Responding to COVID-19 with de novo protein design

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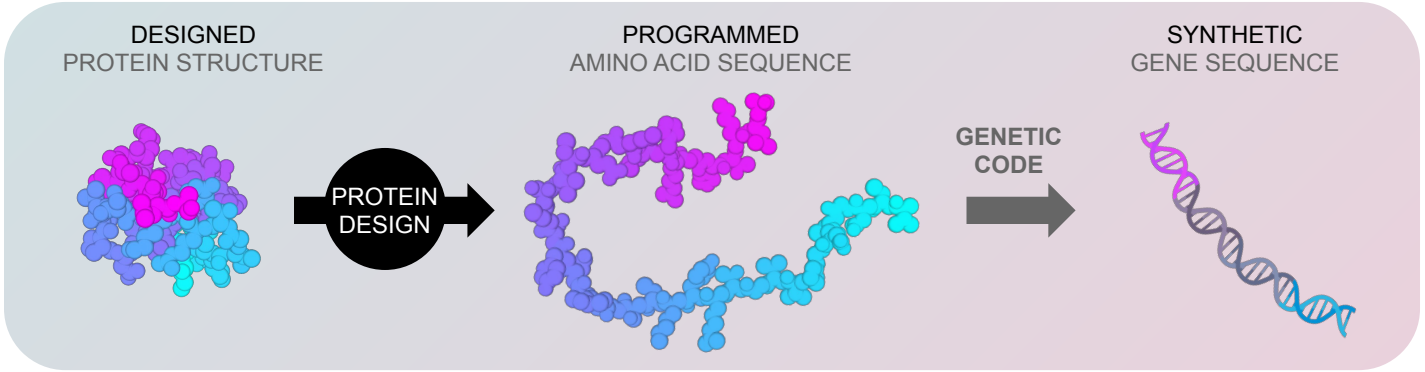
INSTITUTE FOR
Protein Design
UNIVERSITY of WASHINGTON

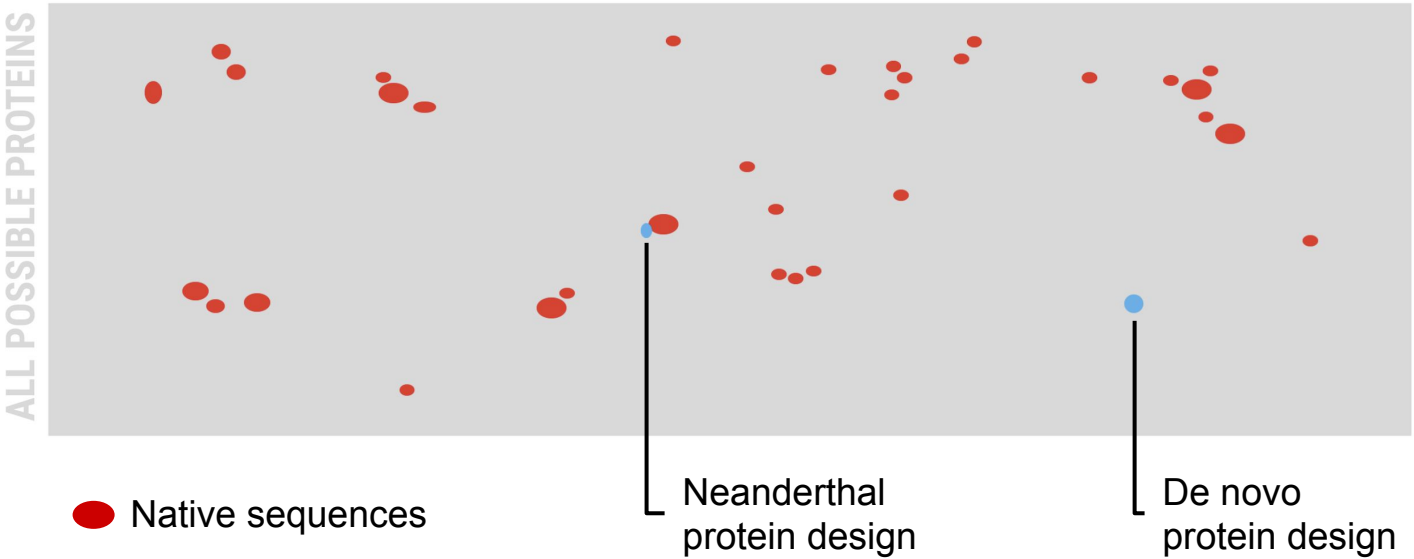
We built Rosetta to predict how proteins fold

We are now using it to create new proteins

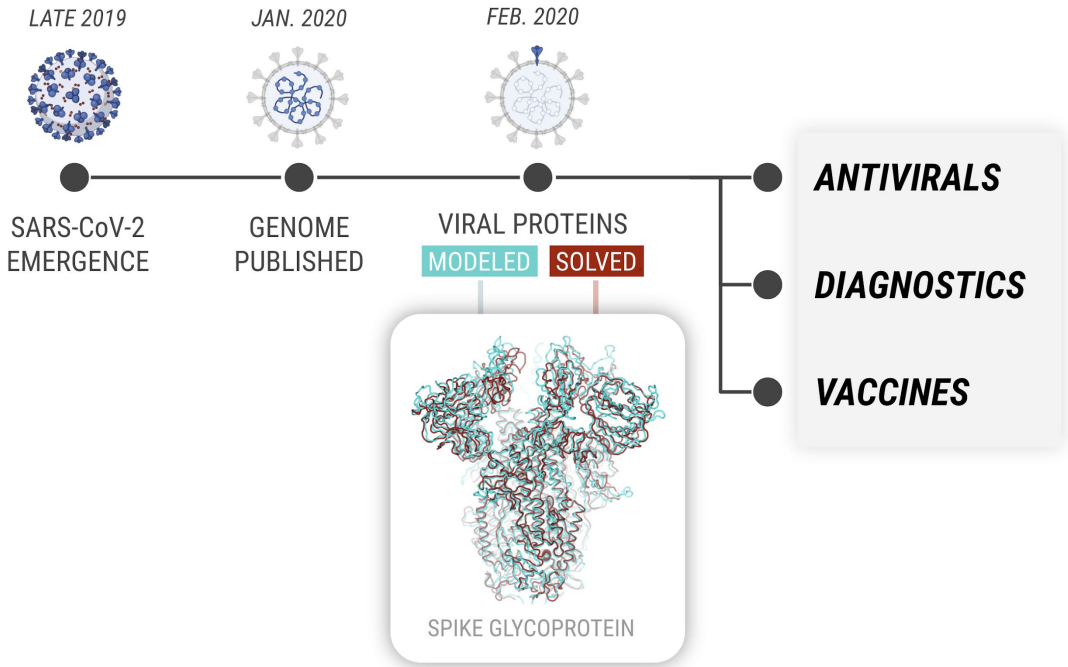


De novo protein design

Number of 100 residue amino sequences: 20^{100} = 1.3x 10^{130}
Number of naturally occurring proteins: ~10^{15}

