Contact US. FAQ.

Total Deaths
183,424

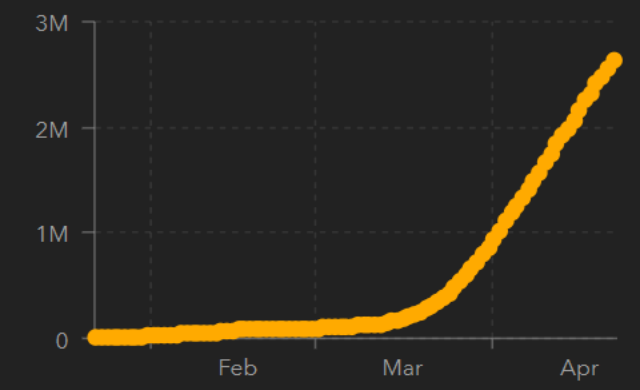
- 25,085 deaths Italy
- 21,717 deaths Spain
- 21,340 deaths France
- 18,100 deaths United Kingdom
- 15,074 deaths New York City **New York** US
- 6,262 deaths

Deaths

Total Test Conducted in U.S.
4,466,559

- 669,982 tested New York US
- 465,327 tested California US
- 288,627 tested Florida US
- 216,783 tested Texas US
- 191,659 tested New Jersey US
- 180,462 tested Massachusetts US

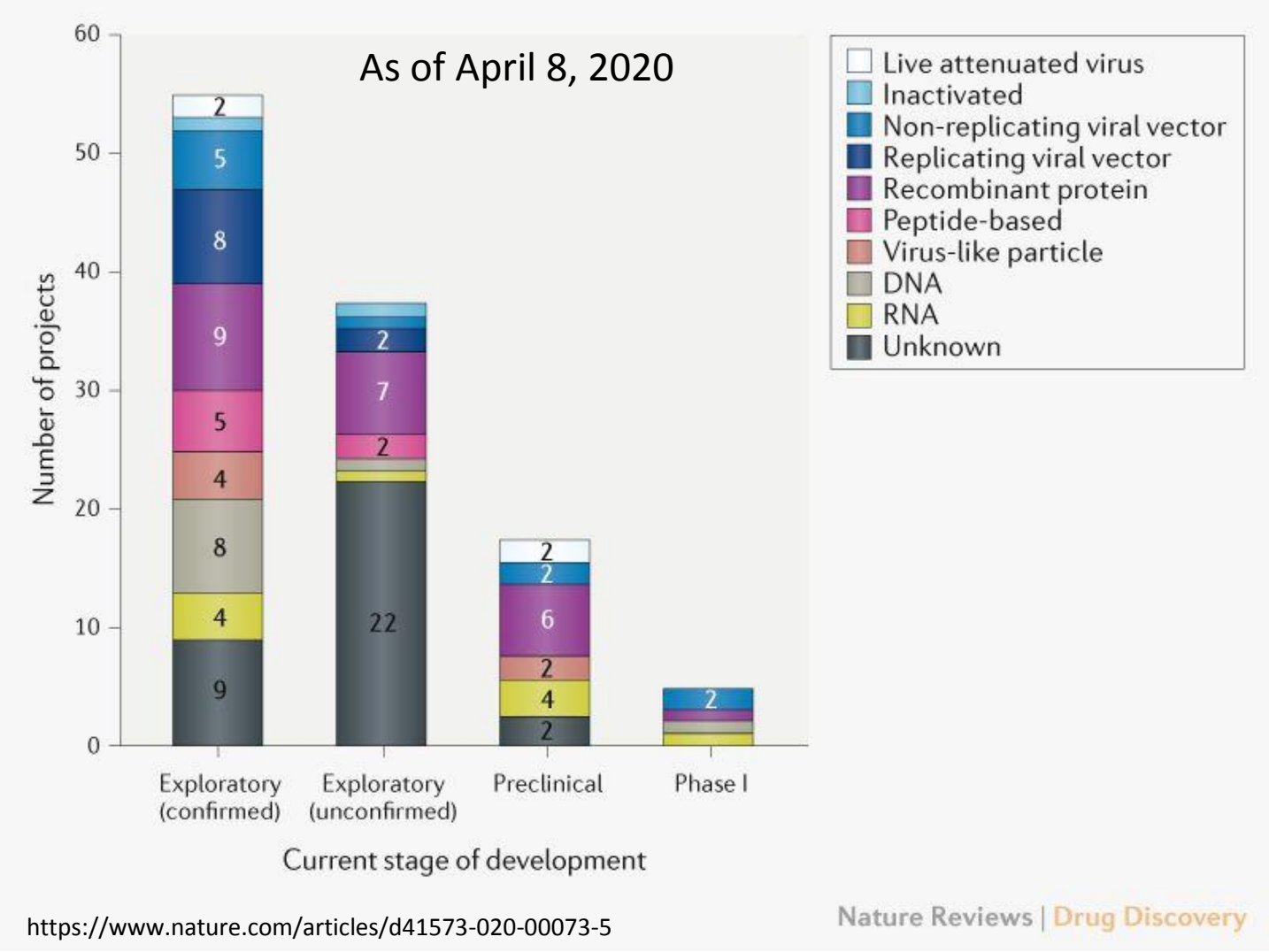
US Tested



Confirmed | Logarithmic | Daily Cases

SARS-CoV-2 vaccines

Over 70 COVID-19 vaccines are in development using either proven or novel platforms



https://www.nature.com/articles/d41573-020-00073-5

A total of 70 COVID-19 vaccines are in development according to the WHO DRAFT landscape of COVID-19 candidate vaccines April 11, 2020:

- Inactivated: 3
- Live-attenuated: 2
- DNA: 6
- RNA: 11
- Non-replicating viral vector: 9
- Replicating viral vector: 6
- Protein subunit: 24
- VLP: 3
- Unknown: 6

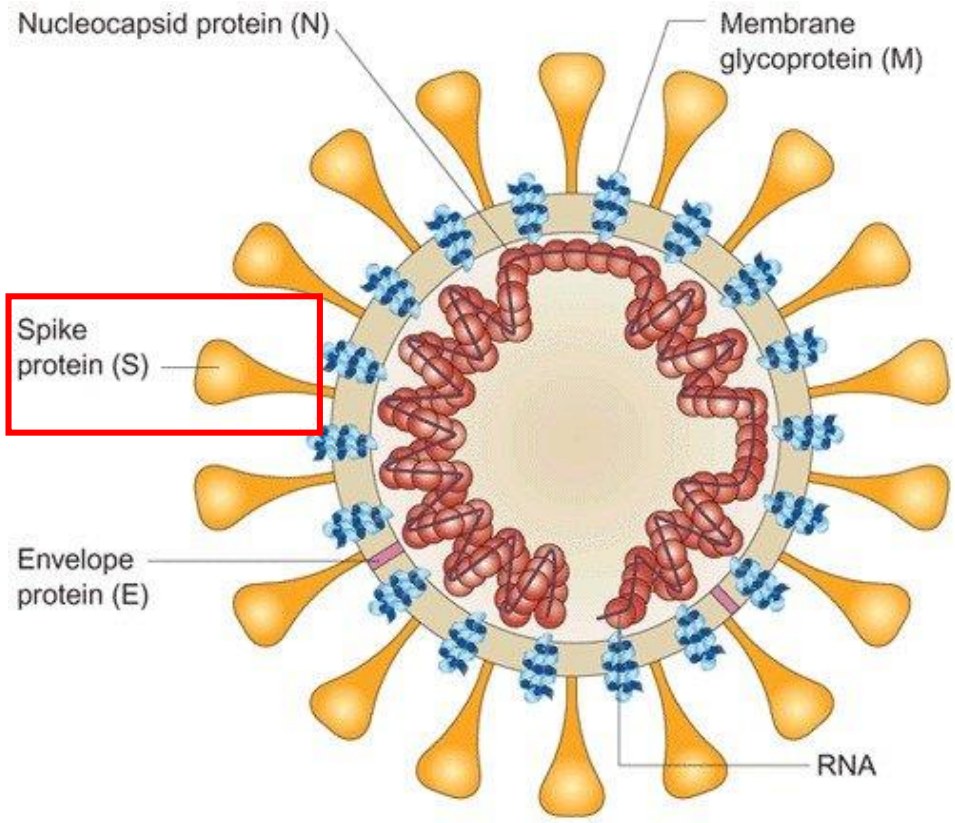
Majority of SARS-CoV-2 vaccines target spike (S) protein

Majority of vaccines entering clinical trial are based on S protein

Company/Institute	Country	Platform	Stage	Antigen
Inovio Pharmaceuticals	**USA**	**DNA delivered by electroporation**	**Phase 1**	**S protein**
Moderna/NIAID	**USA**	**Lipid nanoparticle-mRNA**	**Phase 1**	**Prefusion S protein**
Shenzhen Geno-Immune Medical Institute	**China**	**Lentiviral vector (2 candidates)**	**Phase 1**	**Synthetic peptide**
CanSino Biologics	**China**	**Adenoviral vector**	**Phase 1**	**S protein**
University of Oxford	**UK**	**Adenoviral vector**	**Phase 1**	**S protein**
Sinovac	**China**	**Inactivated virus**	**Phase 1**	**Whole virus**
Symvivo	**Canada**	**DNA delivered by *Bifidobacterium***	**Phase 1**	**S protein**
Institut Pasteur	France	Replicating viral vector	Preclinical	S protein
Codagenix/SII	USA	Live-attenuated virus	Preclinical	Whole virus
Sanofi Pasteur/GSK	USA	Subunit	Preclinical	S protein
Novavax	USA	Subunit	Preclinical	S protein
University of Queensland/GSK	Australia	Subunit	Preclinical	S protein
Baylor College of Medicine	USA	Subunit	Preclinical	S protein
Medigen/NIAID	**Taiwan**	Subunit	Preclinical	Prefusion S protein
Curevac	Germany	RNA	Preclinical	S protein

SARS-CoV-2 spike protein

- SARS-CoV-2 is the virus causing the COVID-19 pandemic.
- S protein acts like a key to enter the cell via the receptor, hACE2.
- S protein also allows the virus to fuse with the cell after attach itself to the receptor



US NIH/NIAID's prefusion spike protein technology

SCIENTIFIC REPORTS

Corrected: Publisher Correction

OPEN

Stabilized coronavirus spikes are resistant to conformational changes induced by receptor recognition or proteolysis

Received: 13 July 2018
Accepted: 12 October 2018
Published online: 24 October 2018

Robert N. Kirchdoerfer[1], Nianshuang Wang[2,3], Jesper Pallesen[1], Daniel Wrapp[2,3], Hannah L. Turner[1], Christopher A. Cottrell[1], Kizzmekia S. Corbett[4], Barney S. Graham[4],

Dr. Barney Graham, NIAID
Dr. Jason McLellan, U Texas

Science

REPORTS

Cite as: D. Wrapp *et al.*, *Science* 10.1126/science.abb2507 (2020).

Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation

Daniel Wrapp[1]*, Nianshuang Wang[1]*, Kizzmekia S. Corbett[2], Jory A. Goldsmith[1], Ching-Lin Hsieh[1], Olubukola Abiona[2], Barney S. Graham[2], Jason S. McLellan[1]†

[1]Department of Molecular Biosciences, The University of Texas at Austin, Austin, TX 78712, USA. [2]Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA.

*These authors contributed equally to this work.

†Corresponding author. Email: jmclellan@austin.utexas.edu

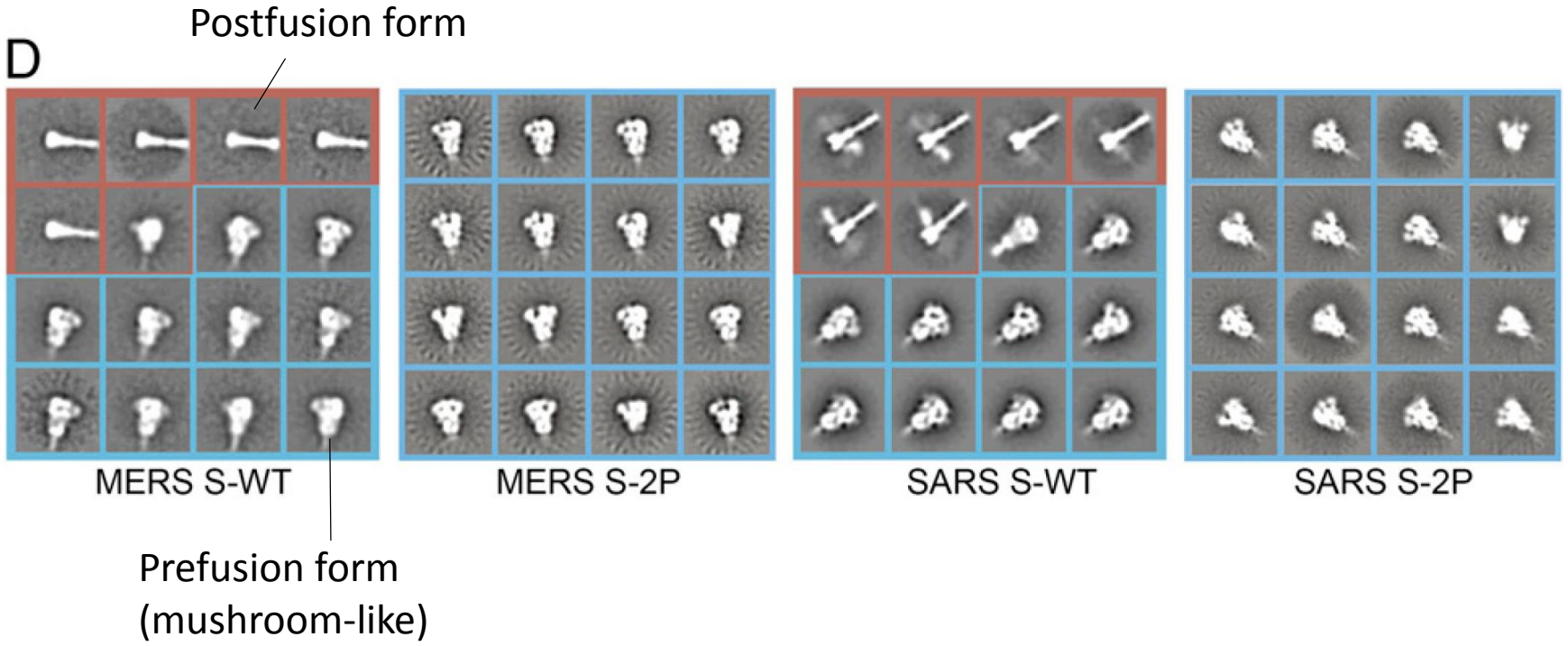
Structure-based engineering of MERS-CoV and SARS-CoV S proteins

PNAS

Immunogenicity and structures of a rationally designed prefusion MERS-CoV spike antigen

Jesper Pallesen[a,1], Nianshuang Wang[b,1,2], Kizzmekia S. Corbett[c,1], Daniel Wrapp[b], Robert N. Kirchdoerfer[a], Hannah L. Turner[a], Christopher A. Cottrell[a], Michelle M. Becker[d], Lingshu Wang[e], Wei Shi[e], Wing-Pui Kong[e], Erica L. Andres[d], Arminja N. Kettenbach[b,f], Mark R. Denison[d,g], James D. Chappell[d], Barney S. Graham[c], Andrew B. Ward[a,2], and Jason S. McLellan[b,2]

