VACCINE RESEARCH CENTER
National Institute of Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services

NIH National Institute of Allergy and Infectious Diseases

PROTOTYPE PATHOGEN APPROACH TO PANDEMIC PREPAREDNESS

HIV→PNEUMOVIRUS→PARAMYXOVIRUS→CORONAVIRUS

ADVAC Alumni
2 April 2020

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Deputy Director
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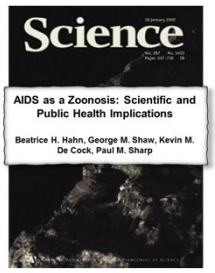
Recent Zoonotic and Vector-borne Viral Threats



- Hanta virus
- Nipah/Hendra
- West Nile virus
- SARS
- Influenza
- Chikungunya
- Ebola
- MERS
- Zika
- EV-D68
- SARS-CoV-2

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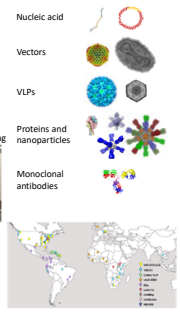
- AIDS/HIV
- Influenza
- Ebola/Marburg
- RSV
- Malaria
- Tuberculosis
- EID
  - West Nile virus, Zika
  - Chikungunya
  - W/E/V equine encephalitis viruses
  - MERS-CoV, SARS, and other CoV
  - Nipah and other paramyxoviruses
  - EV-D68 and other picornaviruses
  - Smallpox



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Public health burden of re-emerging & emerging viruses

Vaccine Challenges

- Vaccines for unmet needs
- Emerging viruses
- Improving licensed vaccines

Traditional Approaches

- Licensed vaccines/antibiotics
- Passive surveillance
- Contact tracing
- Quarantine

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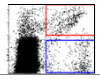
New Technologies are Transforming Vaccinology

- Structure-based vaccine design
- Single-cell sorting, sequencing, and bioinformatics
  - Rapid isolation of human mAbs
  - Definition of antibody lineages
  - Analysis of immune responses
- Protein engineering of self-assembling nanoparticles

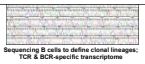
Structural analysis of antigenic sites on viral surface glycoproteins

Precision



- Rapid DNA synthesis
- Recombinant DNA and genetic engineering technology
  - Rapid cell line development
  - Animal model development
- Nucleic acid and vector-based delivery of vaccine antigen

Speed



Sequencing B cells to define clonal lineages; TCR & BCR-specific transcriptome

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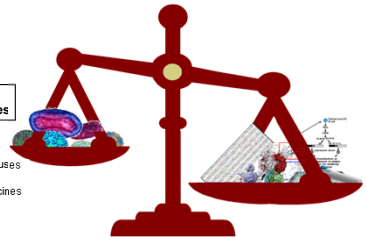
New Technologies Facilitate an Engineering Approach



Vaccine Challenges

- Vaccines for unmet needs
- Emerging viruses
- Improving licensed vaccines

New Technologies

- Structural biology
- Protein engineering
- Single cell sorting and analysis
- High throughput sequencing
- Rapid isolation of human mAbs
- Antibody lineage analysis
- Rapid diagnostic tools
- Systems biology

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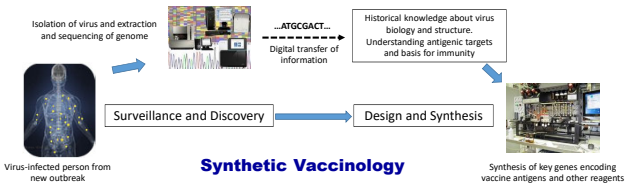
Gene Synthesis and Platform Technologies



