Advances in Vaccine and Immunization Technologies

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National Institute of Allergy and Infectious Diseases

Conflict of Interest Statement

Presenter Disclosure Information

Cristina Cassetti, Ph.D.

Title: Advances in Vaccine and Immunization Technologies

- The presenter has no financial conflicts of interest.
- The lecture was prepared as part of the presenter's official capacity as a U.S. government employee.

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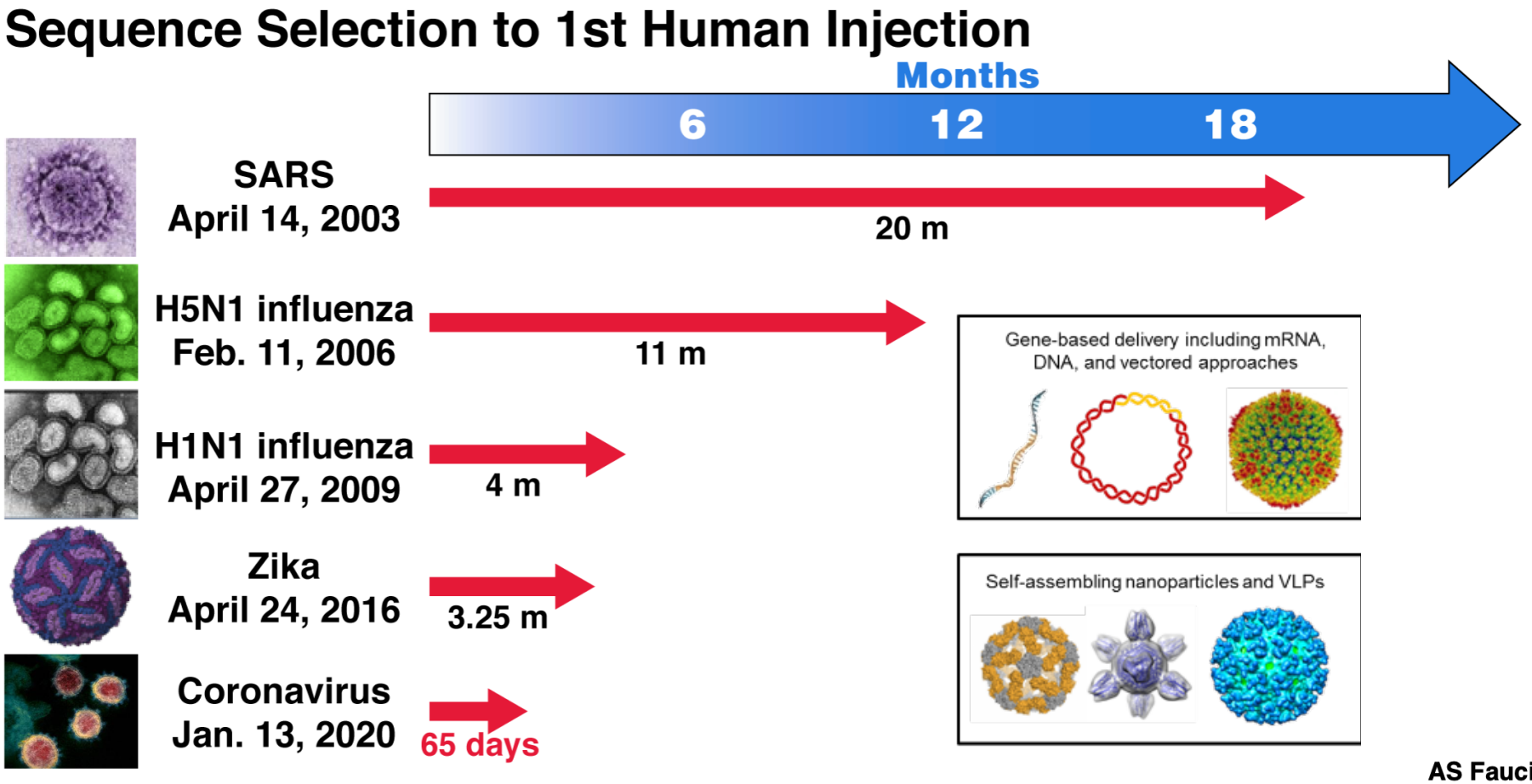
2020-23 were extraordinary years for vaccine technologies

- How has the COVID-19 pandemic pushed vaccine technologies forward?
  - Vaccines were developed and approved at record speed (rational vaccine design)
  - A novel technology (mRNA) was proven safe and very effective (novel technologies)
  - Vaccines have been manufactured at mass scale at unprecedented speed (advances in manufacturing)
  - Understood the urgent need for inexpensive/thermostable vaccines for world-wide (stabilization/delivery)

- Where do we go from here?

Platform Technologies Speed Development



AS Fauci/NIAID

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Graham, Mascola, Fauci. JAMA.

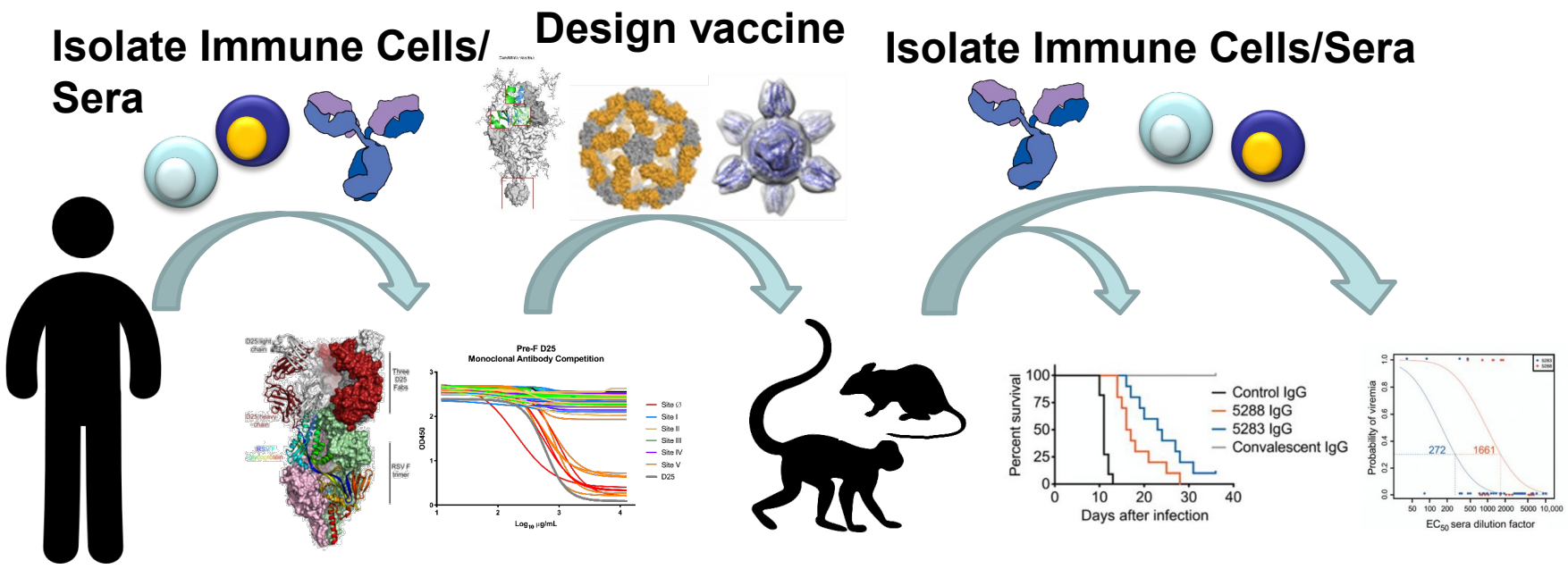
What is Rational Vaccine Design?

- Traditional vaccine development has largely been empirical
  - Whole-inactivated viruses
  - Attenuated viruses through animal or tissue culture passage or cold-adaption

- Rational vaccine development is harnessing the knowledge of effective immune responses to design vaccines that elicit a targeted response predicted to be protective

- Shift towards rational vaccine design enabled by development of new technologies

Rational Vaccine Design Process



Infected Person

Identify epitopes or features associated with potent neutralizing activity

Evaluate in animal models

Confirm elicitation of desired immune response and define correlates of protection

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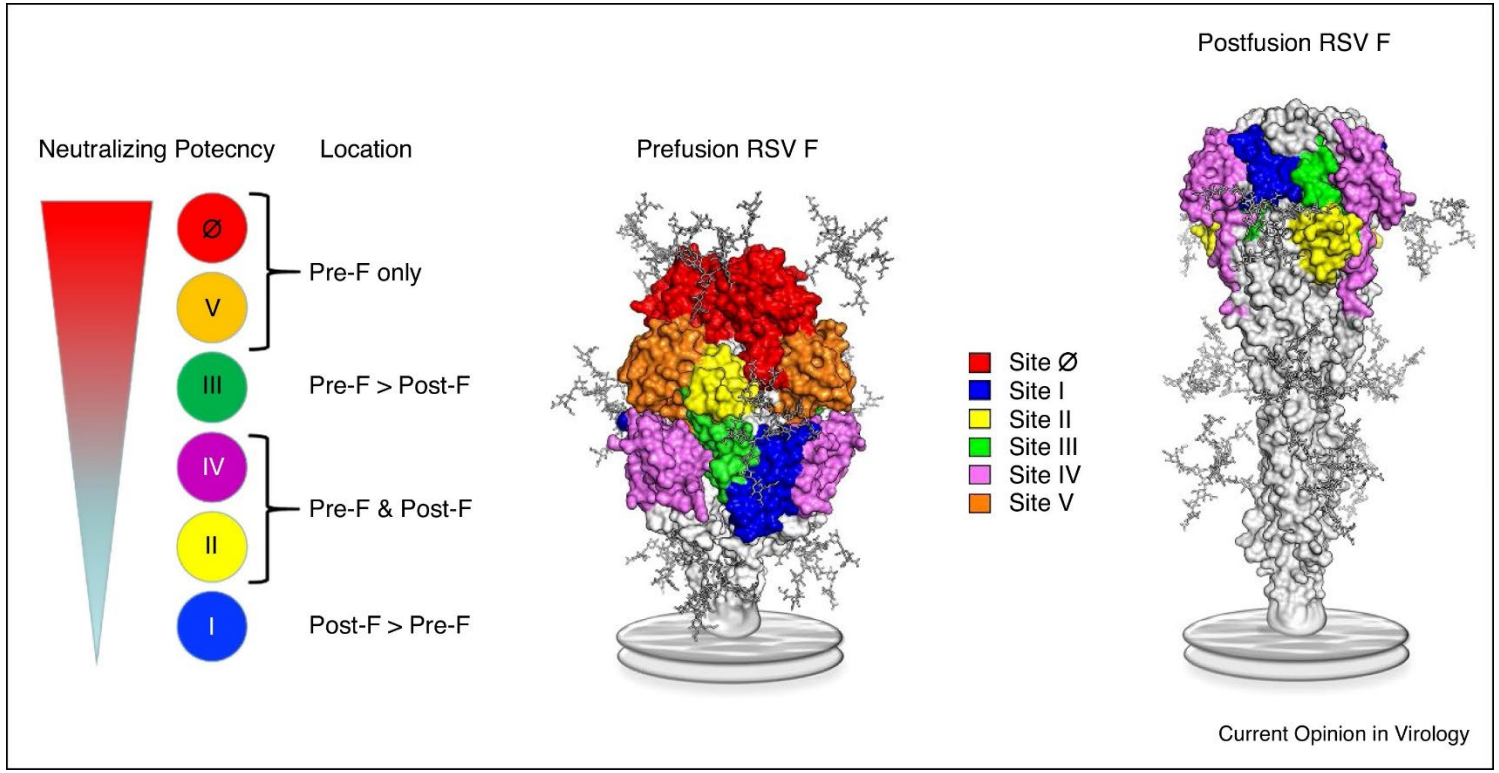
Rational vaccine antigen design: RSV