[a]Department of Integrative Structural and Computational Biology, The Scripps Research Institute, La Jolla, CA 92037; [b]Department of Biochemistry and Cell Biology, Geisel School of Medicine at Dartmouth, Hanover, NH 03755; [c]Viral Pathogenesis Laboratory, Vaccine Research Center, National Institute of Allergy and Infectious Diseases, Bethesda, MD 20892; [d]Department of Pediatrics, Vanderbilt University Medical Center, Nashville, TN 37232; [e]Virology Core, Vaccine Research Center, National Institute of Allergy and Infectious Diseases, Bethesda, MD 20892; [f]Norris Cotton Cancer Center, Geisel School of Medicine at Dartmouth, Lebanon, NH 03756; and [g]Department of Pathology, Microbiology, and Immunology, Vanderbilt University School of Medicine, Nashville, TN 37232



Advantages of NIH/NIAID's S-2P protein as vaccine

- Dr. Barney Graham at NIAID has developed a modified form of S protein as basis for vaccine

- The modified form of S protein, called S-2P has the following advantages over S protein found on virus:

  - ✓ More stable
  - ✓ Better at inducing immune response and antibodies
  - ✓ Cannot fuse with cells

NIH National Institute of Allergy and Infectious Diseases

Vaccine candidates entering human clinical trial

moderna — mRNA vaccine - First to enter phase I clinical trial with prefusion S protein

inovio — DNA vaccine

sinovac 北京科兴 — Inactivated whole virus

UNIVERSITY OF OXFORD — Adenovirus vector

MVC and Moderna licensed the S-2P technology from NIH

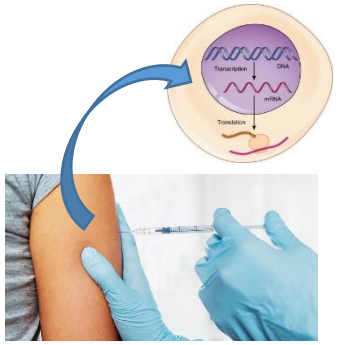
subunit vaccine
(S-2P protein produced by cell culture)

SARS-CoV-2 S-2P
(S protein)

NIH NIAID

SARS-CoV-2 S-2P sequence
from NIH/NIAID

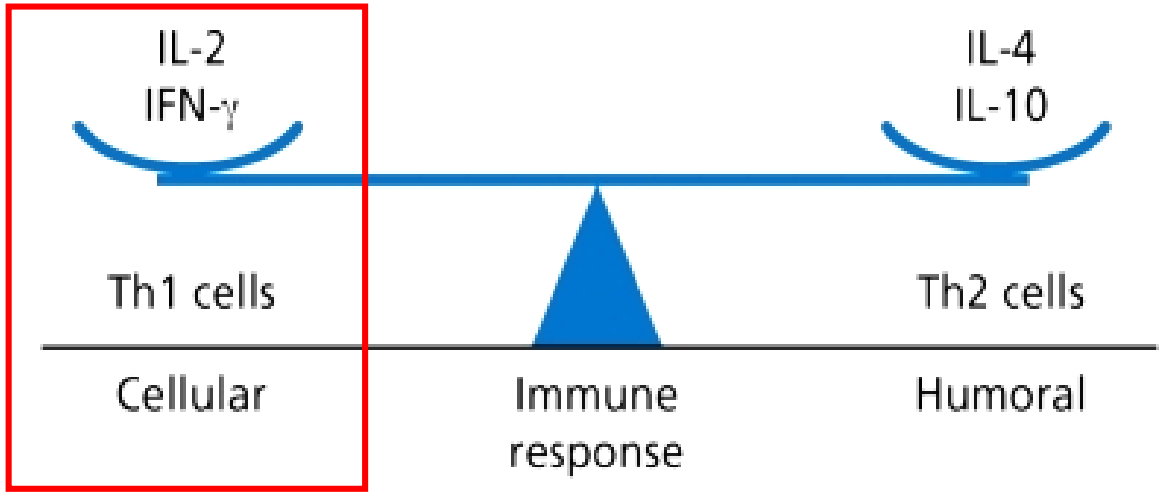
moderna



mRNA vaccine
(S-2P protein produced within the host cell)

Adjuvant:
Substance added to antigen to enhance immune response

A good COVID-19 vaccine adjuvant should induce Th1 response



✓

- Effective early viral clearance
- Effective termination of immune response

✗

- Failure to clear virus
- Lung lymphocyte infiltration
- Immunopathology and tissue damage
- Amplification of allergic inflammation