Graham & Sullivan. Nature Immunology 2018

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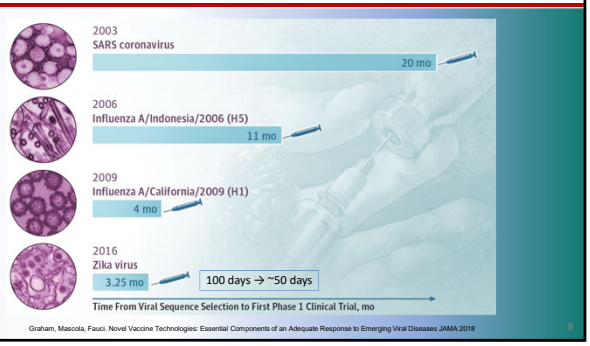
Platform Technologies Shorten Manufacturing Timelines



Graham, Mascola, Fauci. Novel Vaccine Technologies: Essential Components of an Adequate Response to Emerging Viral Diseases JAMA 2018

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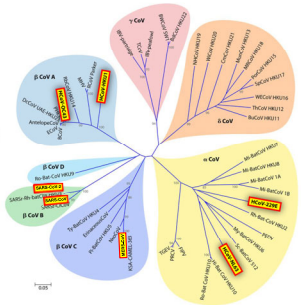
Coronaviruses: A Phylogenetic Tree

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



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

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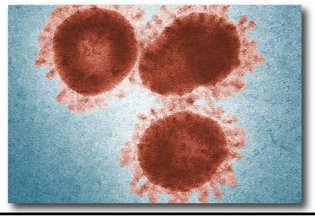
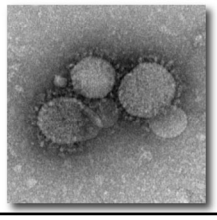
Severe Human Coronavirus Disease: Past as Prologue

Severe Acute Respiratory Syndrome (SARS) (2002–2003)



Middle East Respiratory Syndrome (MERS) (2012–present)



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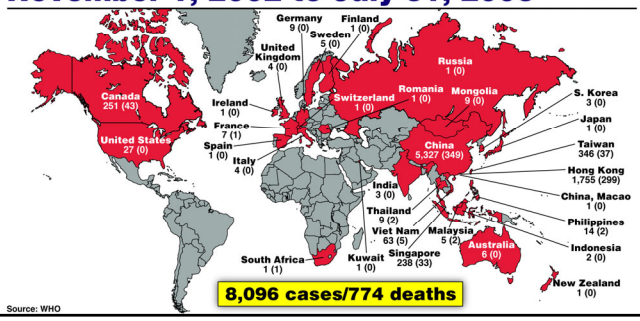
Cumulative Reported Cases of SARS November 1, 2002 to July 31, 2003



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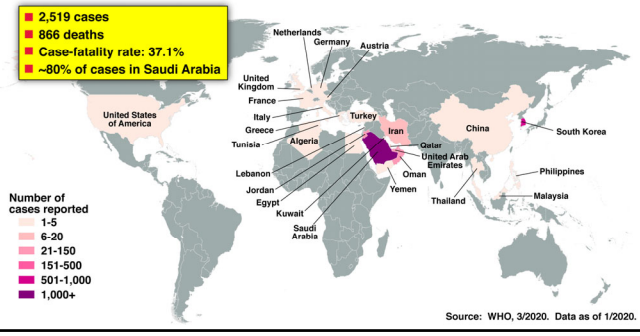
Confirmed Global MERS Cases, 2012–2020

- 2,519 cases
- 866 deaths
- Case-fatality rate: 37.1%
- ~80% of cases in Saudi Arabia



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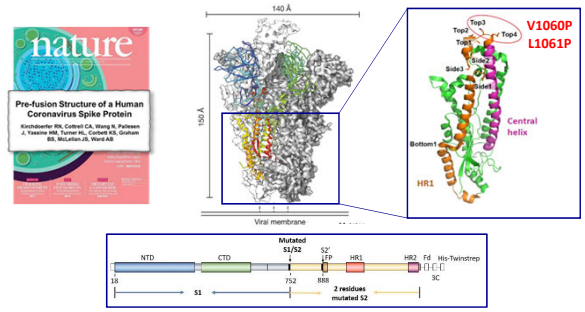
Structure-guided Stabilization of HKU1 CoV Spike