Neutralization-Sensitive Epitopes are Conformation-Dependent
F is a class I fusion protein

Reference: Graham BS. (2017).
Current Opin Virol. 23: 107-112.

FDA U.S. FOOD & DRUG ADMINISTRATION

FDA NEWS RELEASE

FDA Approves First Respiratory Syncytial Virus (RSV) Vaccine

Arexvy Approved for Individuals 60 Years of Age and Older

Share Tweet Linkedin Email Print

May 3, 2023

The New York Times

F.D.A. Panel Recommends R.S.V. Vaccine to Protect Young Infants

A committee of experts voted in favor of a new shot administered to pregnant women, one in a series of new ways to arm the very young against a life-threatening virus.

May 18, 2023

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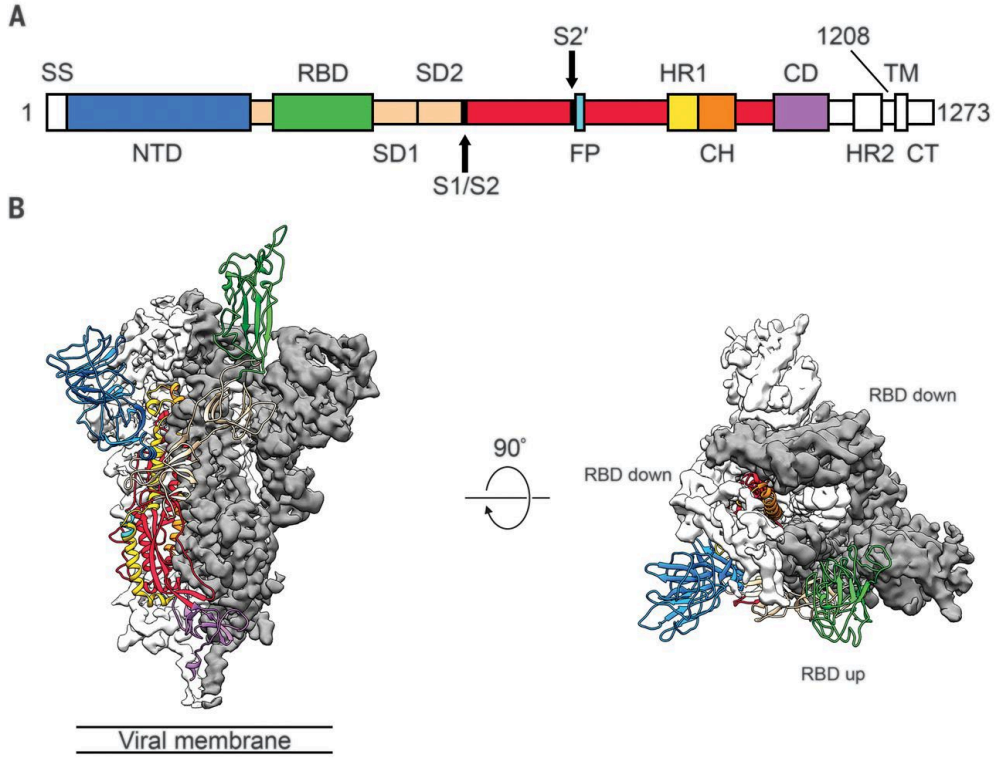
Rational vaccine design: coronaviruses (Class I fusion)

A SARS DNA Vaccine Induces Neutralizing Antibody and Cellular Immune Responses in Healthy Adults in a Phase I Clinical Trial

Julie E. Martin, Mark K. Louder, LaSonji A. Holman, Ingelise J. Gordon, Mary E. Enama, Brenda D. Larkin,Charla A. Andrews, Leatrice Vogel, Richard A. Koup, Mario Roederer, Robert T. Bailer, Phillip L. Gomez, Martha Nason, John R. Mascola, Gary J. Nabel,Barney S. Grahama, the VRC 301 Study Team.

Immunogenicity and Structures of a Rationally Designed Prefusion MERS-CoV Spike Antigen

Jesper Pallesen, Nianshuang Wang, Kizzmekia S Corbett, Daniel Wrapp, Robert N Kirchdoerfer, Hannah L Turner, Christopher A Cottrell, Michelle M Becker, Lingshu Wang, Wei Shi, Wing-Pui Kong, Erica L Andres, Arminja N Kettenbach, Mark R Denison, James D Chappell, Barney S Graham, Andrew B Ward, Jason S McLellan.



Stabilized SARS-CoV-2 Spike protein
Wrapp D, et al. Science. 2020 Feb 19.

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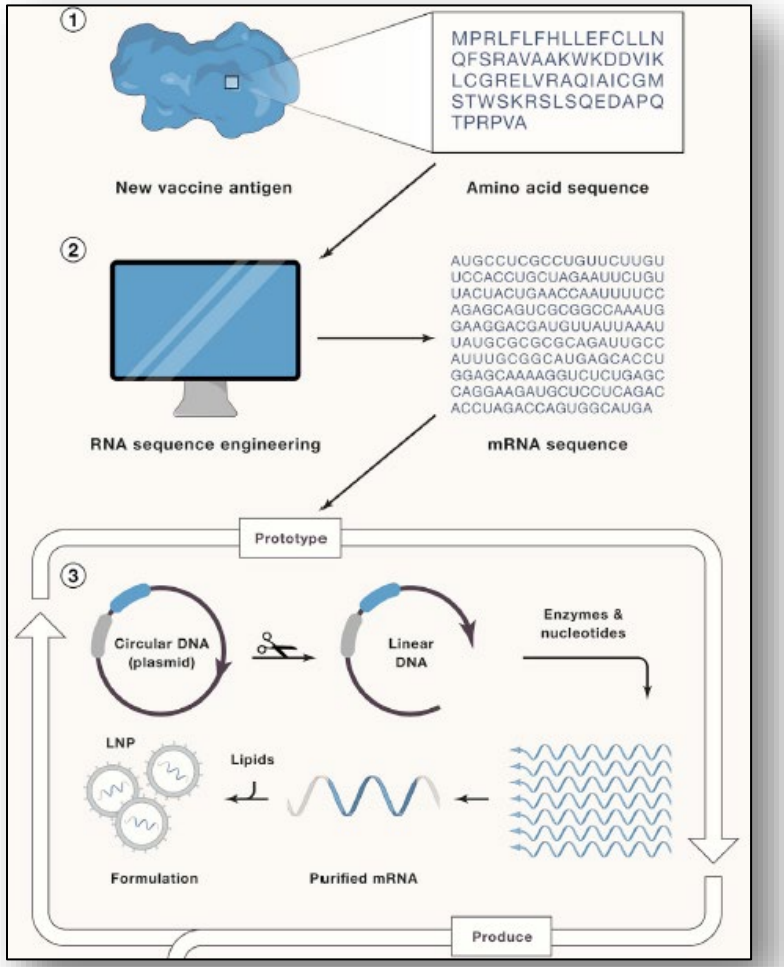
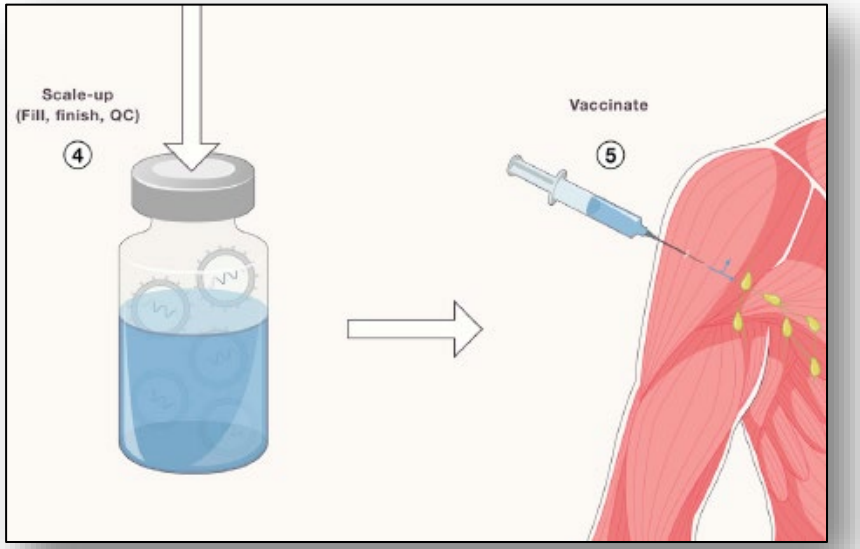
mRNA Vaccine Platform