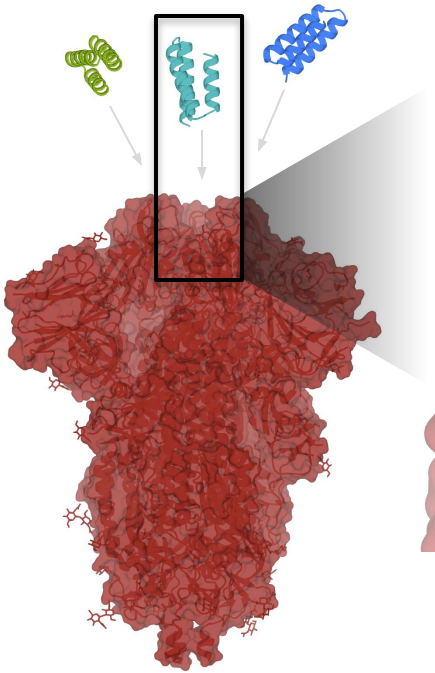


Computational platforms enabled rapid pandemic response

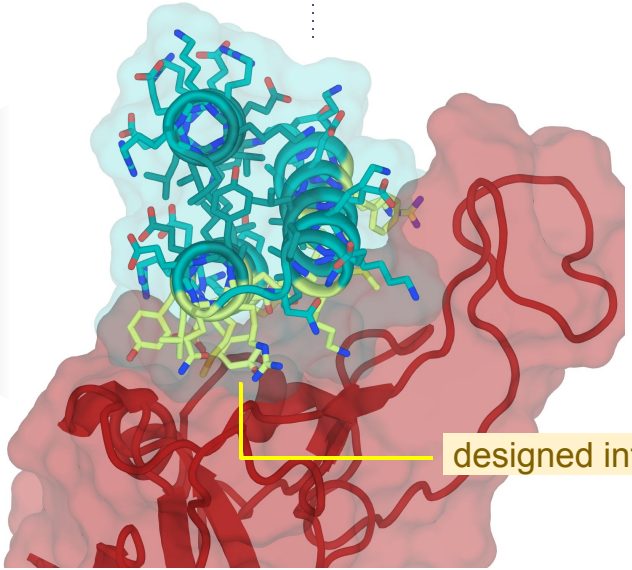


Computational design of potent SARS-CoV-2 antiviral proteins

Computer-generated protein scaffolds



SARS-CoV-2 Spike glycoprotein



Receptor binding domain (RBD)

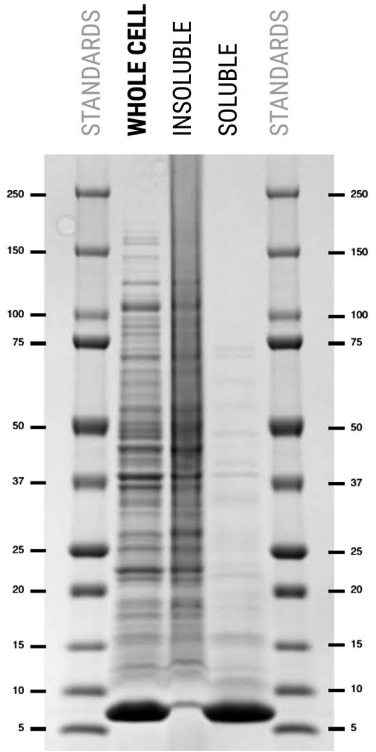
Miniprotein inhibitor

Length: 55 amino acids

Stability: >95°C T_m

Blocks binding to ACE-2

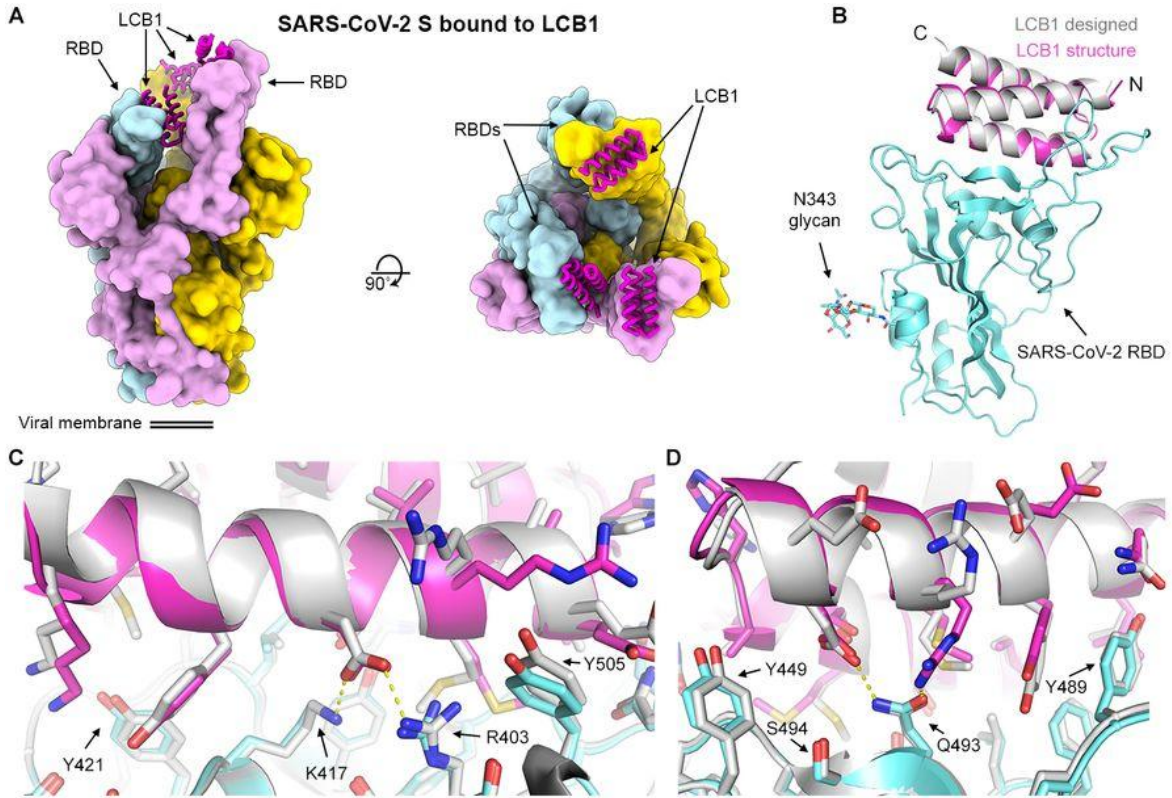
Cell culture live virus IC50: 11pM (*Vero-6 cells*)



