This information was presented by Steven Chamow, PhD on Tuesday, June 23 2020 during the educational webinar, "What Does it Take to Develop A New Drug for COVID-19?”

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What Does it Take to Develop a New Drug for COVID-19?

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CHAMOW & Associates
Biopharmaceutical Product Development

Webinar Series
Two sessions

	Date*	Topic
Session 1	Tuesday 23 June	What does it take to develop a new drug for COVID-19?
Session 2	Tuesday 30 June	Technologies for new vaccines for COVID-19

*Both sessions via Zoom at 5:00-6:30 pm PDT

Overview – Session 1

Coronavirus

- COVID-19

Regulation by FDA

The drug development process

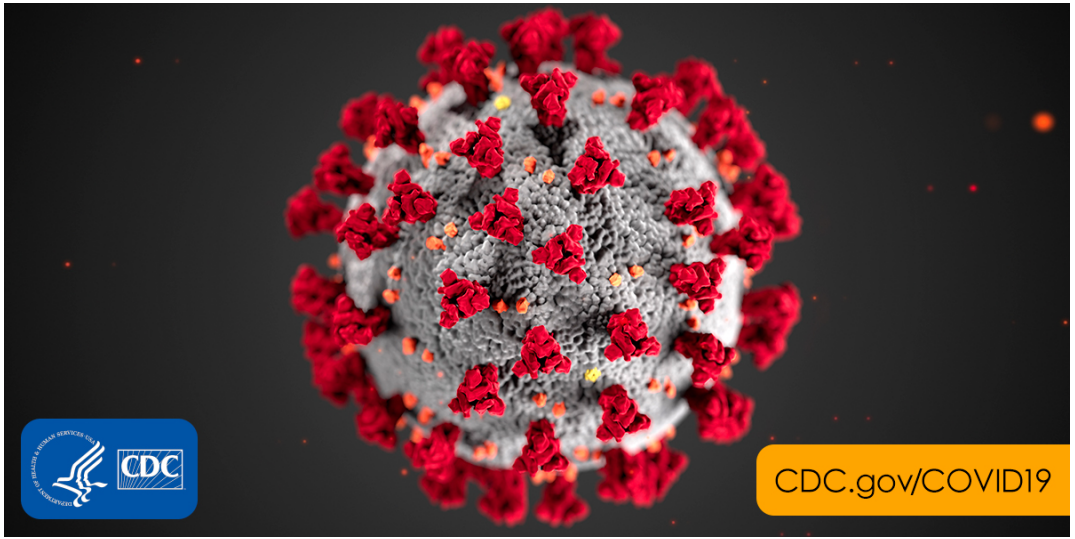
- How it normally works for drugs and vaccines
- Emergency solutions
- Timeline implications of new vs. existing drugs

New drugs and vaccines

- How would they work and what are the options?
  - Therapeutics
  - Vaccines

Coronavirus

Coronavirus



- All coronaviruses have spiky projections on their outer surfaces that resemble the points of a crown ("corona" in Latin)
- Very small; visible only with electron microscope
- Susceptible to antiviral, monoclonal antibody treatments