- Advantages
  - Very rapid to produce
  - Safe and non-toxic
    - Non-infectious
    - Non-integrating
    - Degrade in 2-3 days
  - Ag expressed intracellularly
  - Don’t induce vector-specific immunity
    - Repeated immunizations are possible
- Disadvantages
  - Until 2021, never been licensed in humans
  - Booster shots required
  - Expensive to produce
  - Stability
    - 30 days at 4C
    - Up to 9 months at -15 to -75C

mRNA Vaccine Development Process





First cell-free system to manufacture vaccines

- *in vitro,* cell-free transcription reaction
- No cell derived impurities and contaminants

https://pubmed.ncbi.nlm.nih.gov/33740454/

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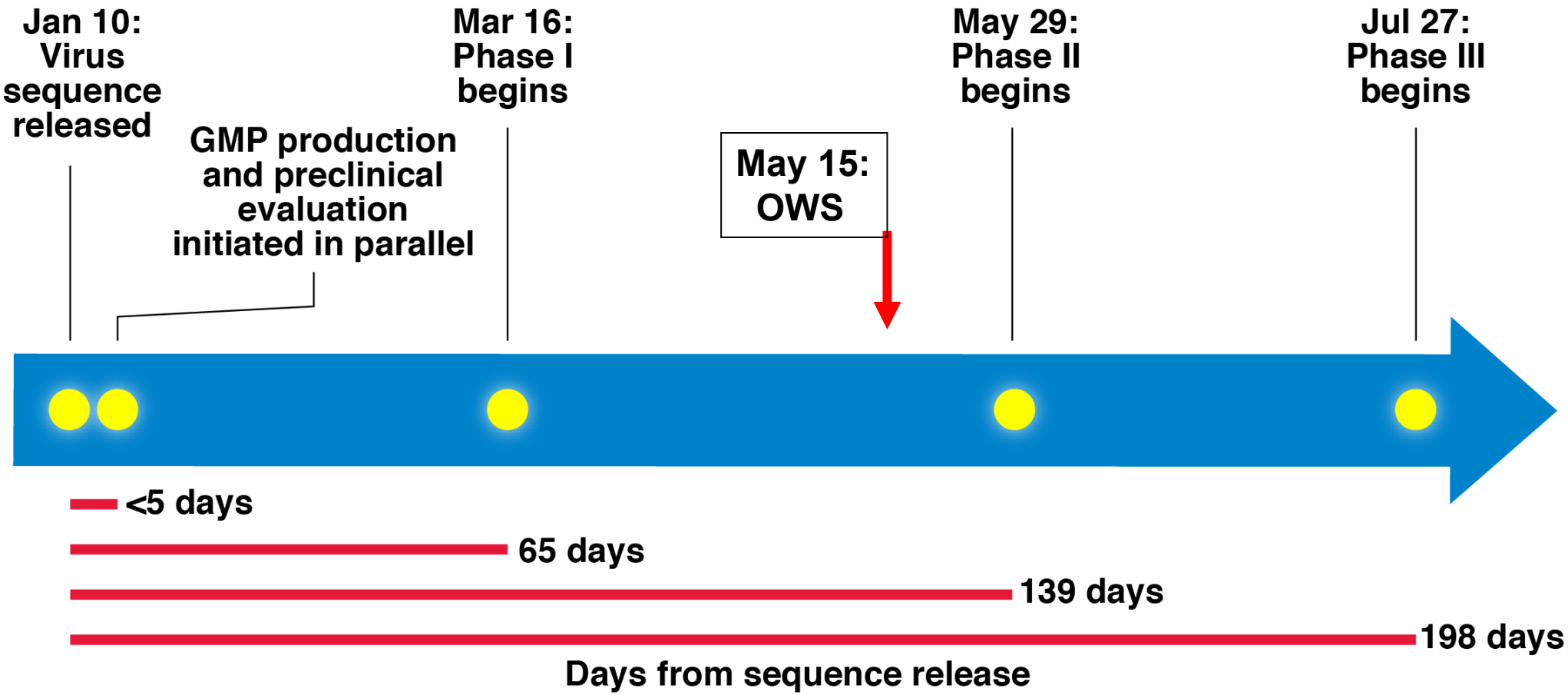
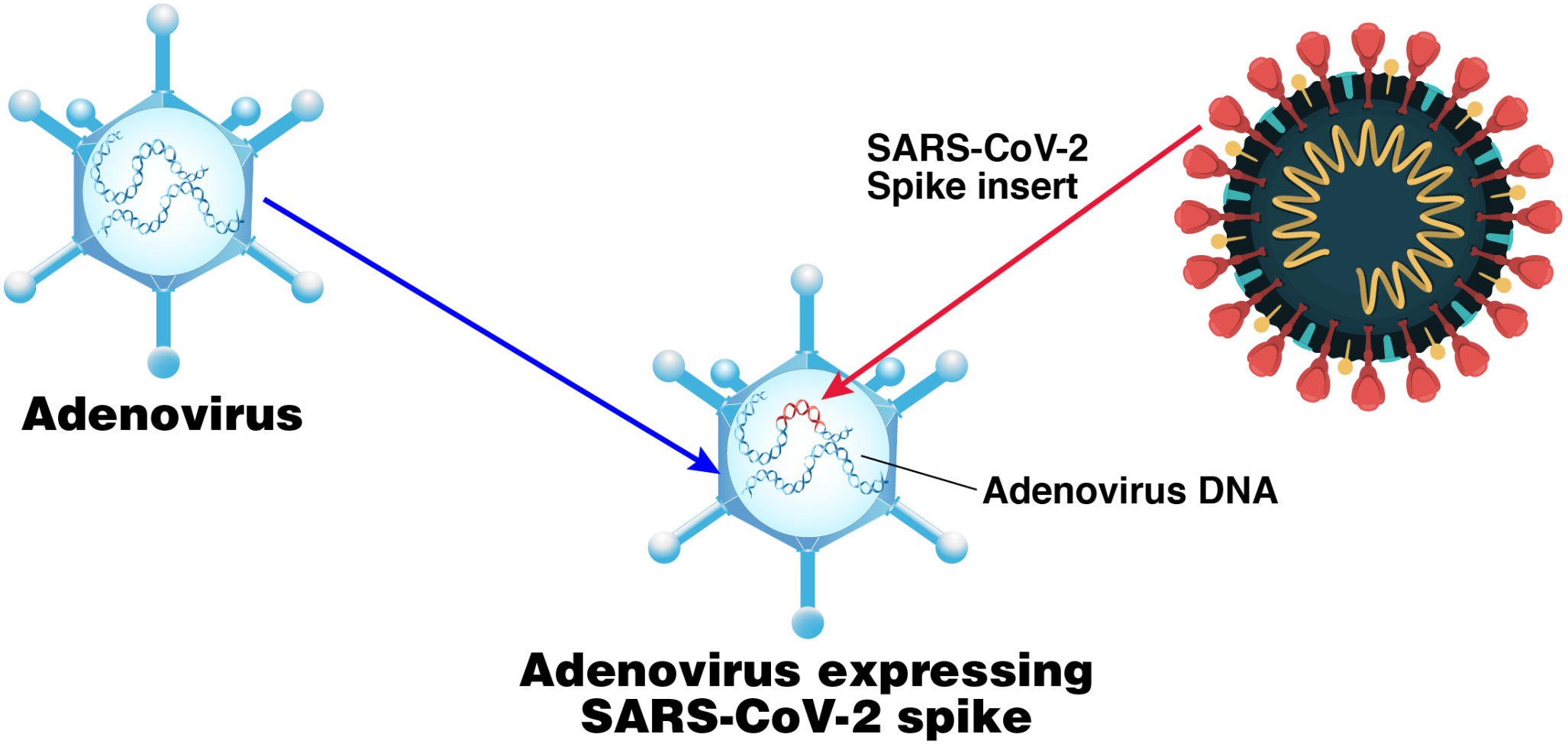
SARS-CoV-2 Vaccine Development: mRNA-1273



Slide source: AS Fauci

Adenovirus-Vectored Vaccines: Janssen and Oxford

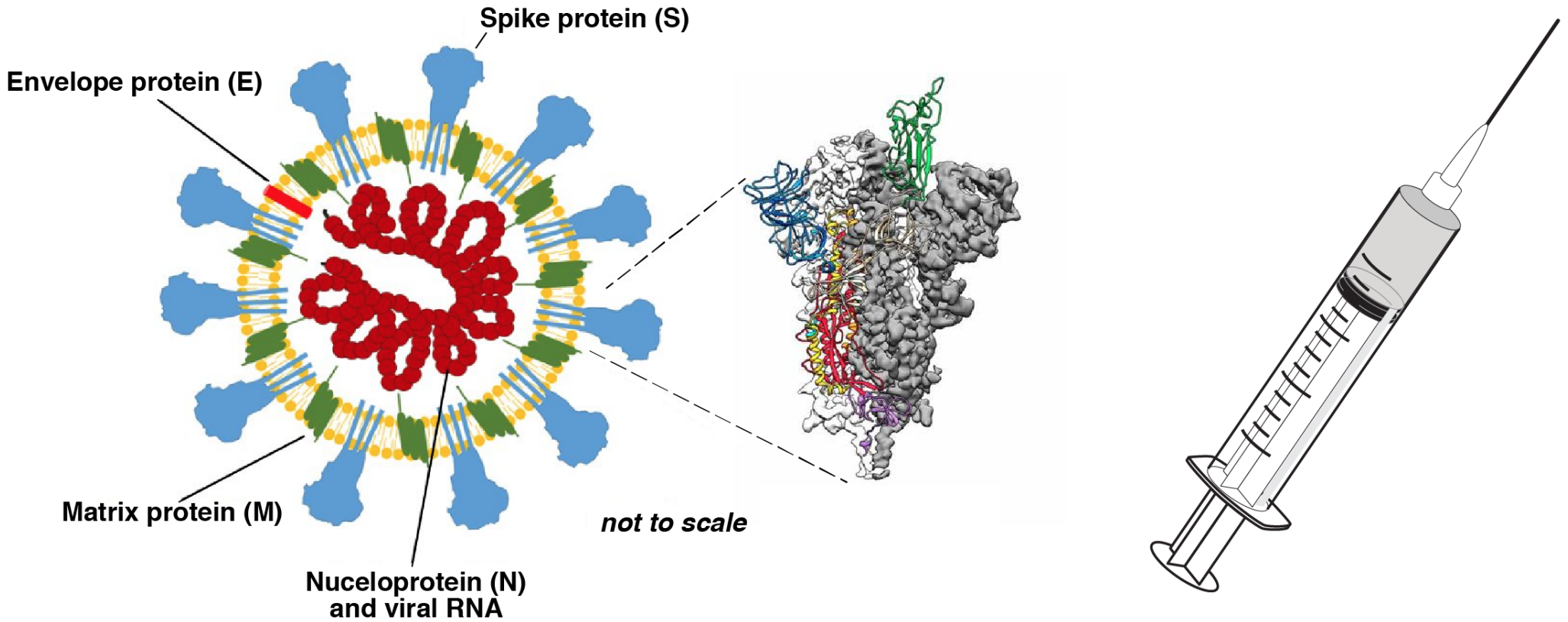


Slide source: AS Fauci

Adenovirus-Vectored Vaccine Platform

- Advantages
  - Well-established technology (plug and play)
  - Strong immune response involving both B and T cells
  - Thermostable
    - 2-8 C for 6 months
  - Scalable production
  - Low cost
- Disadvantages
  - Previous exposure to vector could reduce effectiveness
  - Relatively complex to manufacture