Standard *E. coli* expression

Cao L, *et al. De novo design of picomolar SARS-CoV-2 miniprotein inhibitors.* ***Science*** (2020)

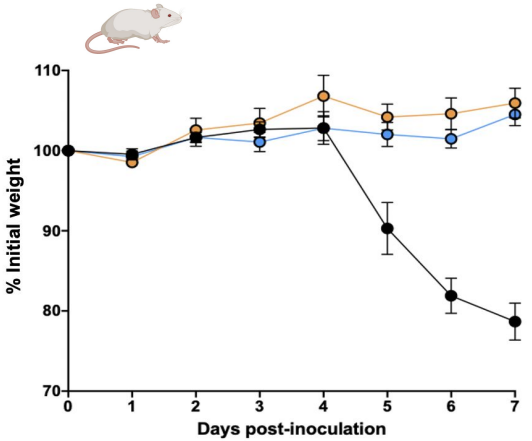
Lead miniprotein candidate (LCB1) binds Spike as designed

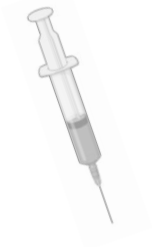


Cryo-EM complex by Lexi Walls (Veesler Lab, UW)

Cao L, *et al.* ***Science***. 2020

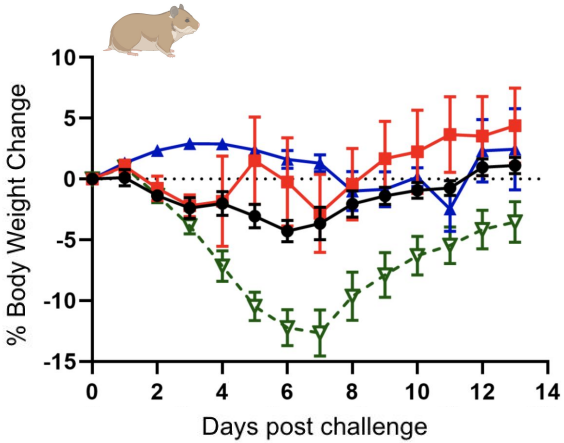
LCB1 protects mice and hamsters from infection





hACE2-mice received **systemic administration** of LCB1-Fc fusions 24h prior to SARS-CoV-2 challenge.

- LCB1-Fc9
- LCB1-Fc10
- Inactive control



Hamsters received **nasal administration** of LCB1 16h prior to SARS-CoV-2 challenge.

- Not Challenged
- LCB1-PBS
- LCB1-KA
- Buffer Control

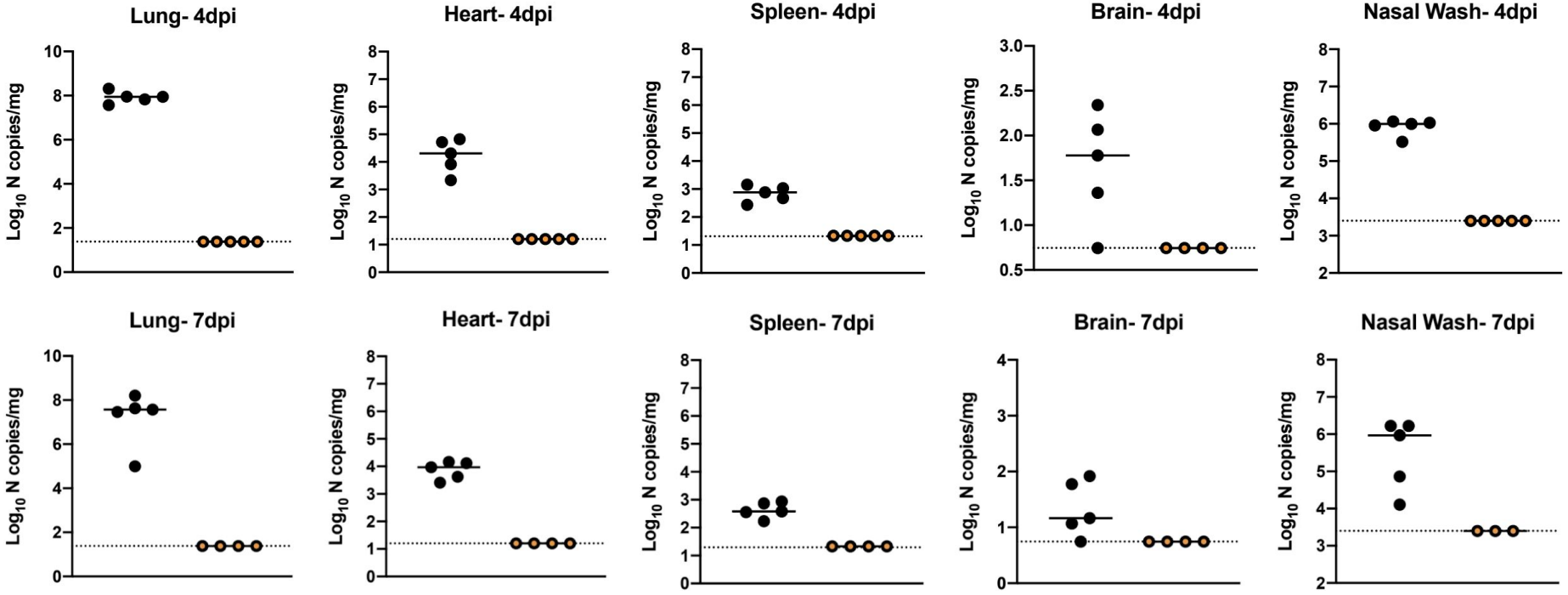
with Barouch Lab (Harvard), Diamond Lab (WUSTL), Veesler Lab (UW)

Experiments Still in Progress, Not yet Complete or Reproduced

Intranasal binder administration blocks viral replication

● Inactive control
○ LCB1

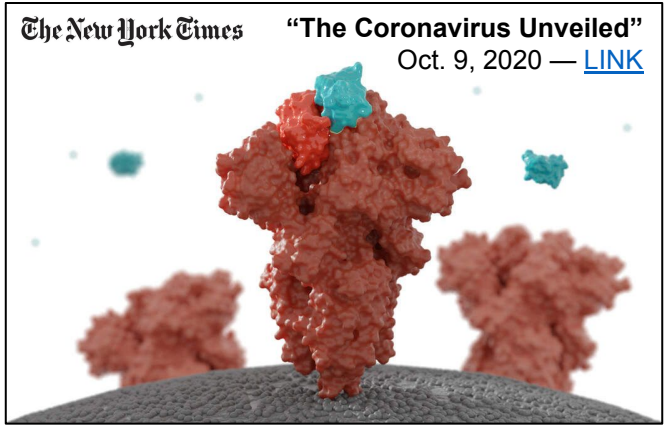
–6 hours, 50ug/mouse 10^3 PFU/mouse SARS-CoV-2