Coronavirus and disease

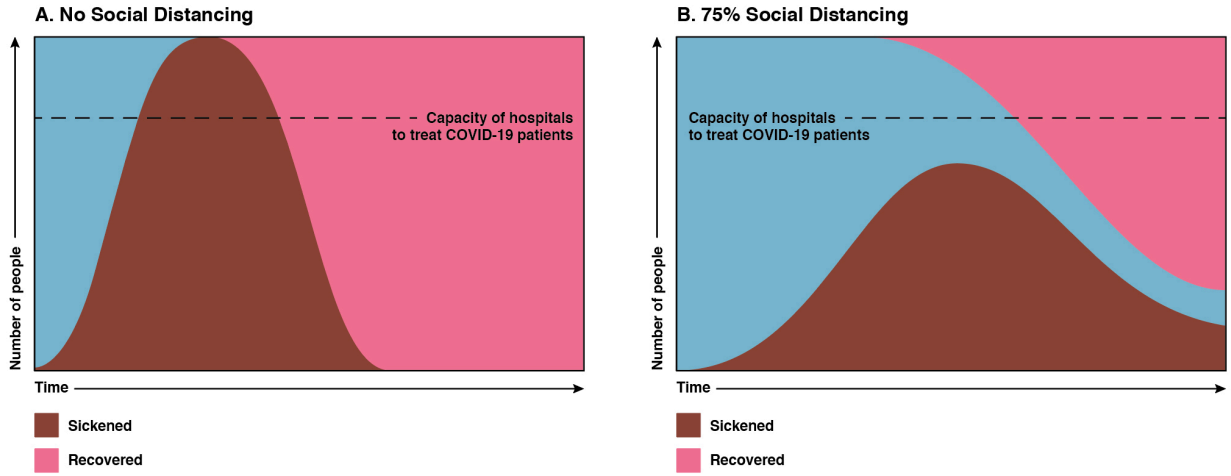
- First discovered in 1930s as acute respiratory infection of chickens; human coronaviruses discovered in 1960s
- All coronaviruses are transmitted to humans from animals
- Seven known coronaviruses have infected humans
  - Severity of disease has been variable
    - Some cause mild to moderate respiratory infections (common cold is caused by both coronavirus and rhinovirus)
    - Others have caused devastating epidemics
- Three viruses have caused recent serious epidemics
  - Severe acute respiratory syndrome (SARS) pandemic of 2002-03 from SARS-CoV
  - Middle East respiratory syndrome (MERS) outbreak in South Korea in 2015 from MERS-CoV
  - COVID-19 outbreak beginning in China in December 2019 from SARS-CoV-2

How does COVID-19 compare with flu?

	Seasonal flu	COVID-19
Symptoms	Fever, cough, sore throat, muscle aches, headaches, runny nose, fatigue	Fever, cough, shortness of breath
Complications	Pneumonia	Pneumonia
Virus transmission (R0)*	1.3	2.2
Death rate	0.09%	5.2%
UNITED STATES 2019-20 (as of 22 June 2020)		
Illnesses	45 million	2.3 million
Hospitalizations	500,000	300,000
Deaths	40,000	120,000

R0 is the average number of people who catch the virus from a single infected individual. COVID-19 has **60x higher mortality than seasonal flu.*

Our only tool to combat SARS-CoV-2: Social distancing



- In the two scenarios, the same number of people will eventually be infected
- Social distancing reduces peak healthcare demand to avert crisis at hospitals
- ”Flattens the curve” so that infections occur at a lower rate over a longer period of time
- Assumes no vaccine available in the period shown

From a study by the Imperial College COVID-19 Response Team, published 17 March

Pharmaceuticals are regulated by the Food and Drug Administration

Regulation of drugs/vaccines by FDA

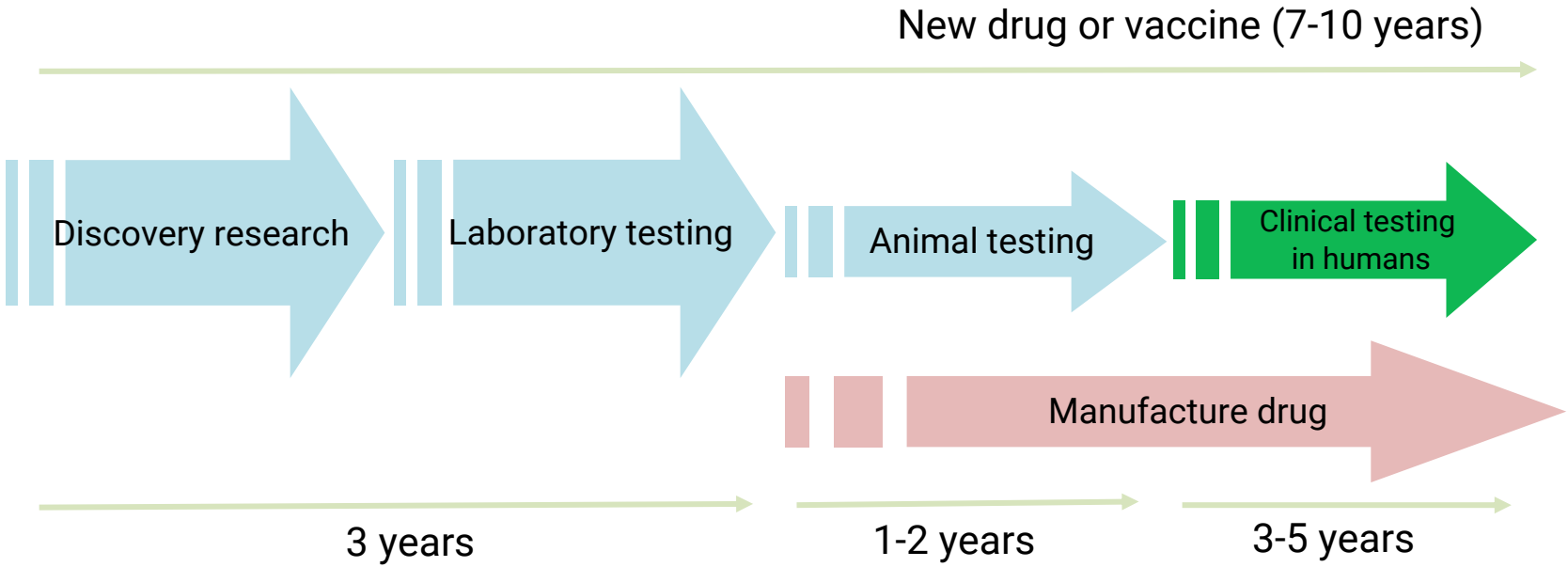
FDA's mission is to "**protect consumers and enhance public health by maximizing compliance of FDA regulated products and minimizing risk associated with those products**."