Adjuvanted Protein Subunit: Novavax, Sanofi/GSK



Protein Subunit + Adjuvant

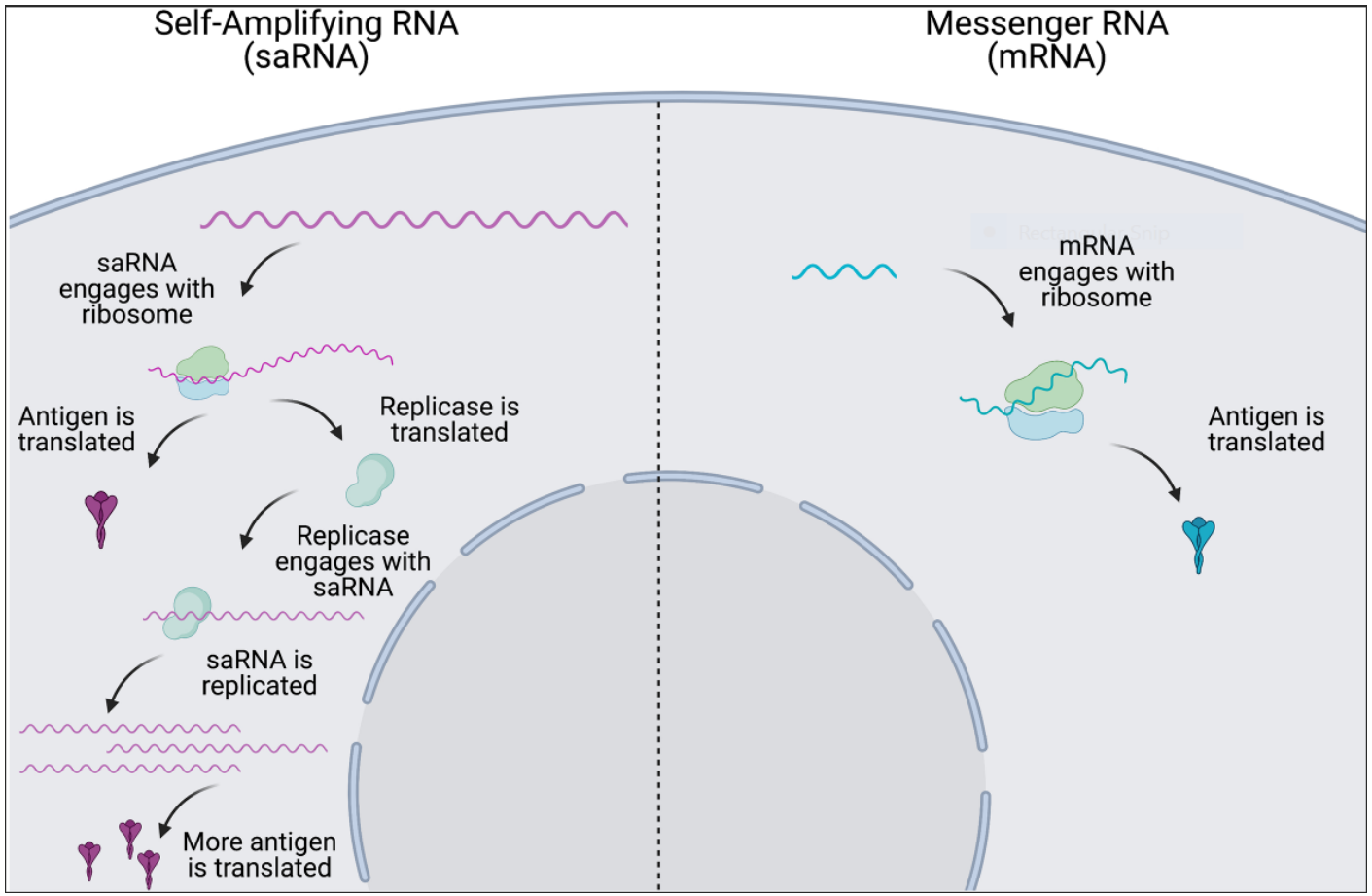
Images: Florian Krammer; NIAID VRC
Slide source: AS Fauci

Protein Subunit Vaccine Platform

- Advantages
  - Well-established technology
  - Suitable for people with compromised immune systems
  - No live components, so no risk of vaccine triggering disease
  - Relatively stable
- Disadvantages
  - Relatively complex to manufacture
  - Adjuvants and booster shots may be required
  - Determining the best antigen combination takes time

Source: GAVI

Self-replicating mRNA platform



- Lower dose-reduced cost
- Several COVID 19 vaccines in development
  - Gennova- approved in India
  - Arcturus- in Phase 3 trials in Vietnam
  - Others in clinical development

https://doi.org/10.1042/bio_2021_142

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Project NextGen-UPDATE

The Washington Post

April 10, 2023

White House launching $5 billion program to speed coronavirus vaccines

- Current vaccines are highly protective against severe disease and death
- Protection from **infection** decreases over time and with the emergence of variants

- Priorities of Project NextGen
  - Mucosal vaccines
  - Broadly protective vaccines
  - New Monoclonal Antibodies

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The Potential of Mucosal Vaccines

- Faster immunity recall after viral exposure
- Infection and transmission blocking
- Needle free delivery

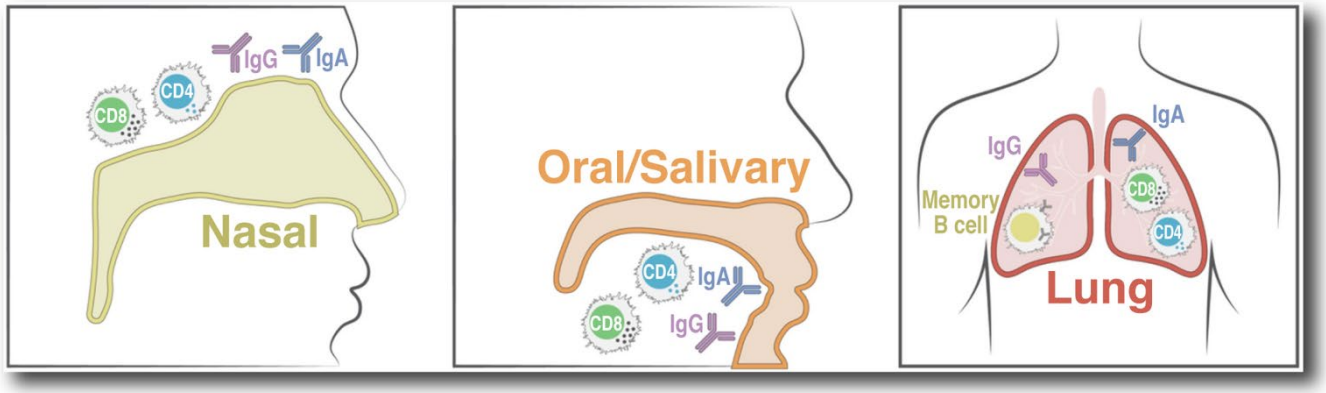

Image Credit: Sette and Crotty. *Immunological Reviews* 2022

- Workshop on November 7-8, 2022 on SARS CoV-2 mucosal vaccines
- NIAID, CEPI, BMGF, BARDA, Wellcome Trust and vax developers
- 5 COVID mucosal vaccines authorized/registered and 13 in clinical development
- Gaps in research include mucosal correlates of protection, standardized assays and sampling protocols, regulatory pathways to approval
- https://doi.org/10.1038/s41541-023-00654-6

Vaccine Manufacturing

Must be reliable, efficient, low-cost, and flexible to allow on-demand production

- In vitro
  - mRNA
- Cultured cells
  - Recombinant viral vector
  - Live attenuated
  - Recombinant Protein
- Eggs-based
  - Live-attenuated, inactivated
- Plants

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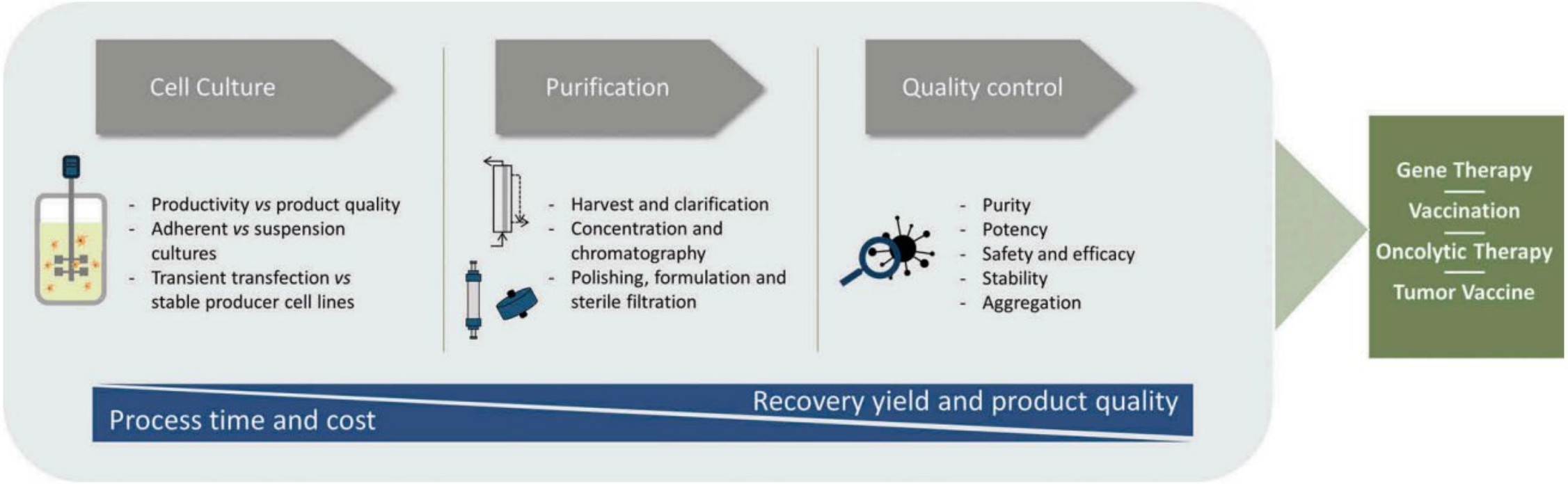
Main steps in biomanufacturing