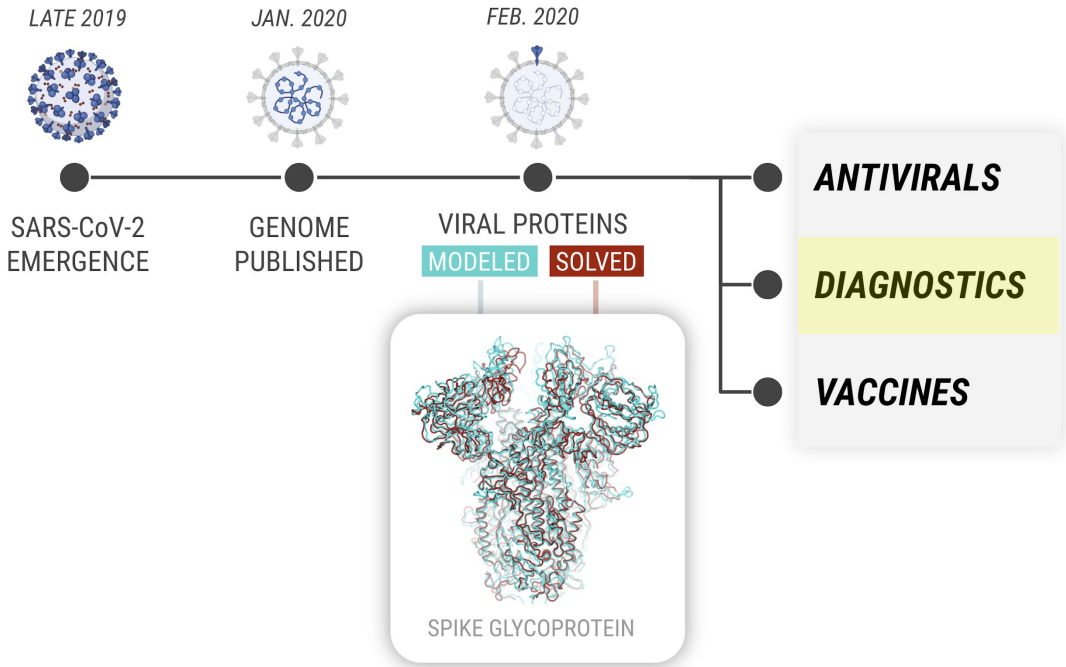
with Diamond Lab (WUSTL)

Next steps for SARS-CoV-2 antivirals

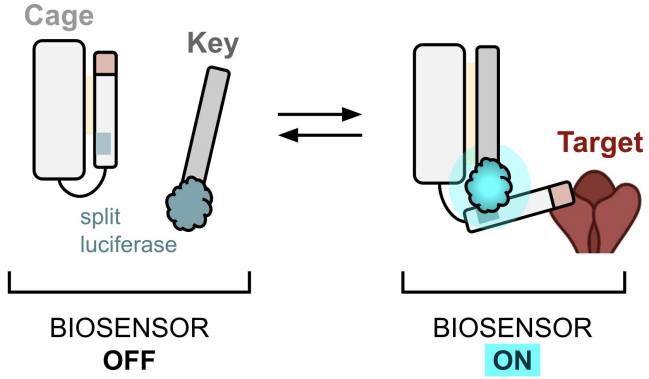
- Optimize formulation and delivery mode
- Develop large-scale manufacturing protocol with very low cost of goods
- Partner for clinical trials
- Nasal drops or inhaled spray conferring prophylactic and therapeutic protection
  - Ultracheap production and hyperstability allow widespread distribution
- **Before the next pandemic:** Improve design pipeline so we can go from *emergence* to *trial-ready treatment* in two weeks.

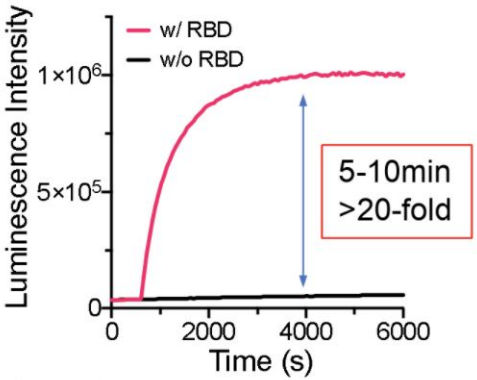


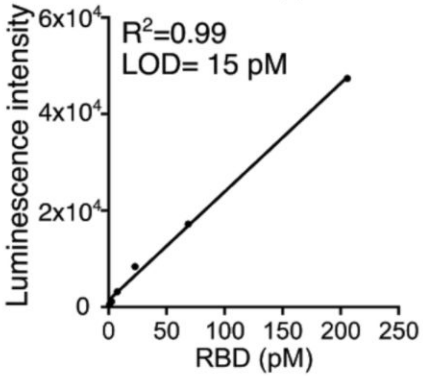
Responding to COVID-19

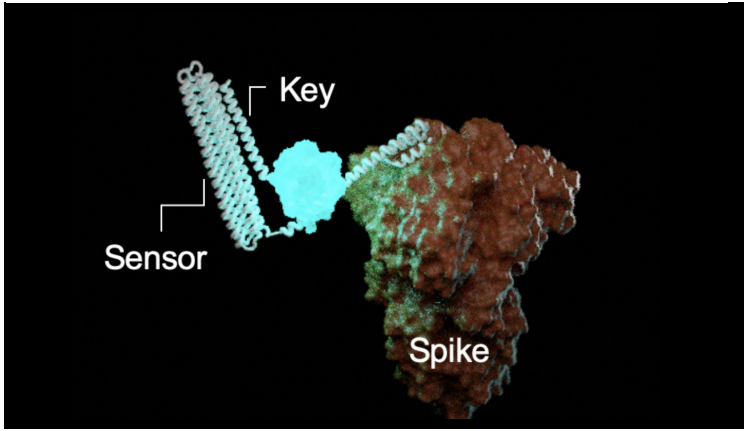


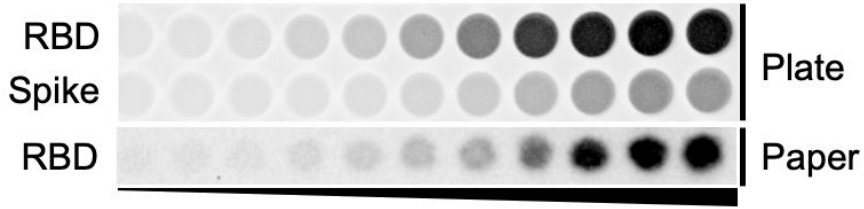
Biosensors emit light when mixed with virus protein