Year	Act of Congress	What It Did
1906	FDA established under the Pure Food and Drugs Act signed by President Theodore Roosevelt	• Created government agency to improve food and drug processing conditions
1938	Food, Drug and Cosmetic Act	• Required that manufacturers demonstrate that drugs are safe before marketing • Created prescription drugs
1962	Kefauver-Harris Drug Amendments	• Required that manufacturers demonstrate effectiveness using controlled testing in clinical trials • FDA would regulate marketing of drugs

What is the drug/vaccine development process?

Drug/vaccine development occurs in stages

In normal circumstances, 4 stages take a long time to complete



Phases of clinical testing in humans

3–5 years

Clinical Phase I

- Safety only
- 20-100 normal volunteers

Clinical Phase II

- Test for efficacy in patients with disease
- Several hundred patients
- Several doses and treatment regimens
- May be double blind, placebo controlled

Clinical Phase III

- Test for efficacy in patients with disease
- Many hundreds to thousands of patients to confirm efficacy vs. harm
- One dose and treatment regimen
- Must be double blind, placebo controlled
- Regulatory application for approval will follow

FDA Approval and Market Launch

Criteria for approval

- The drug is safe
- The drug is efficacious

NOTE: In a public health emergency, FDA can fast-track approval under an Emergency Use Authorization (EUA)

Emergency solutions: What is in our toolbox?

Therapeutic vs. Vaccine

Type of Drug	
Therapeutic	**Vaccine**
Acts **directly or indirectly** on virus	Acts **indirectly** on virus
Used to treat COVID-19-infected patients	Used to prevent infection of the community

What are potential sources of drugs to treat COVID-19?

Type	Description	Stages required to develop and test	Abbreviated timeline (under EUA)
Repurposed therapeutic or vaccine	Existing and marketed for another clinical indication or disease	Human clinical testing	Fast 4-9 mo
Convalescent therapy	Processed blood from recovered COVID-19 patients	Human clinical testing	Fast 6-9 mo
New drug or vaccine [new chemical entity]	Newly developed, never before tested	Discovery research-laboratory testing- animal testing-human clinical testing	Slow 12-24 mo

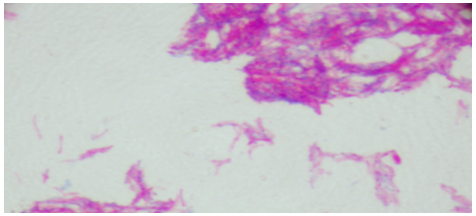
Examples of repurposing existing drugs and vaccines

Remdesivir

- Antiviral developed to treat Ebola
- First approved 2014
- Shows efficacy against SARS-CoV-2 in vitro
- Data recently released from Ph3 clinical study sponsored by NIAID
- For hospitalized patients, drug reduced time that people were hospitalized by 4 days-31% faster recovery time.
- Approved by FDA under EUA on 1 May