https://doi.org/10.1080/14712598.2020.1693541

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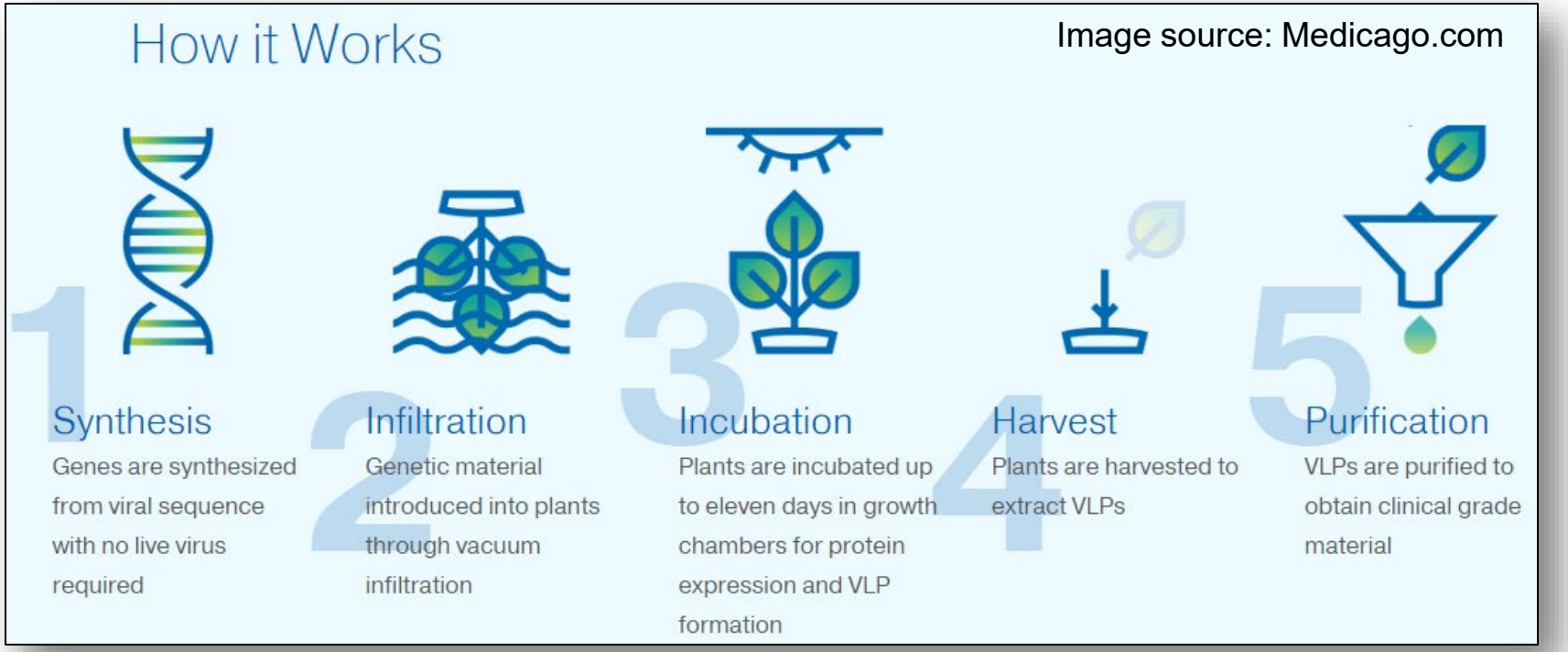
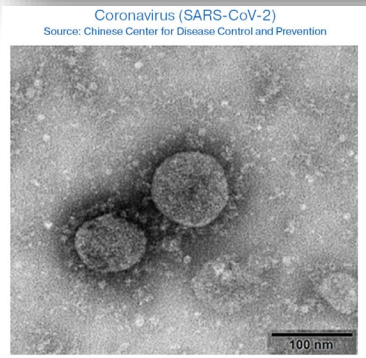
Recent innovations in biomanufacturing

- Single use bioreactors
  - Greater flexibility
  - Less risk of contamination
  - “Ready-to-use manufacturing rooms”
- Automation of process analytical technologies
  - To monitor manufacturing through timely measurements of critical quality and performance attributes
- Continuous manufacturing (vs batch manufacturing)
  - Improve efficiency and control
  - Smaller footprint
  - Reduce cost

https://bioprocessintl.com/topic/manufacturing/

Plant-based expression and manufacturing





Medicago VLP based SARS-CoV2 vaccine approved in Canada (Feb 2022)

Medicago shuts down (Feb 2023)

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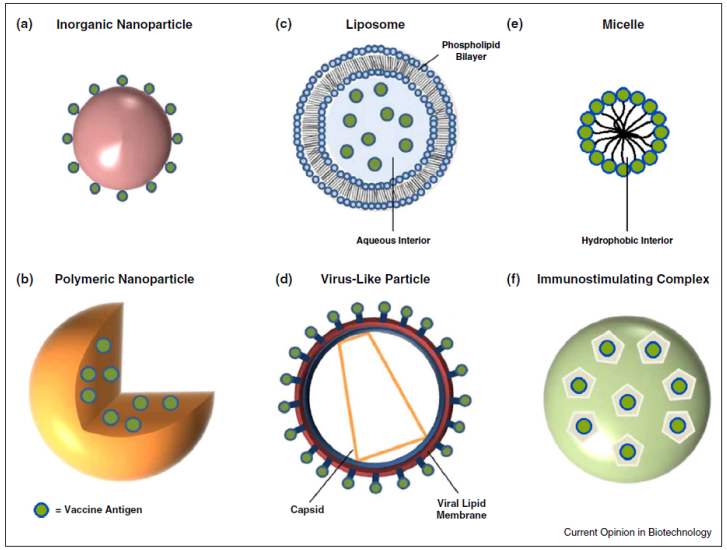
Vaccine Delivery

- Needle and syringe
- Mucosal delivery
- Microneedles
- Nanoparticles

Credit: James Gathany, CDC



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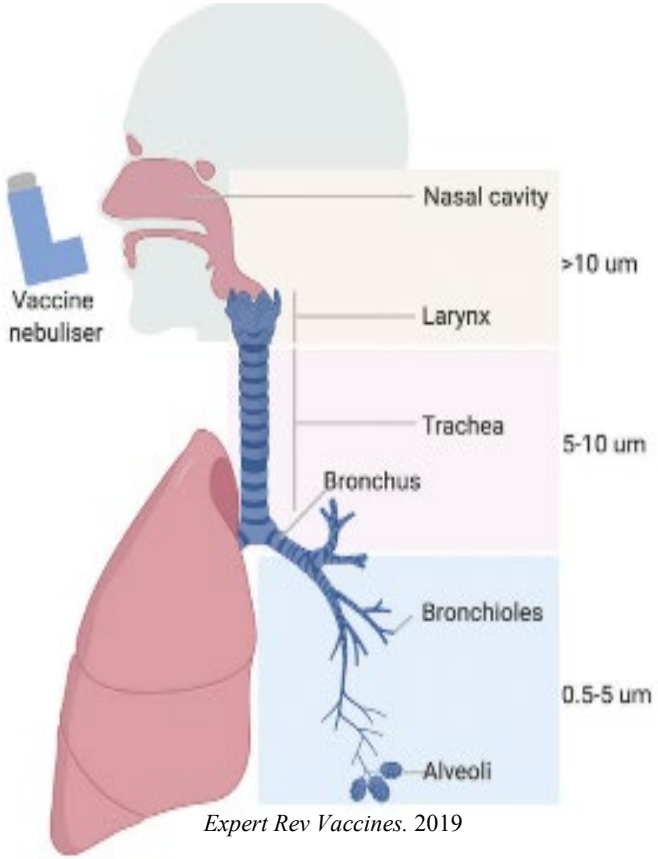
Characterization of Aerosolized Ad5-nCoV

Vaccine deposition following aerosol delivery

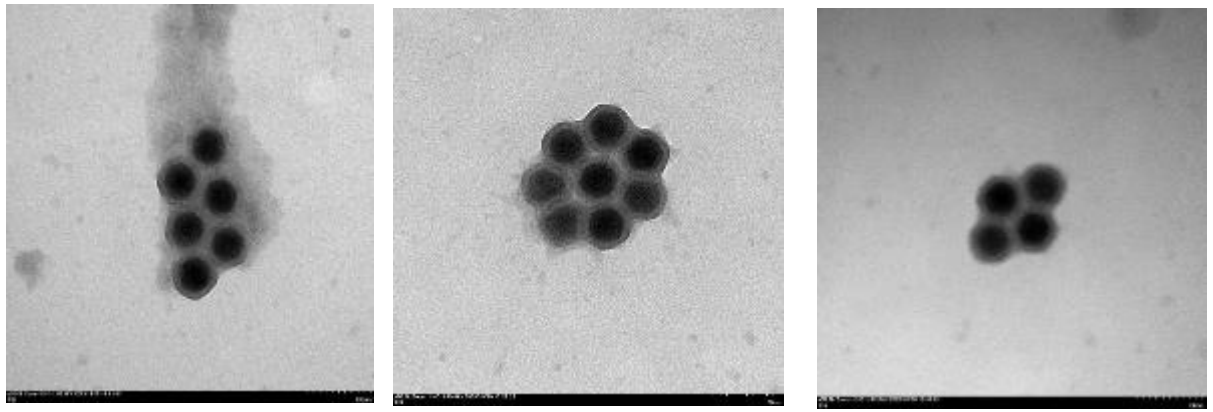


Expert Rev Vaccines. 2019

Viability of aerosolized vaccine

Dosage (ml)	Infections unit (IFU) recovery (%)	Viral particles (VP) recovery (%)
0.1	81.28%	97.54%
0.2	98.62%	96.45%