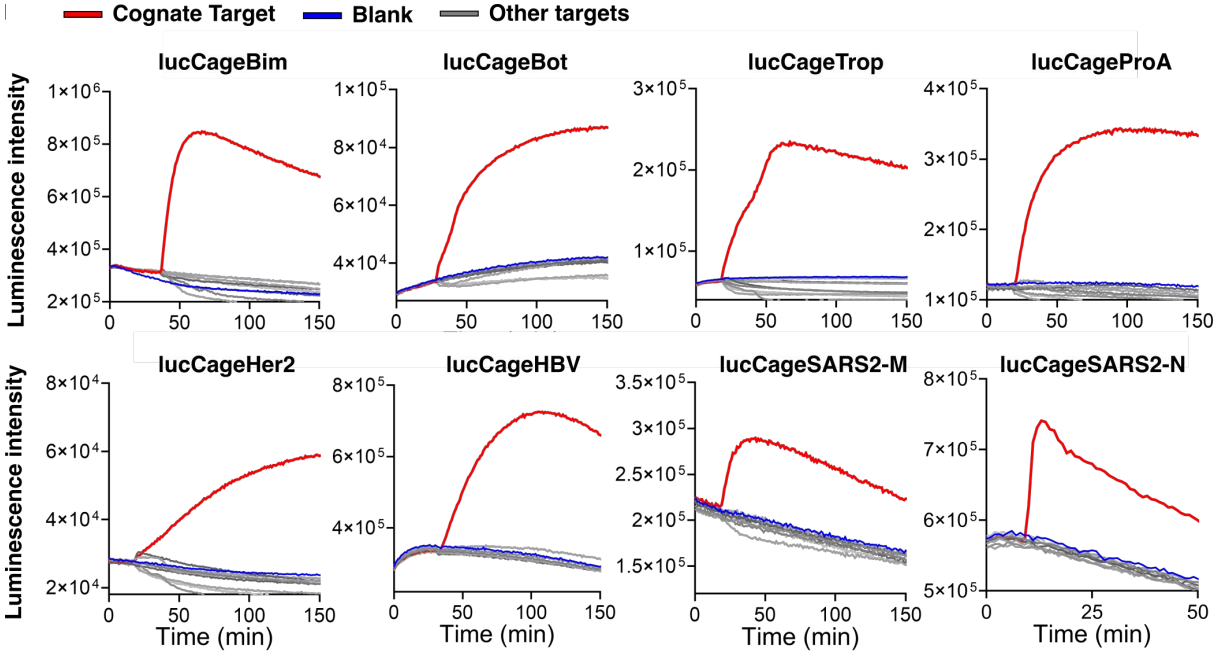




Alfredo Quijano-Rubio, Hsien-Wei Yeh, Byung-Ha Oh

Quijano-Rubio A, et al. bioRxiv. 2020. DOI: 10.1101/2020.07.18.206946

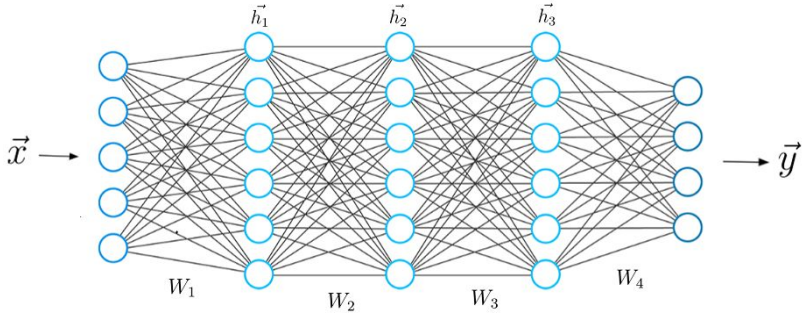
Can build molecular devices for sensing a wide range of compounds



We are integrating deep learning into design pipeline

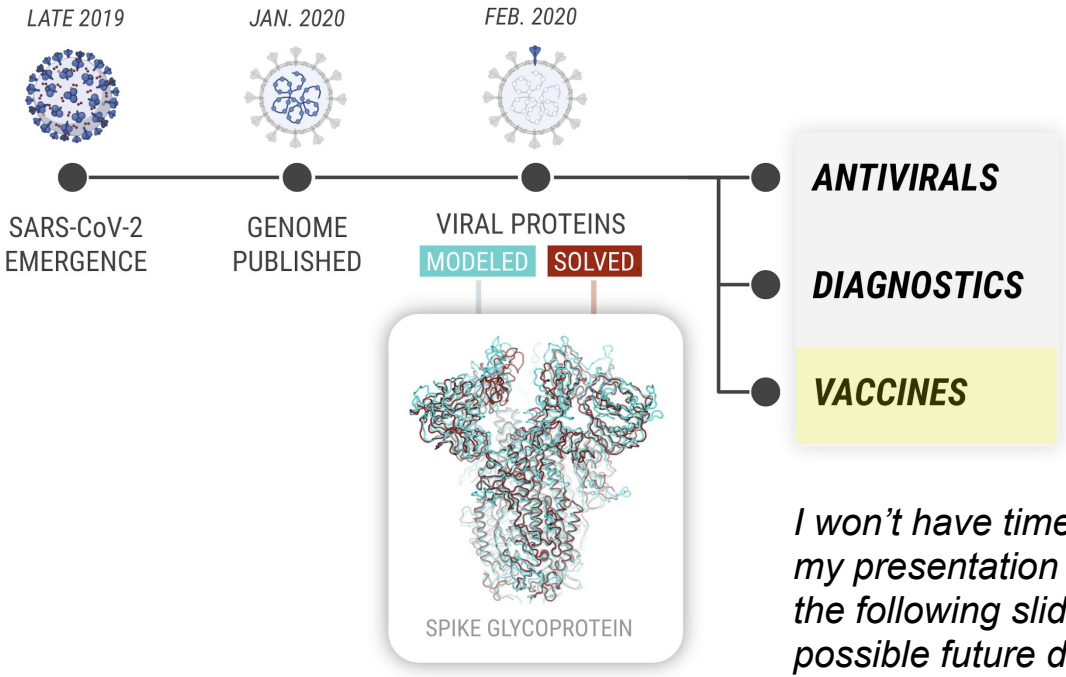
Goal: Capability to design high potency anti-pathogen therapeutics within two weeks of pandemic outbreak.

General challenge: How to integrate Rosetta protein design calculations, high-throughput experimental characterization, and machine learning into iterative design-build-test cycle to increase design robustness and accuracy.