Dexamethosone

- Corticosteroid
- First approved in 1961 an an anti-inflammatory; used to treat many inflammatory and autoimmune conditions
- Research team at Oxford found that it can be effective in very severe cases of COVID-19
- Tested 6000 COVID-19 patients (2000 drug vs. 4000 control)
- For patients on ventilators, drug reduced risk of death by 30%
- Approved in the UK; pending in US



Bacille Calmette-Guerin (BCG)

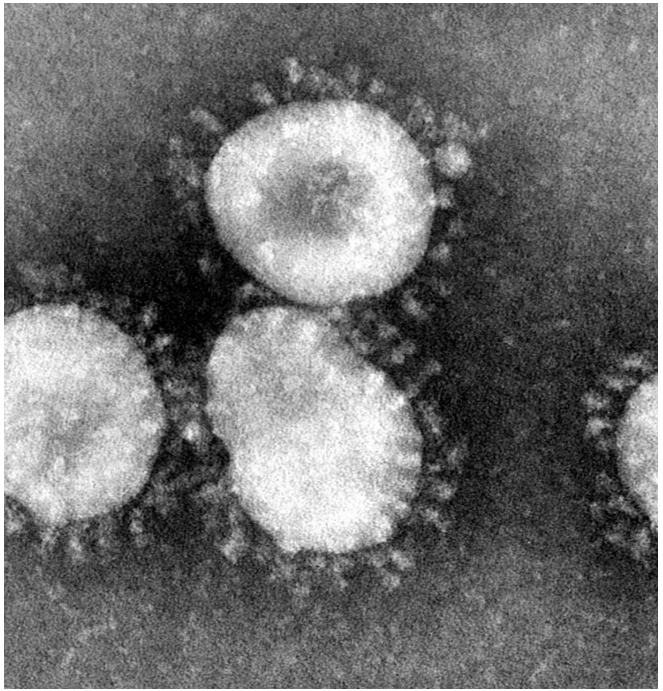
- Vaccine for tuberculosis
- First used 1920s
- Stimulates immune system
- Clinical studies underway in Australia, the Netherlands, and Germany

Convalescent therapy

- Polyclonal hyperimmune immunoglobulin, sourced from recovered COVID-19 patients
- FDA is facilitating collaboration among blood banks and medical centers to conduct clinical testing
- International alliance of 10 companies and NIAID to develop and test plasma-derived therapy
- Clinical trial to begin this summer