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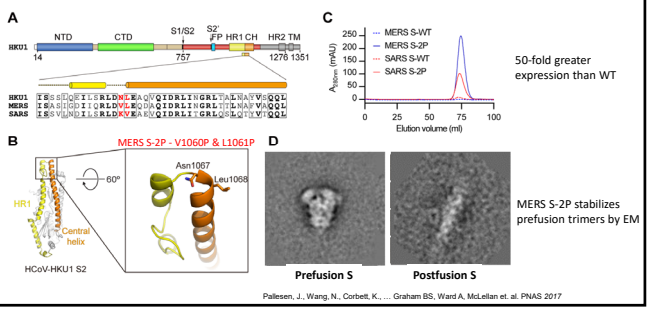
2-P Mutation Stabilizes MERS and SARS CoV S

Improved expression, prefusion structure, immunogenicity



Pallesen, J., Wang, N., Corbett, K., ... Graham BS, Ward A, McLellan et. al. PNAS 2017

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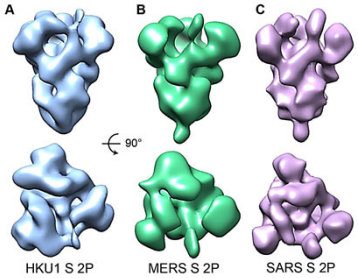
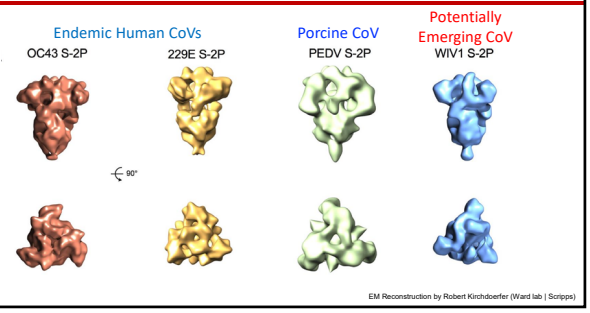
2P mutations effectively stabilize multiple CoV prefusion S



Pallesen, J.*, Wang, N.*, Corbett, K.*, et. al. PNAS. 2017.

15

2P mutations effectively stabilize multiple CoV prefusion S



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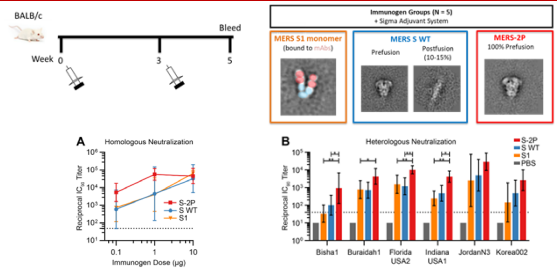
Immunogenicity of MERS S-2P in Mice



Pallesen, J., Wang, N., Corbett, K., et. al. PNAS 2017 | EM by Yaroslav Tsybovsky

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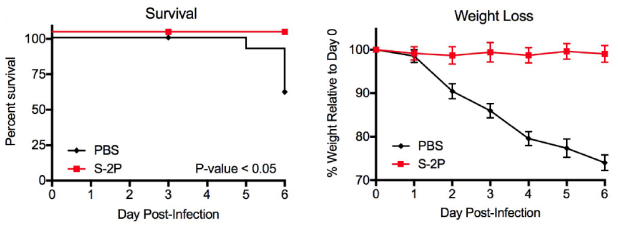
Stabilized MERS Spike-2P Protects hDPP4 Knock-in Mice from Lethal Challenge



Adam Cockrell, Ralph Baric, Kizzmekia Corbett

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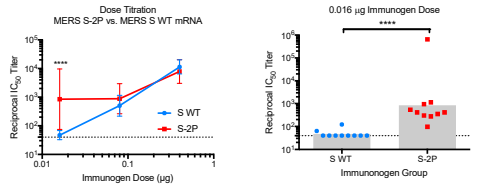
MERS S-2P mRNA elicits better neutralizing antibodies than MERS S-WT mRNA