Commonly used adjuvants in human

Adjuvant	Class	Component	Company	Mechanism of action	Vaccines
Licensed adjuvants					
Alum	Aluminium mineral salts	- Potassium aluminium sulphate - Often wrongly classified		- Necrosis causing urate crystals - Induction of inflammasome - IL-1 secretion	Multiple
MF59	Oil-in-water emulsion	- Squalene - Polysorbate 80 - Sorbitan trileate	Novartis Seqirus/CSL	- Slow release of antigen - Nonspecific immune stimulation	Fluad (seasonal influenza) Focetria (pandemic influenza) Aflunov (prepandemic influenza)
Virosomes	Liposomes	- Lipids - Haemagglutinin	Berna Biotech	- Slow release of antigen	Infexal (seasonal influenza) Epaxal (hepatitis A)
AS04	Alum-absorbed TLR4 agonist	- Aluminium hydroxide - MPL	Glaxo SmithKline	- induction of Th_1 response	Fendrix (hepatitis B) Cervarix (human papilloma virus)
AS03	Oil-in-water emulsion	- Squalene - Tween 80 - α-Tocopherol		- Slow release of antigen - Nonspecific immune stimulation	Pandremix (pandemic influenza) Prepandrix (prepandemic influenza)
CpG	TLR9 agonist	- CpG oligonucleotides ±alum/emulsion	DYNAVAX	- Induction of Th_1 response - Direct activation of B cells	HEPLISAV-B (hepatitis B)
AS01	Combination	- Liposome - MPL - Saponin	Glaxo SmithKline	- Slow release of antigen - Induction of Th_1 response	Mosquirix (malaria)

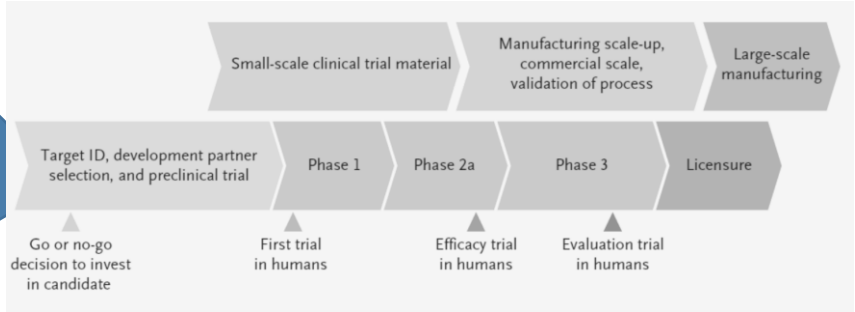
Modified from *Swiss Med Wkly*. 2014;144:w13940.

MVC’s SARS-CoV-2 vaccine development

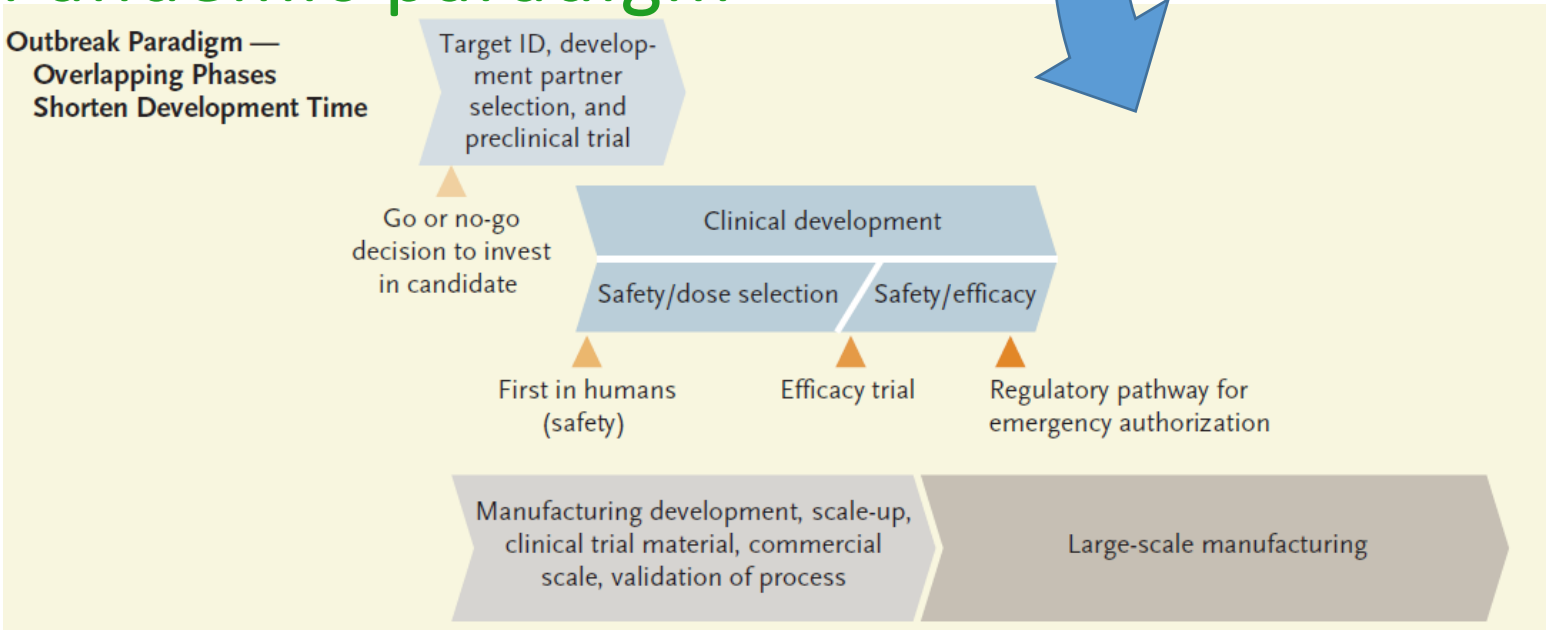
Developing COVID-19 vaccine at pandemic speed