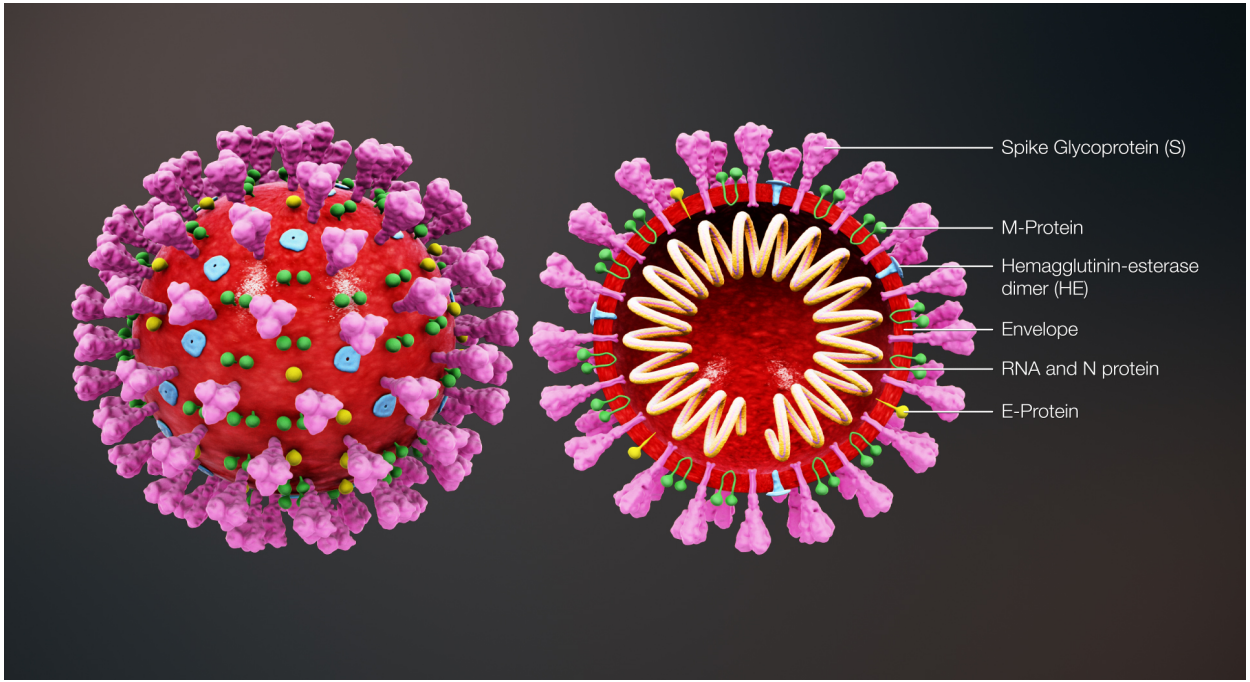
New treatments

Viruses

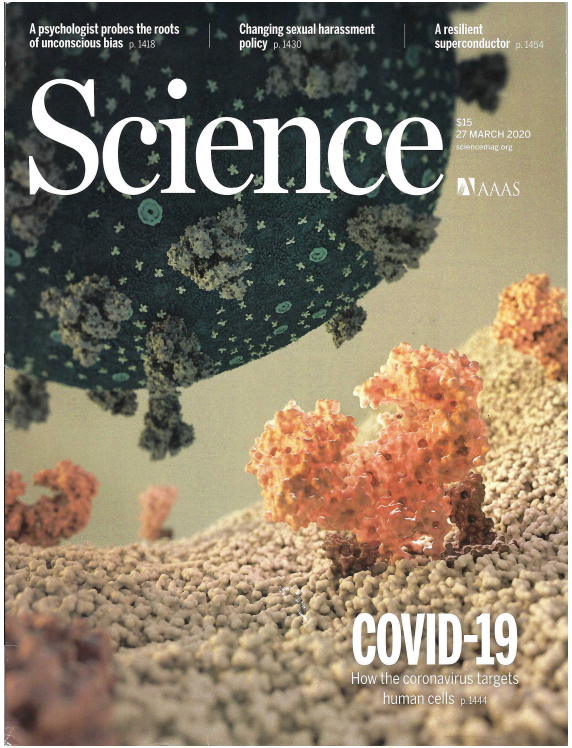


- Smallest living things
- Contain protein and DNA or RNA and sometimes lipid envelopes
- Not capable of propagating on their own
  - Require infection of a host cell to reproduce
- Once infection occurs, the virus hijacks the cell to make more copies of itself
- Often kills the cell upon release of newly made virus particles

Structure of SARS-CoV-2



We must understand the biology of SARS-CoV-2



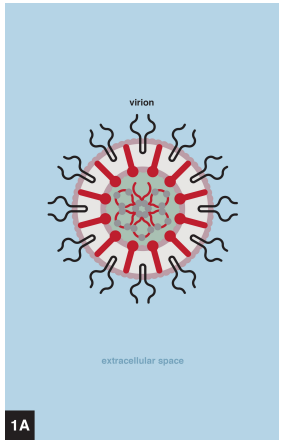
SARS-CoV-2

host cell

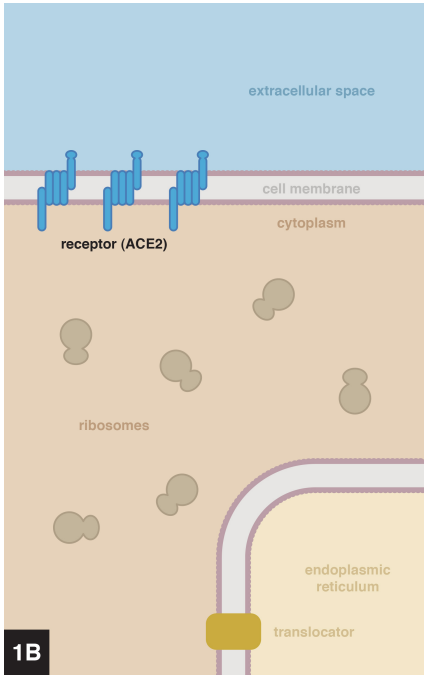
What happens when SARS-CoV-2 infects a human lung cell?