Dr. Kizzmekia Corbett in collaboration with Moderna Therapeutics

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Summary

- S from multiple CoV strains can be stabilized in the prefusion conformation using homologous 2P mutations
- Stabilized prefusion S trimers are more immunogenic and protective than WT trimers or monomeric subunits
- May be a general solution for beta-CoV vaccine antigen design

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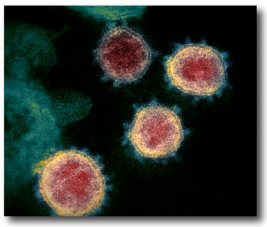
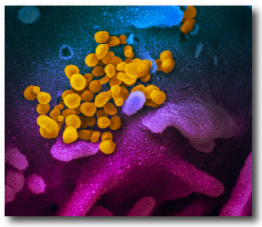
Coronavirus Disease 2019 (COVID-19) (December 2019 – Present)

- **COVID-19** is the name of the disease caused by the novel coronavirus **SARS-CoV-2**





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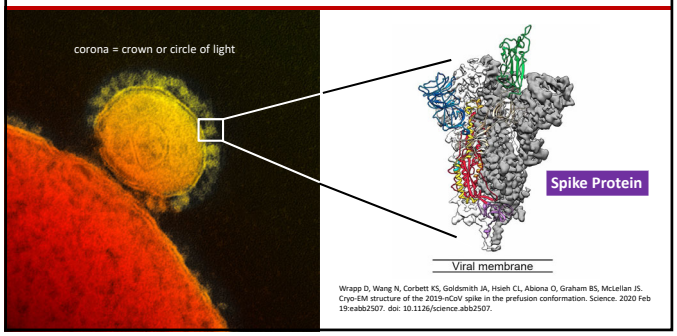
Coronavirus Biology and Nomenclature



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.

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Vaccine Target: Coronavirus Spike Protein

- Coronavirus spike protein is on the viral surface and mediates attachment to cells to start the infection process
- Ideal vaccines target coronavirus spikes in order to block viral infection

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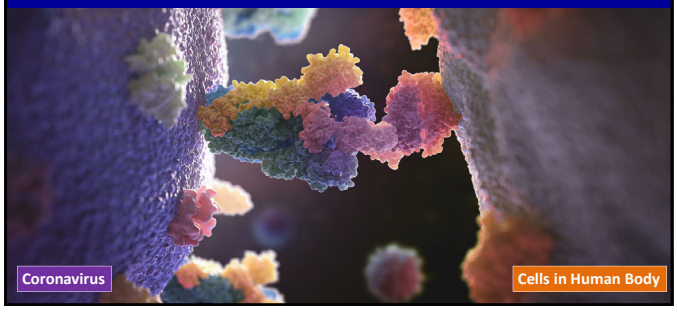
Vaccine Target: Coronavirus Spike Protein

- Coronavirus spike protein attaches to ACE2 protein to start infection



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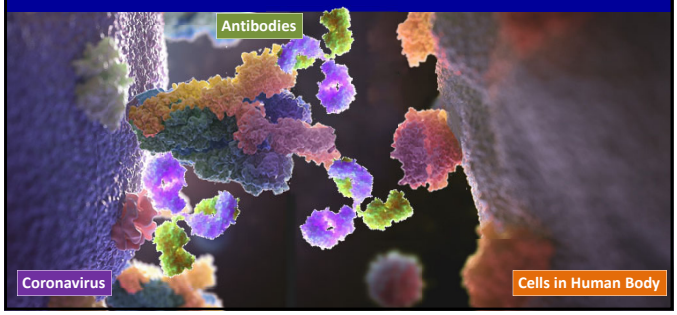
Vaccine Target: Coronavirus Spike Protein

- Vaccine-induced antibodies will block the interaction and function of CoV spike protein



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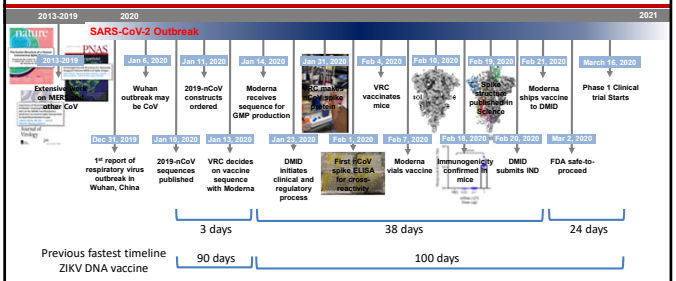
COVID-19 Vaccine Development