Emergency Use Authorization (EUA)

Traditional vaccine development



Pandemic paradigm



EUA guidelines for rapid development of COVID-19 vaccine

EUA Criteria		
Immunogenicity	Required	Immune response induced by vaccine candidate in animal model
Toxicology data	skip	Toxicology data referred to the same platform technology
	simplify	Prioritize the toxicity assay and expedite it
	parallel	Accrue comprehensive data as clinical trials running
Efficacy	parallel	Vaccine efficacy in animal models is not required prior to first-in-human (FIH) clinical trials.
CMC characterization	GLP batch	Adequate to support the safety of the SARS-CoV-2 vaccine construct prior to proceeding to FIH clinical trials
	GMP batch	

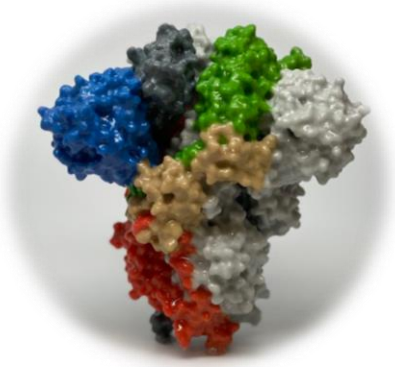
*Theoretical risk disease enhancement needs to be addressed.

Success precedents following EUA criteria

EUA Criteria		Example
Immunogenicity	Required	
Toxicology data	skip	Skipped toxicology study • Moderna (mRNA vaccine) • Inovio (DNA vaccine)
Efficacy	parallel	Simultaneous preclinical and clinical trial • Oxford University (Adenovirus vector)
CMC characterization	• GLP batch • GMP batch	