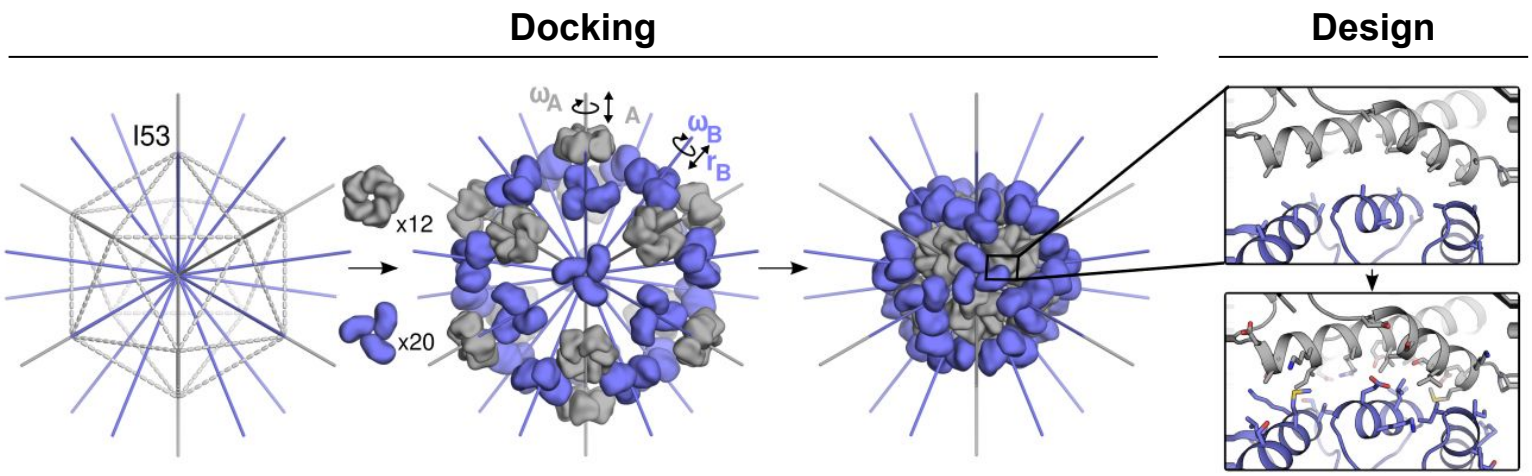
- Can now generate new proteins by deep network hallucination.
- Have trained deep learning models to identify most accurate designs.

Responding to COVID-19



I won't have time to cover this in my presentation but am including the following slides here for possible future discussion.

A general computational method for designing self-assembling proteins



Bale J, et al. (2016) *Science* **353**: 389-94.

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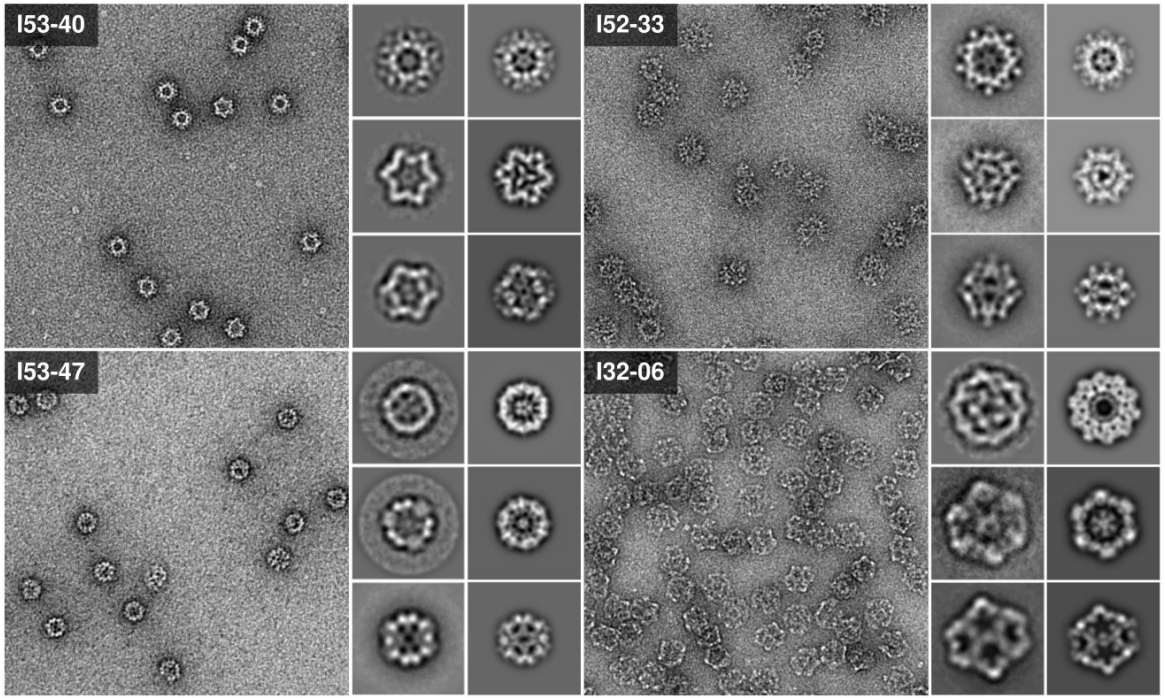

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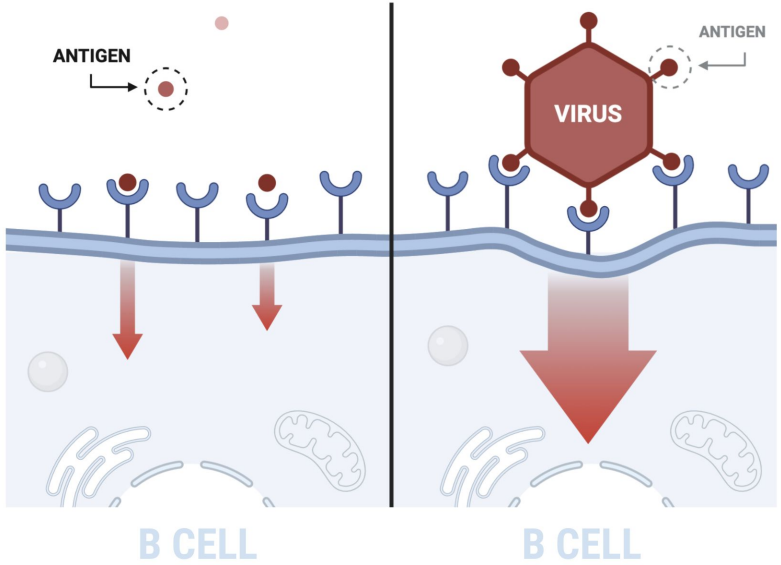
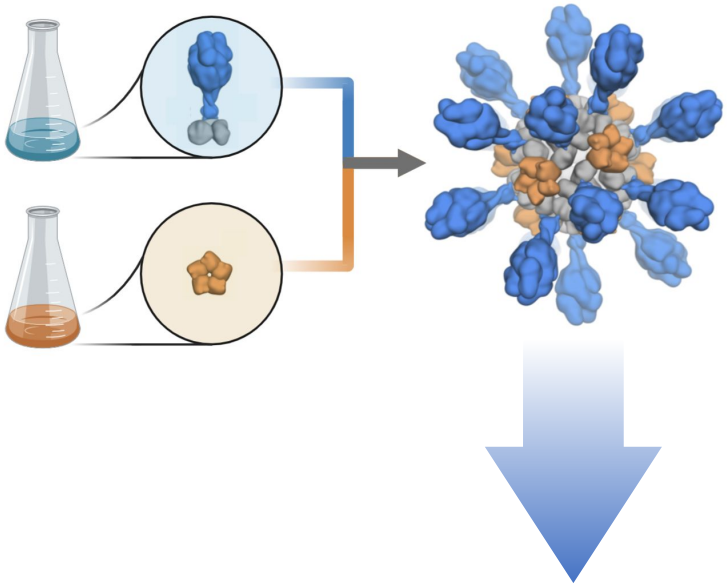
Designed two-component nanoparticles are a robust and versatile next-gen vaccine platform