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COVID-19 Vaccine Consortium

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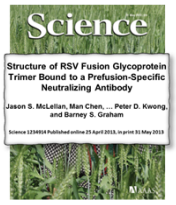
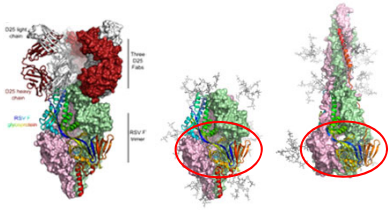
Structure of Prefusion RSV F Glycoprotein





Prefusion Postfusion

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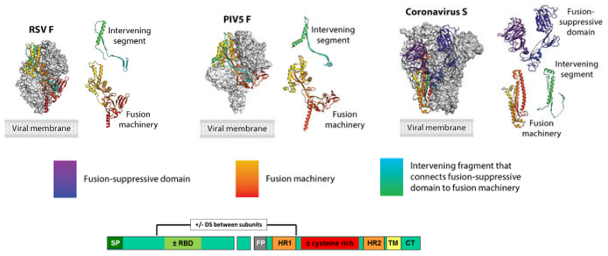
Generalized Application to Other Fusion Proteins



Graham, Gilman, McLellan, Annual Review of Medicine 2019

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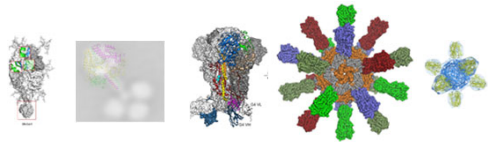
Summary

- New technologies are transforming vaccinology providing solutions for long-standing problems and emerging viral diseases
- Combining atomic level antigen design with computationally designed nanoparticles and platform manufacturing approaches provides a modular, engineering approach to achieve generalizable solutions for vaccine antigen design
- The advent of precision vaccinology with rapid platform manufacturing makes a prototype pathogen approach for pandemic preparedness feasible



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Julie Ledgerwood & Clinical Trial Program
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David Lindsay & Vaccine Clinical Material Program
Kevin Carlton & Project Management

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Judy Stein/Will Adams
Marybeth Daucher

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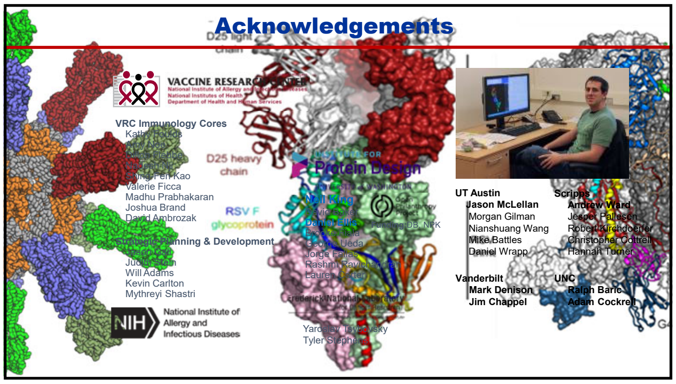
Acknowledgements
D25 light chain
VACCINE RESEARCH CENTER
VRC Immunology Cores
Shing-Fen Kao
Valerie Ficca
Madhu Prabhakaran
Joshua Brand
David Ambrozak
D25 heavy chain
RSV F glycoprotein
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Kevin Carlton
Mythreyi Shastri
NIH National Institute of Allergy and Infectious Diseases
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Brooke Fiala
George Ueda
Jorge Fallas
Lauren Carter
Funding:DB, NPK
Yaroslav Tsybovsky
Tyler Stephens
UT Austin
Jason McLellan
Morgan Gilman
Nianshuang Wang
Mike Battles
Daniel Wrapp
Scripps
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