Development roadmap of NIH/MVC SARS-CoV-2 vaccine

Technology from the US NIH/NIAID

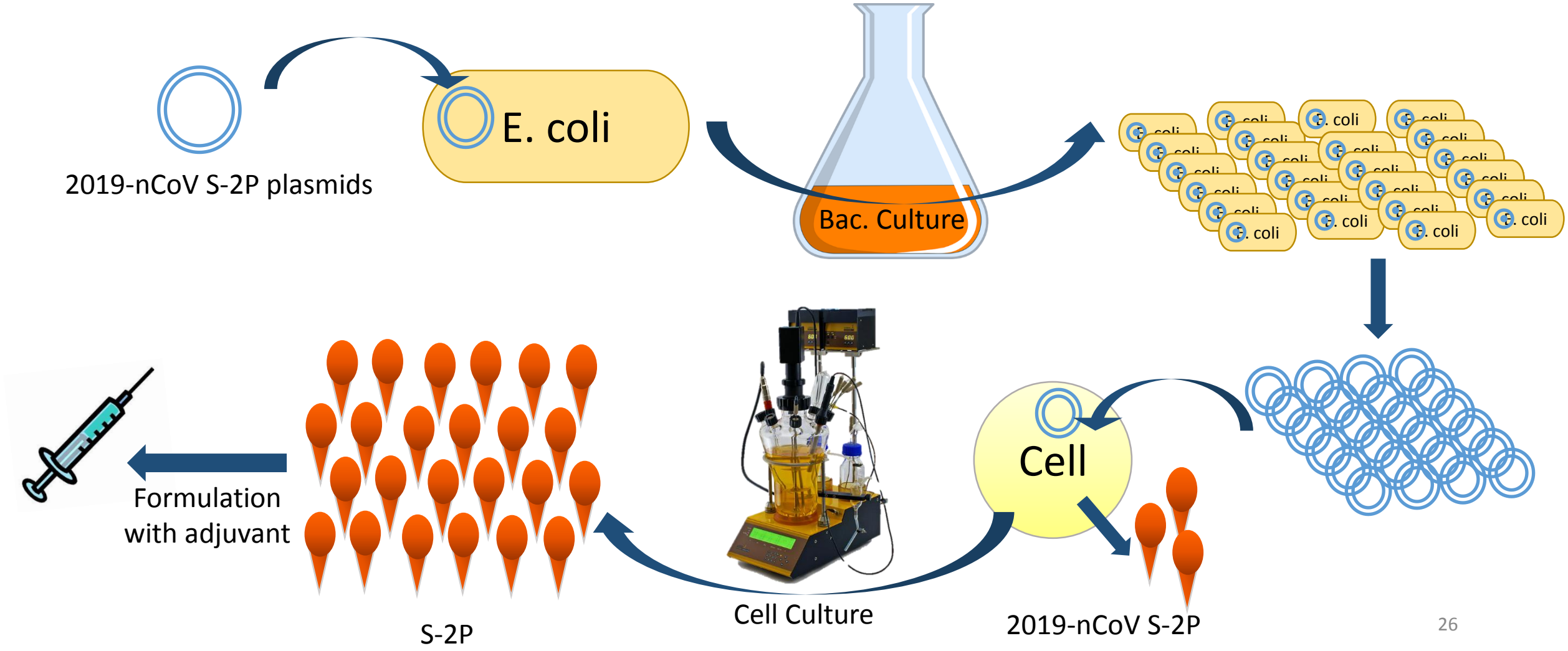


Animal studies → Clinical trial

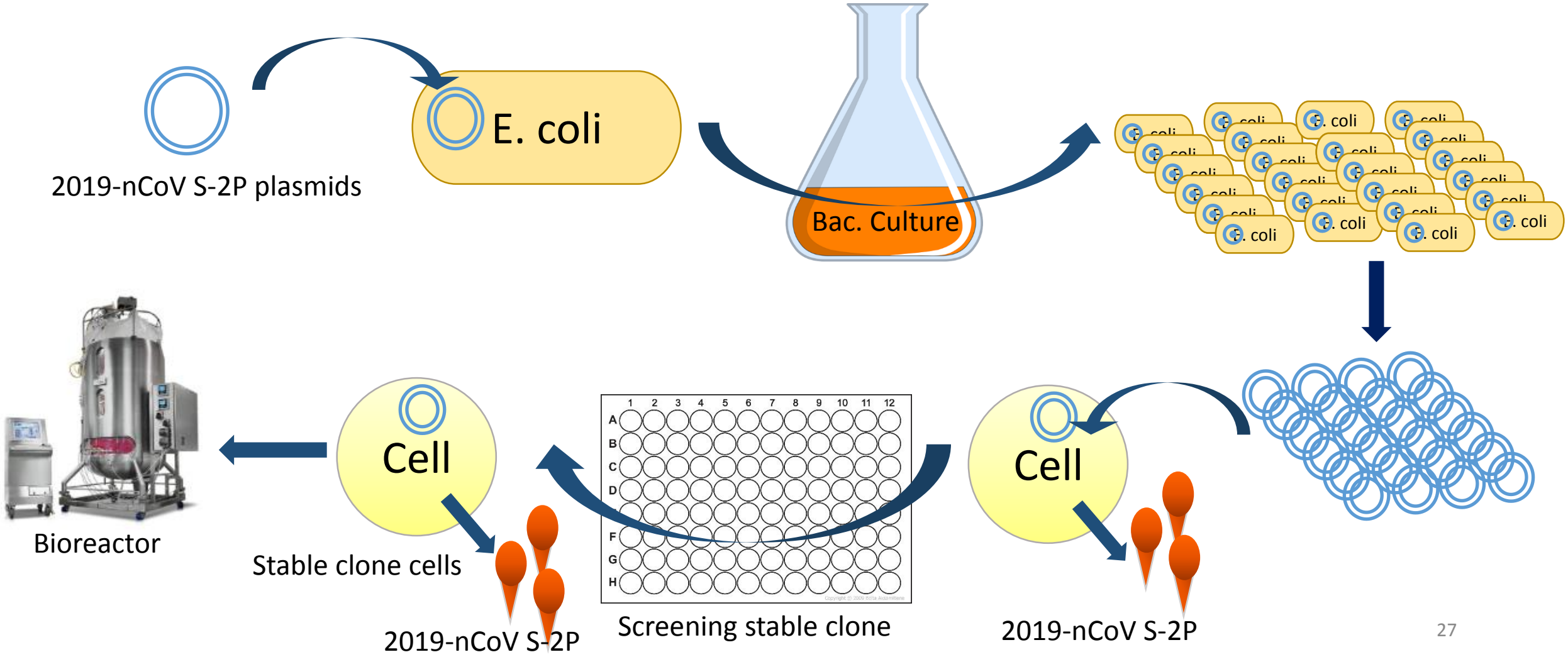
Formulation optimization → Pilot Production

Commercial Production

Vaccine production for pre-clinical trial (small scale)



Vaccine production for clinical trial (scale-up)

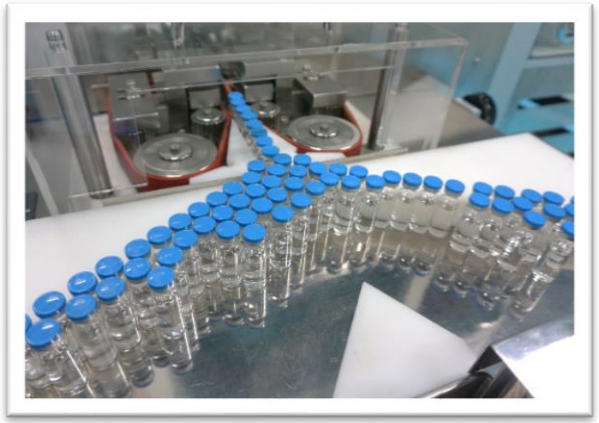


Scale-up vaccine production Scenarios

Vaccine doses
500,000
1,000,000
5,000,000
20,000,000
50,000,000

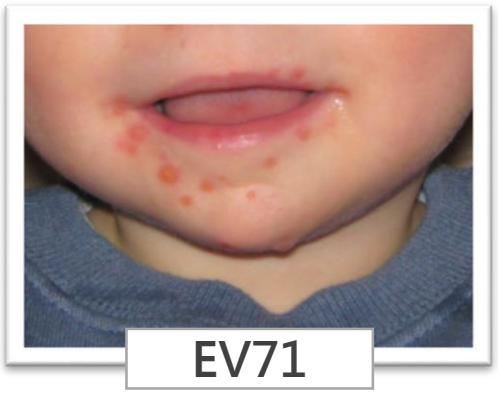
MVC’s competitive edge

MVC: PIC/S GMP-certified vaccine manufacturer



Product Pipeline: Collaboration with world-class partners

- MVC develops **novel vaccines** & biologics to **prevent emerging infectious diseases**
- Current pipeline includes **Enterovirus 71**, **H7N9**, **Seasonal flu**, **Dengue** vaccines, and **RSV biosimilar** drug