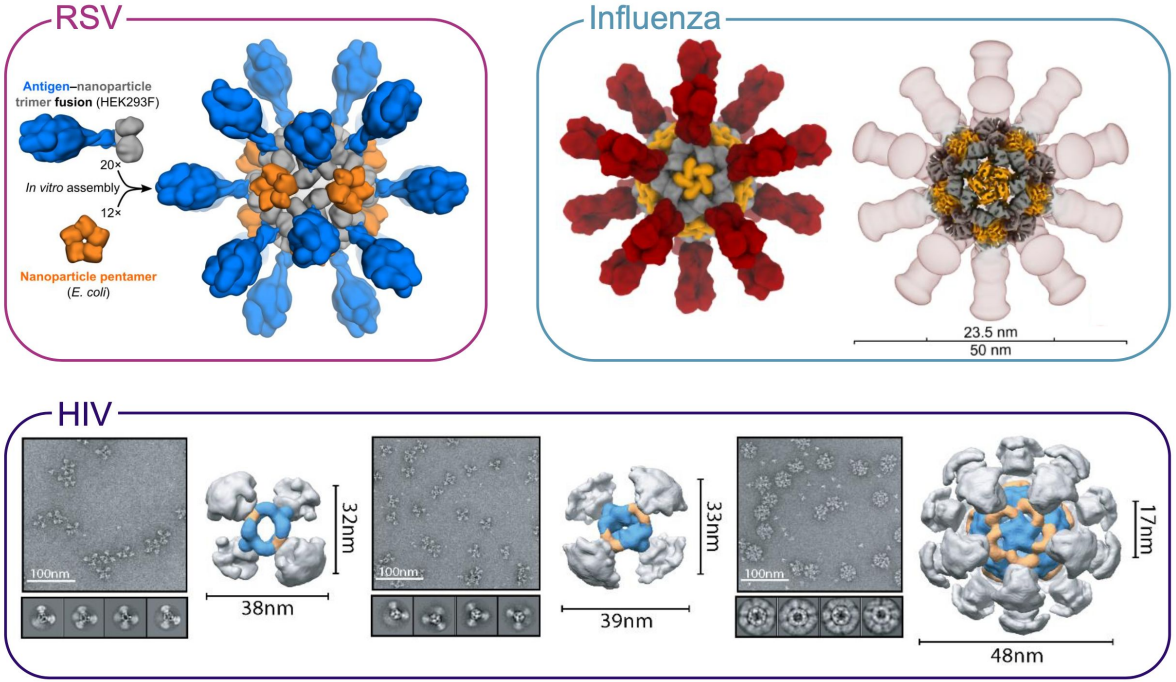
Biological problem



Technological solution



Designed two-component nanoparticles are a robust and versatile next-gen vaccine platform

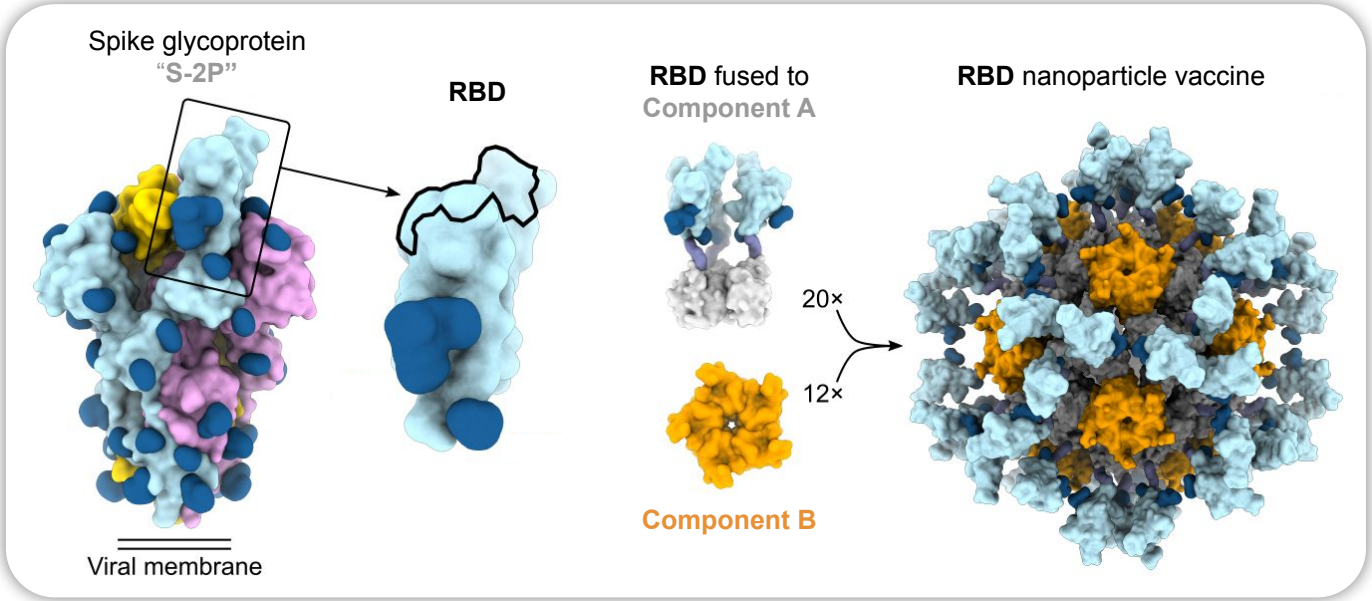


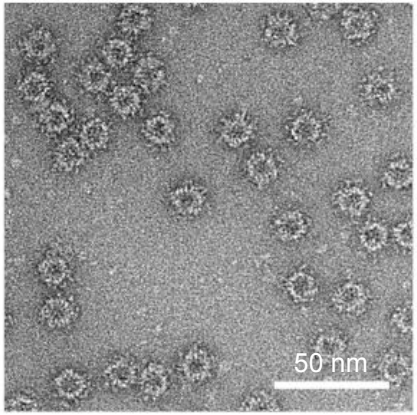
Also confirmed:

- hMPV preF
- PIV1-4 preF
- p67C (East Coast Fever)
- Plasmodium f (malaria)
- **Coronavirus S**
- Lassa GP
- HCV E1/E2
- EBV gH/gL
- HIV gp120
- Rotavirus VP8*
- Ovalbumin
- Peptide epitopes
- DARPins
- Ice-binding proteins
- MHC II
- De novo targeting proteins

with the groups of L. Perez, K. Loré, R. Sanders, J. Moore, A. Ward, V. Nene, B. Correia, A. McGuire, D. Veesler, P. Kwong, M. Kanekiyo, B. Graham, etc.