No impact on morphology of Ad5-nCoV

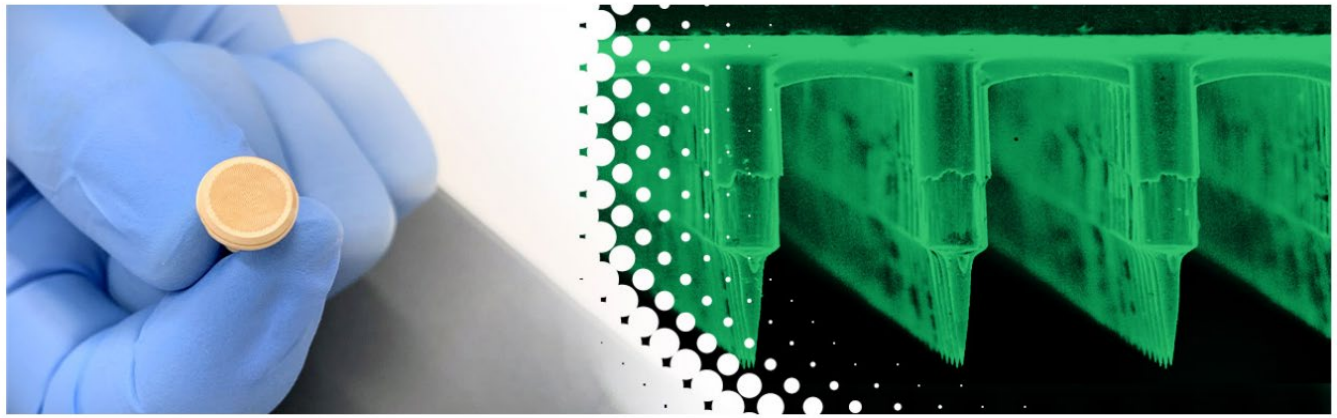


Pre | Nebulize 0.1ml | Nebulize 0.2ml

Credit: Chunlin Xin-CanSino Biologics INC.

Vaxxas Microarray Patch

NEEDLE-FREE TECHNOLOGY



The core of Vaxxas technology platform is a High Density Microarray Patch (HD-MAP). Vaxxas' HD-MAP is readily fabricated by injection molding to produce small patches each with thousands of very short (~0.25mm) microprojections.

Coming in from the cold: needle-free patch technology for mRNA vaccines aims to end need for frozen storage and improve access

17 Jan 2023 By CEPI News

https://www.vaxxas.com/technology-platform/

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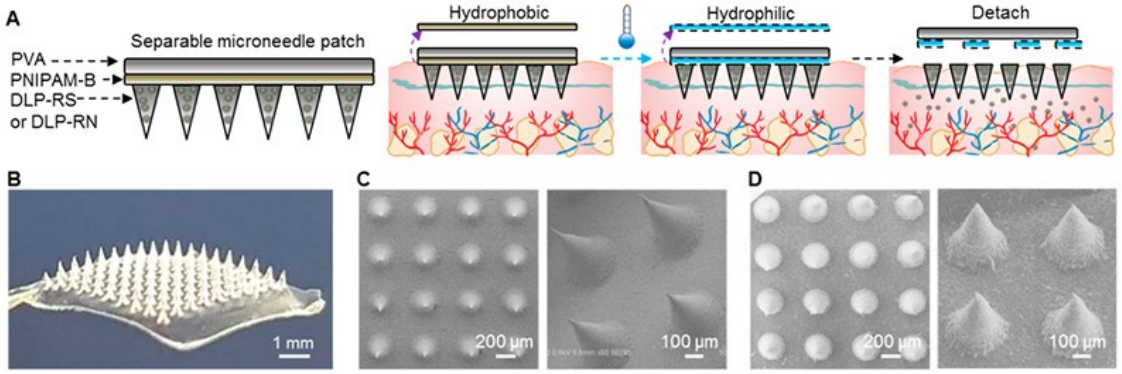
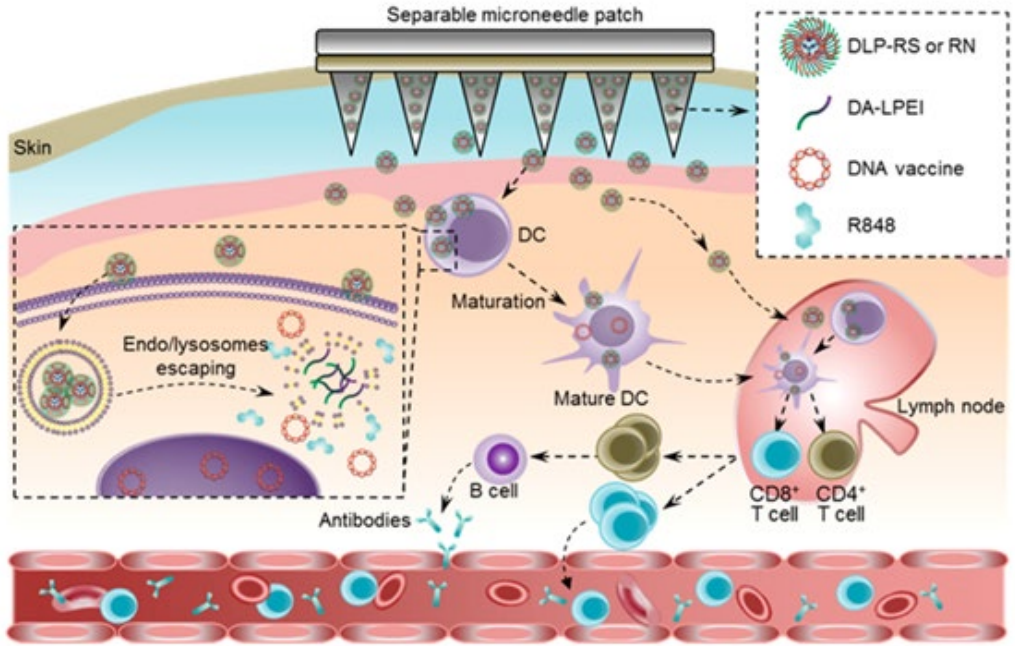
Separable Microneedle Patch to Protect and Deliver DNA Nanovaccines Against COVID-19





Nanoparticles containing DNA vaccines + adjuvant

ACS Nano 2021, 15, 14347−14359

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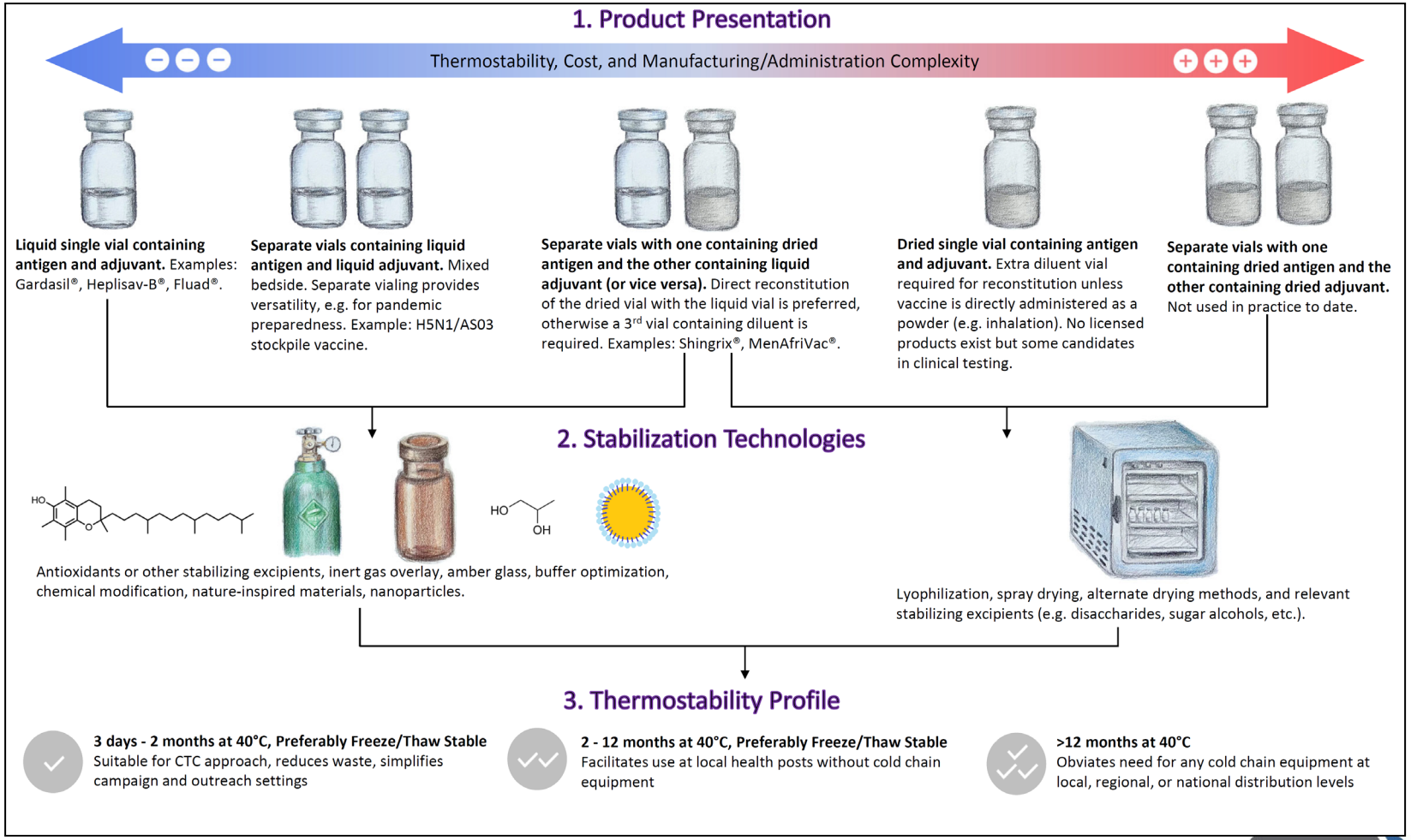
Thermostability and vaccines



Artwork by Yizhi Qi. Qi Y, Fox CB, Expert Rev Vaccines 2021, doi: 10.1080/14760584.2021.1902314