EV71

Taiwan NHRI

國家衛生研究院 National Health Research Institutes

Seasonal Flu

Korea GC Pharma

GC Pharma

Dengue

US NIH

NIH National Institute of Allergy and Infectious Diseases

H7N9

Taiwan NHRI

國家衛生研究院 National Health Research Institutes

RSV Antibody

WHO / UCAB

UCAB Affordable Biotherapeutics

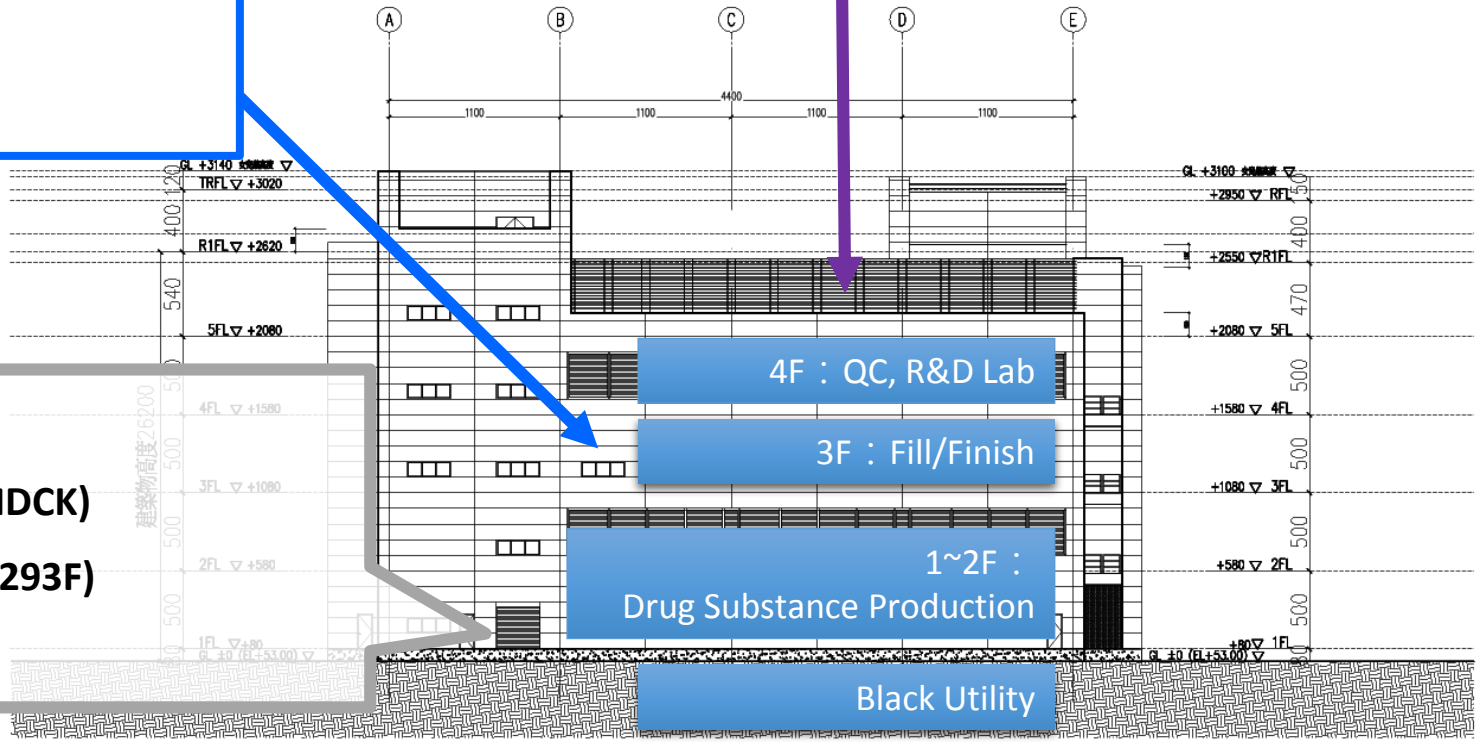
State-of-the-art vaccine production facility

3rd Floor: Fill & Finish

- 10,000 pre-filled syringes and 3,500 vials per hour

4th Floor: QC, R&D Lab

- Fulfill PIC/S requirements



1st Floor: Drug Substance Production

- **Adherent cell culture production (Vero, MDCK)**
- **Suspension cell culture production (CHO, 293F)**

2nd Floor: HVAC floor

MVC is ready to tackle the COVID-19 pandemic

- Technology from the US NIH:
  - Culmination of over 15 years of research since SARS and MERS
  - Candidate vaccine - ready to use for animal and clinical study

- MVC is well-prepared:
  - State-of-the-art cell culture technology
  - Rigorous QC/QA process
  - Excellent track record of clinical trials
  - Experience in vaccine formulation
  - PIC/S GMP compliant manufacturing facility
  - Team led by veterans in the industry

Thank You

Innovations for a Better Life