We rapidly deployed our platform to generate nanoparticle vaccines for SARS-CoV-2

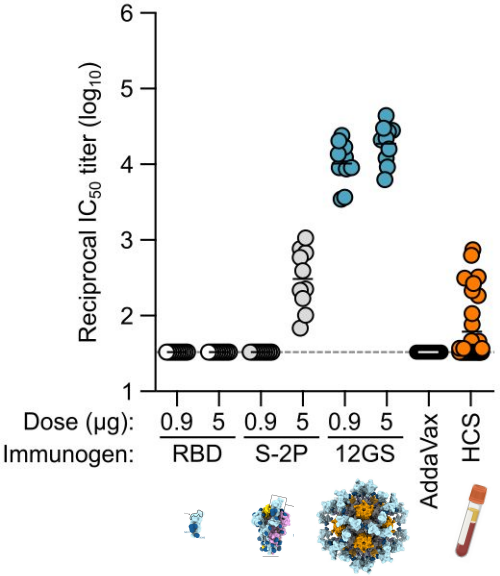




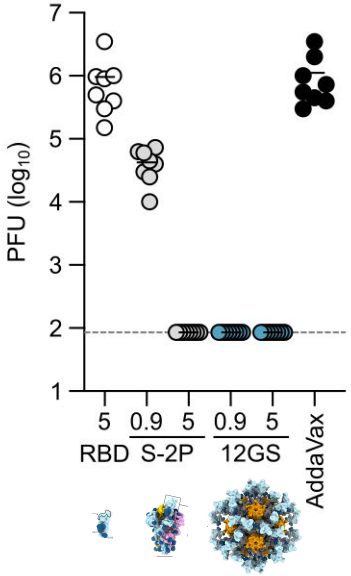
Walls AC & Fiala B et al. (2020) *Cell*, in press (***bioRxiv***).

The RBD nanoparticles induce potent and protective neutralizing antibody responses

Neutralizing antibodies



Protection

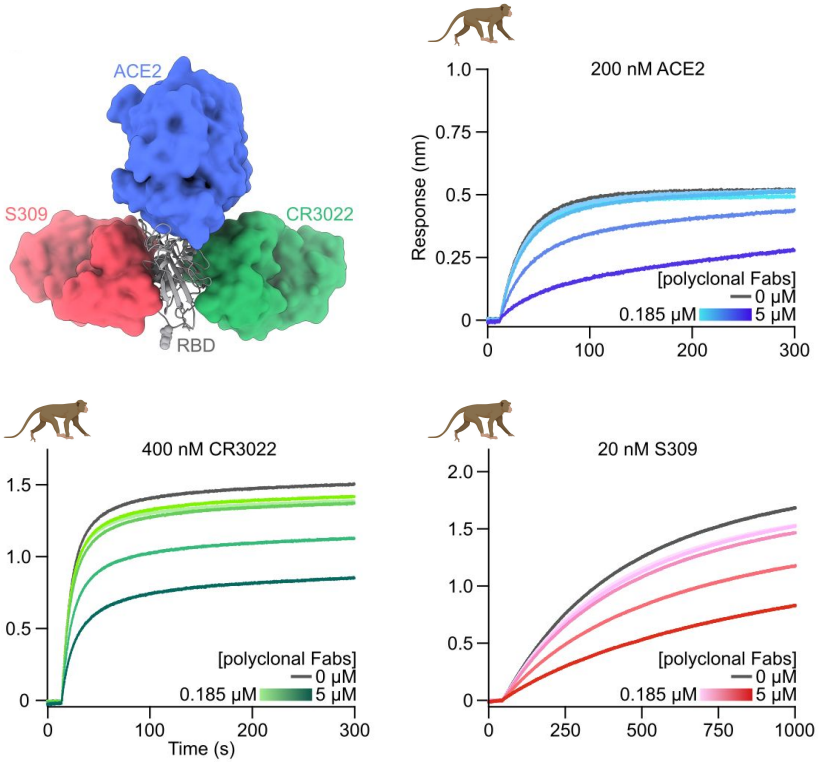


The **RBD nanoparticles**, even at a ~6-fold lower dose, are **≥10 times more potent** than the **Spike trimer.**

The **RBD nanoparticles** **completely prevent replication of the virus** in the nose and lungs, while the virus breaks through when the **Spike trimer** is given at low dose

Walls AC & Fiala B et al. (2020) *Cell*, in press (***bioRxiv***).

The nanoparticle vaccines induce antibodies that hit multiple sites on the Spike protein



Targeting multiple sites lowers the likelihood of the virus escaping the vaccine through mutation

Walls AC & Fiala B et al. (2020) *Cell*, in press (***bioRxiv***).

The RBD nanoparticle vaccine is a differentiated vaccine candidate and is on its way to clinical trials

- **Safe:** Proteins are a standard vaccine modality with a long track record of safety
- **Effective:** RBD nanoparticles induce ultra-potent neutralizing antibody responses that provide complete protection in mice
- **Scalable:** High-yielding, stable, and can be produced using standard techniques and existing capacity for recombinant biologics production
- **On its way:** Manufacturing underway at two different vaccines manufacturers, first-in-human clinical trials slated for December

Recent Papers

COVID-19

Walls AC & Fiala B, et al. Elicitation of potent neutralizing antibody responses by designed protein nanoparticle vaccines for SARS-CoV-2. bioRxiv (2020)

Cao L, et al. De novo design of picomolar SARS-CoV-2 miniprotein inhibitors. Science (2020)

Quijano-Rubio A, et al. De novo design of modular and tunable allosteric biosensors. bioRxiv. (2020)

Protein Logic Gates

Lajoie M, et al. Designed protein logic to target cells with precise combinations of surface antigens. Science (2020)

New Ion Channels

Xu C & Lu P, et al. Computational design of transmembrane pores. Nature (2020)