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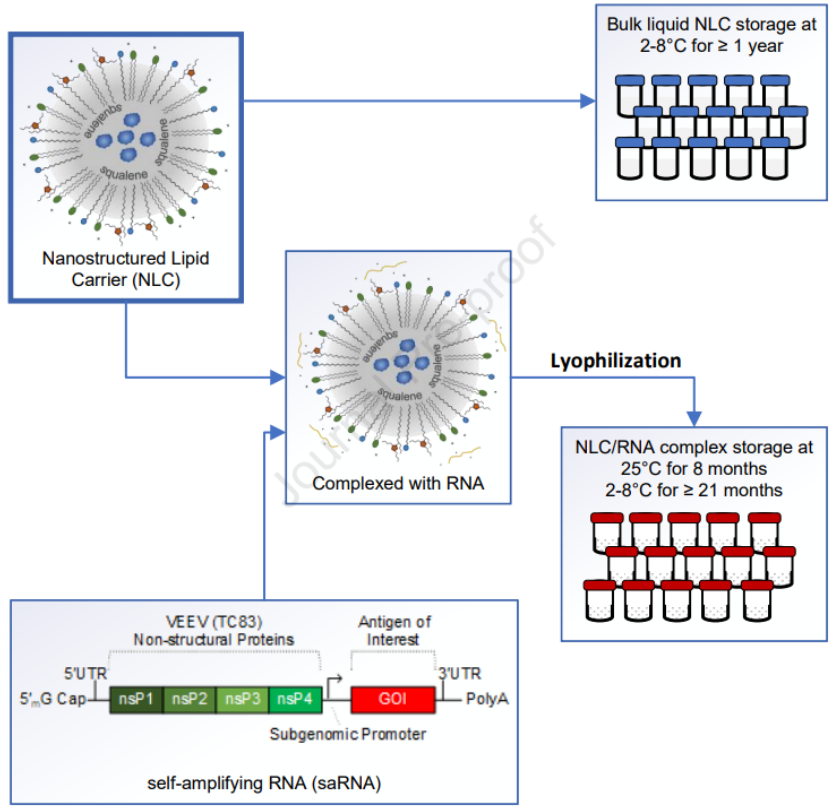
Flexible, Thermostable Platform for RNA Vaccine Delivery

- Current RNA vaccines against SARS-CoV-2 are limited by instability of both the RNA and the lipid nanoparticle delivery system, requiring storage at -20°C or -70°C.

- This study demonstrates the thermostability and adaptability of a **nanostructured lipid carrier (NLC) delivery system for RNA** vaccines that has the potential to address these concerns.



Gerhardt A et al. Molecular Therapy: Methods & Clinical Development (2022). https://doi.org/10.1016/ j.omtm.2022.03.009

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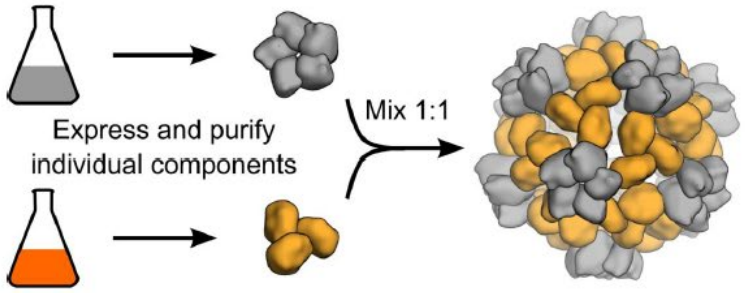
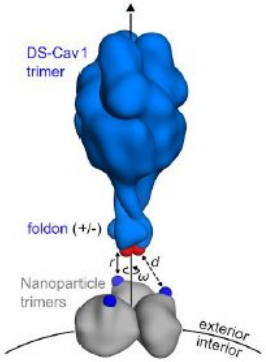
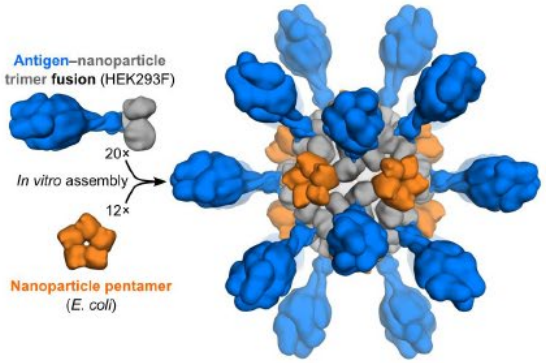
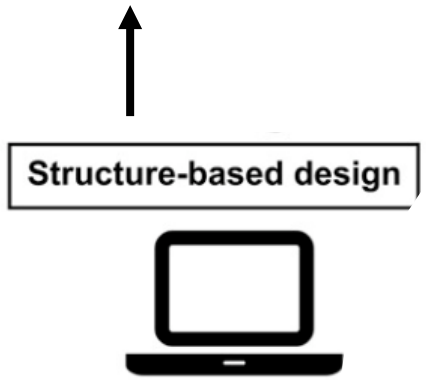
WHAT'S NEXT?

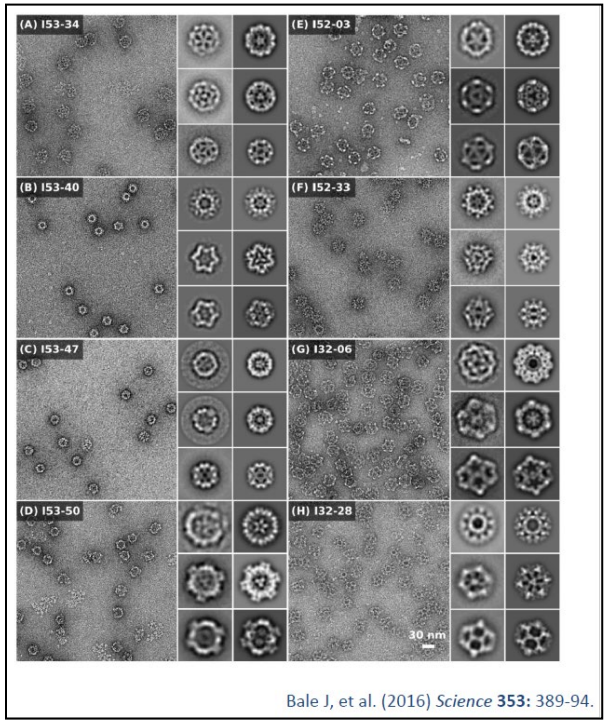
Rationally Designed Nanoparticles for Vaccines











Reference: Marcandalli J, et. Al. (2019).
Cell **176**: 1420-1431.

Slide source: AS Fauci

SKYCovione approved in South Korea

COVID-19 vaccine with IPD nanoparticles wins full approval abroad

June 29, 2022

- *Clinical testing found the vaccine outperforms Oxford/AstraZeneca's*
- *The protein-based vaccine, now called SKYCovione, does not require deep freezing*
- *University of Washington to waive royalty fees for the duration of the pandemic*
- *South Korea to purchase 10 million doses for domestic use*

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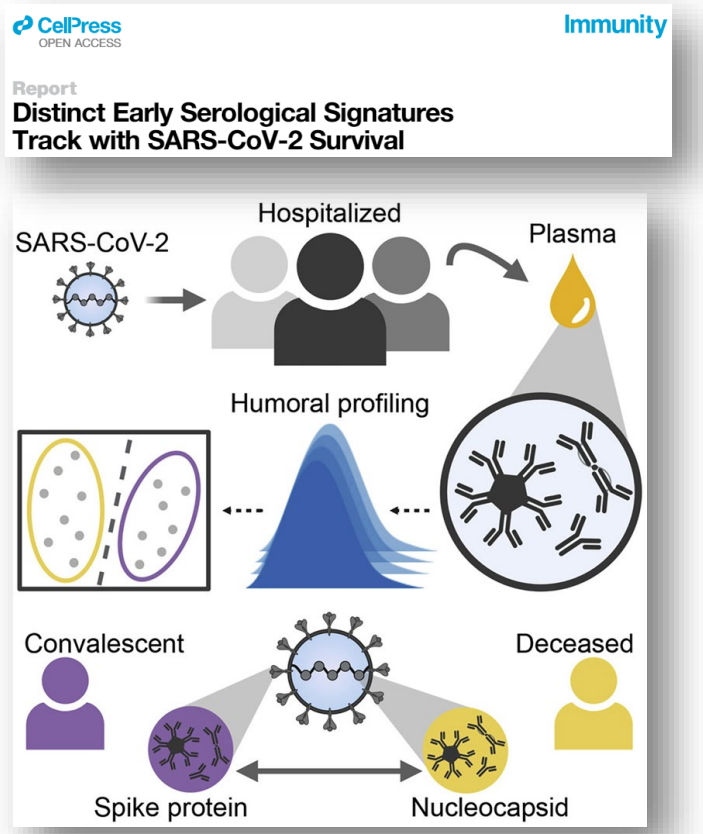
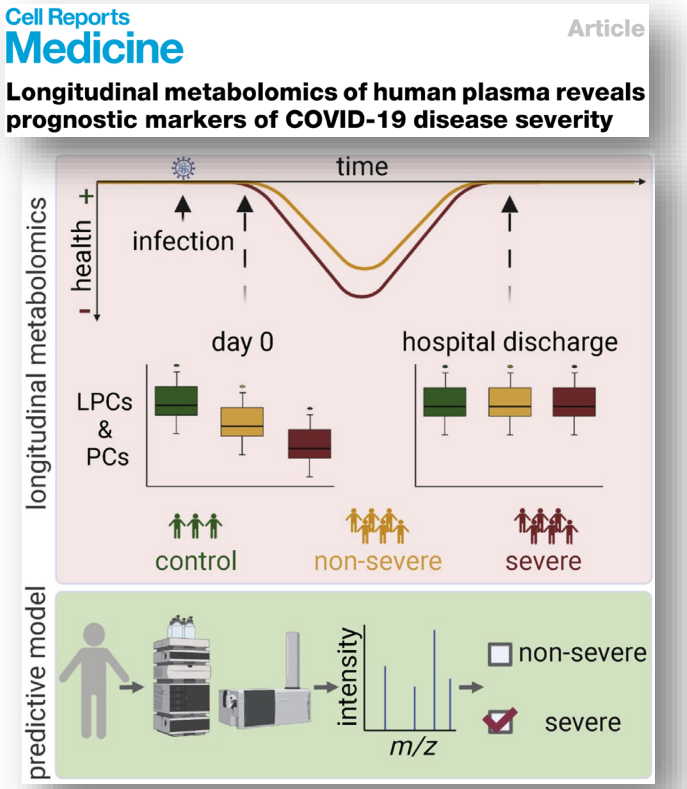
“Omics” and identification of infection and vaccination biomarkers

Omics-based **‘systems serology’** can inform effective vaccine responses



Metabolomics informs COVID severity, and the technology can identify vaccination biomarkers



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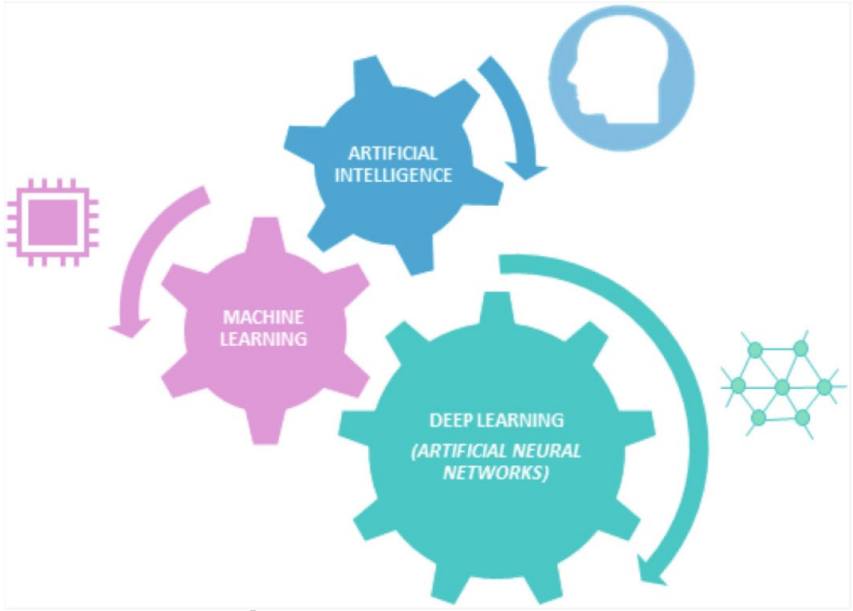
Artificial intelligence and vaccine design

- Adjuvant–ag match
- Protein determination
- The identification of antigenic proteins that induce immunity
- Models to predict linear or conformational B cell epitopes
- Ability to predict how different individuals may respond to vaccination and to understand which epitopes might best protects individuals from infection (personalized vaccines)



Citation: Petovsky, *et. al*. (2021. Vaccine Design.
https://link.springer.com/protocol/10.1007/978-1-0716-1884-4_6

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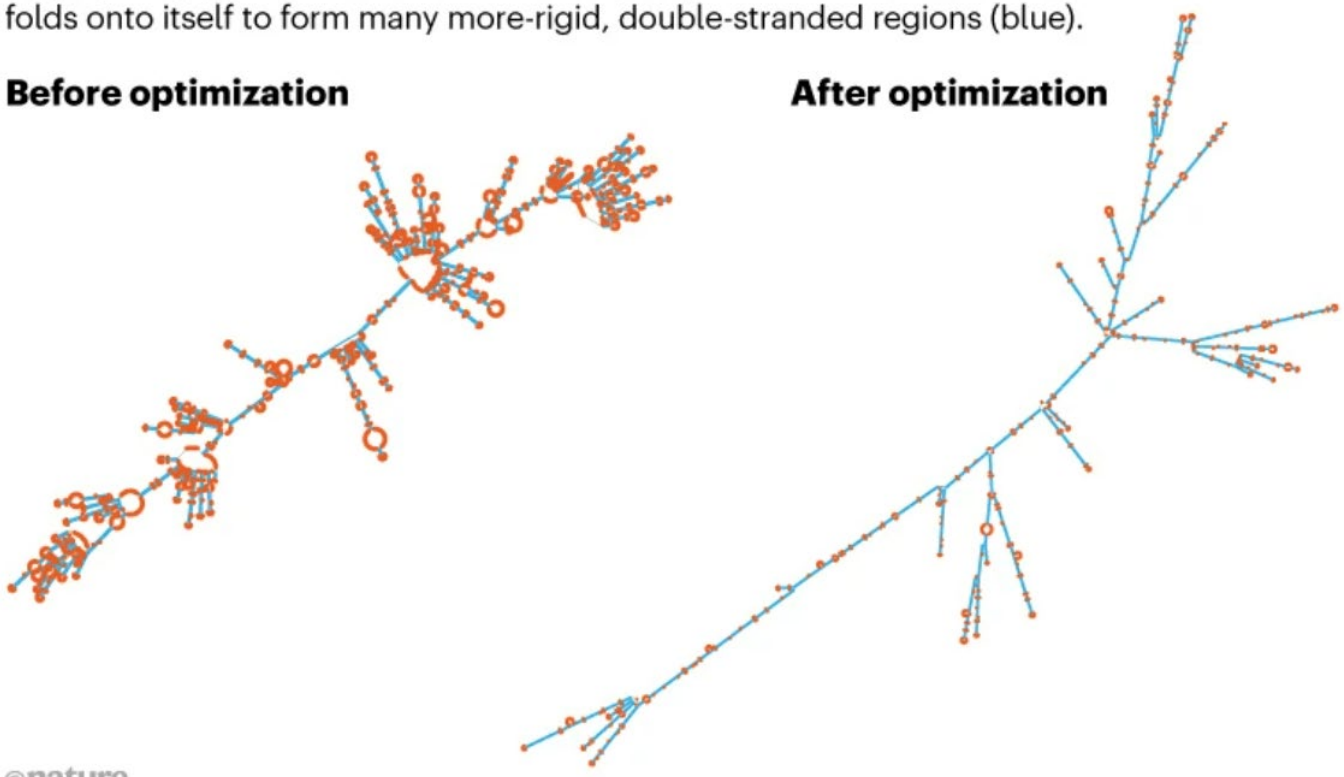
AI to design mRNA vaccines that are more potent and stable

DESIGN OPTIMIZATION

An AI tool developed by the California division of Baidu Research can create mRNA sequences for vaccines that are more stable than usual and therefore can elicit a stronger immune response. It starts with a sequence full of floppy loops (orange) and, after about 11 minutes, outputs one in which the mRNA folds onto itself to form many more-rigid, double-stranded regions (blue).

Before optimization **After optimization**



©nature

Source: Adapted from Ref. 1

Compared to conventional vaccines, optimized mRNA induced ab levels 128 greater in mice and extended shelf stability by 6 fold

Zhang H. *et al. Nature* https://doi.org/10.1038/s41586-023-06127-z (2023).

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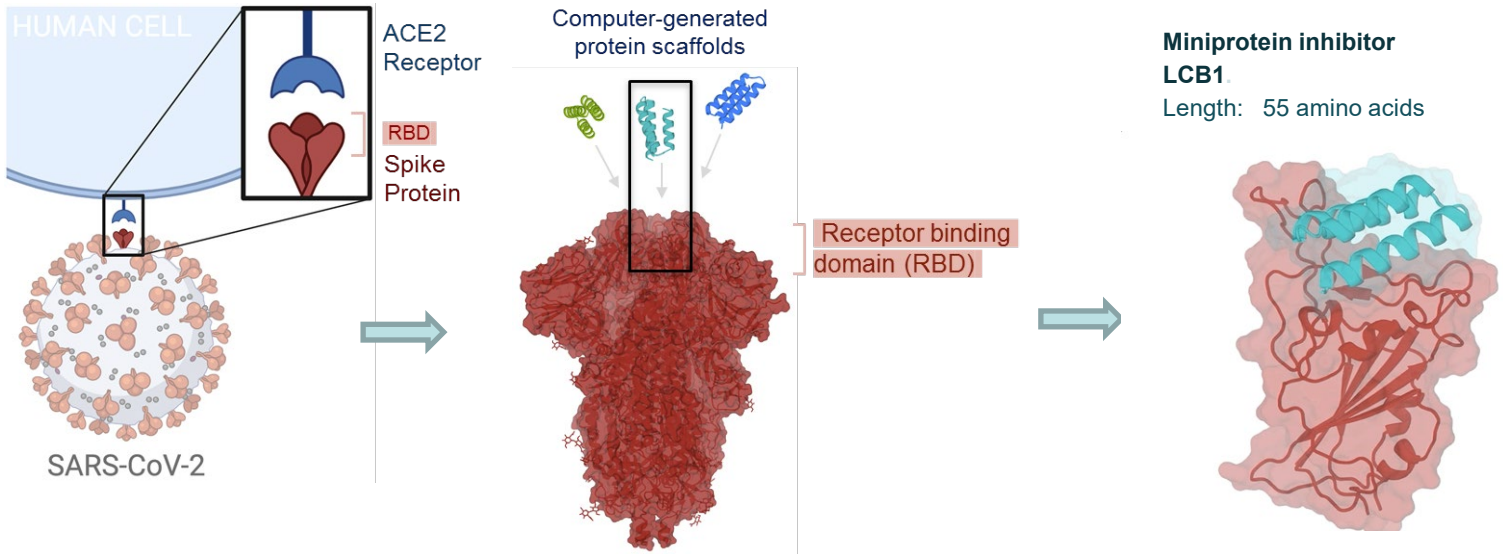
AI and Machine Learning Accelerate Structure-based Design



Deep Learning for structure-based sequence design gives >10-fold improvement on retrospective datasets. Preliminary experimental results are extremely encouraging.

Current Status: Minibinder inhibitors are heading to clinical trials in 2022 for Pre-exposure prophylaxis and Early post-exposure prophylaxis

Cao L, *et al.* (2020) ***Science***
Cao L, *et al.* (2022) ***Nature***

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Conclusions

- The current SARS-CoV 2 pandemic has catalyzed a major renaissance in vaccine technologies
- These new technologies should help advance other important vaccine areas (e.g. HIV, TB, malaria, influenza etc)
- Vaccine technologies don’t solve all the problems. It’s of critical importance to understand basic pathogen biology to rationally design effective vaccines
  - Correct antigens/epitopes, antigen conformation, most appropriate expression platform for a given target, etc.
- Investments in basic research and vaccine platform development are essential to support the development of future vaccines