Step 1

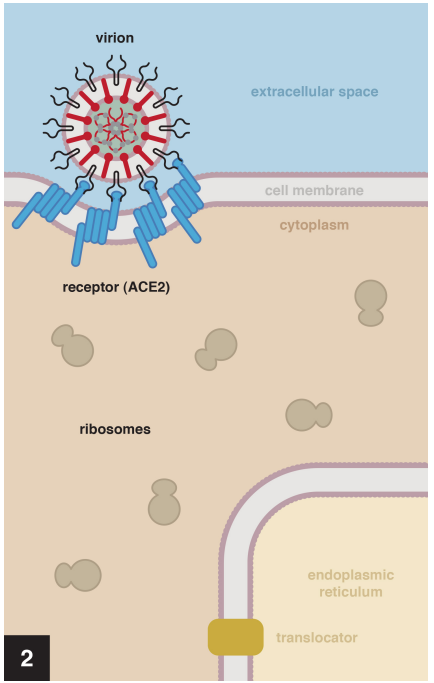
SARS-CoV-2



Human lung cell

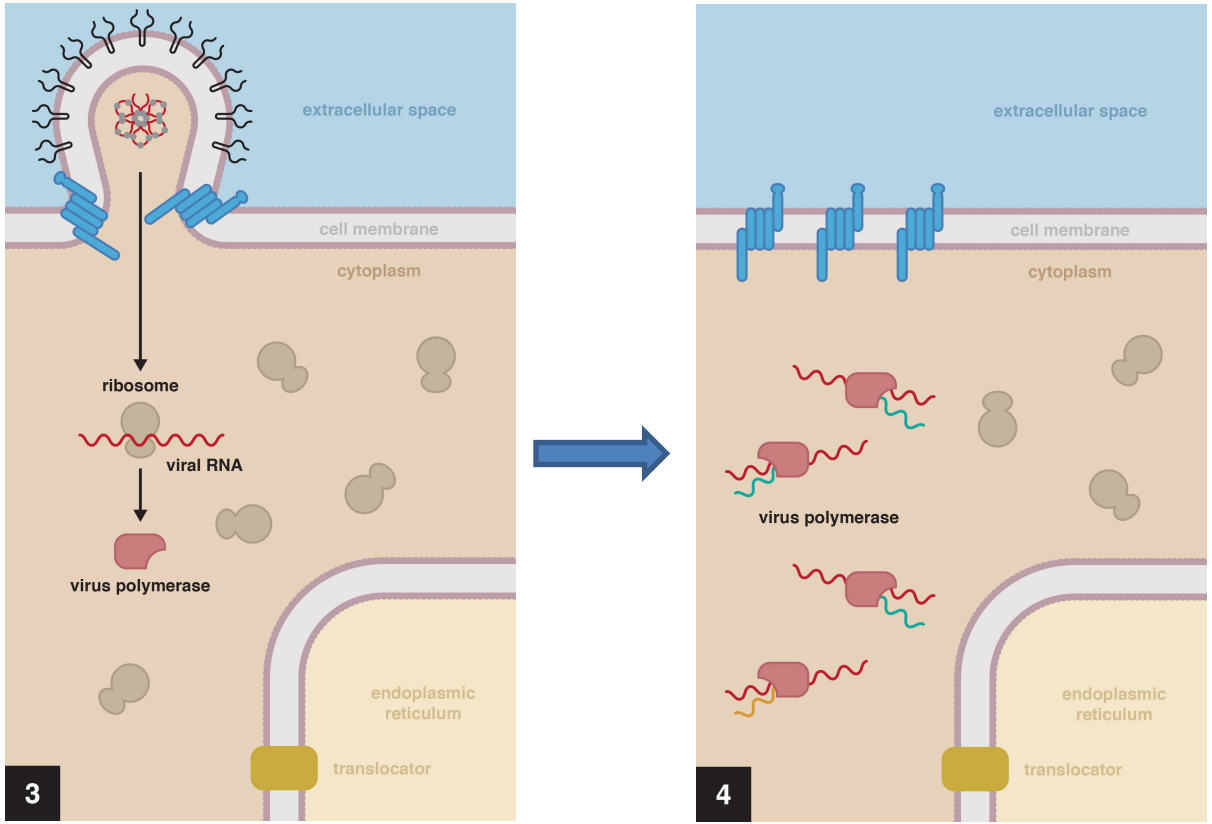


SARS-CoV-2 recognizes and binds to specific receptors on surface of cell



Step 2

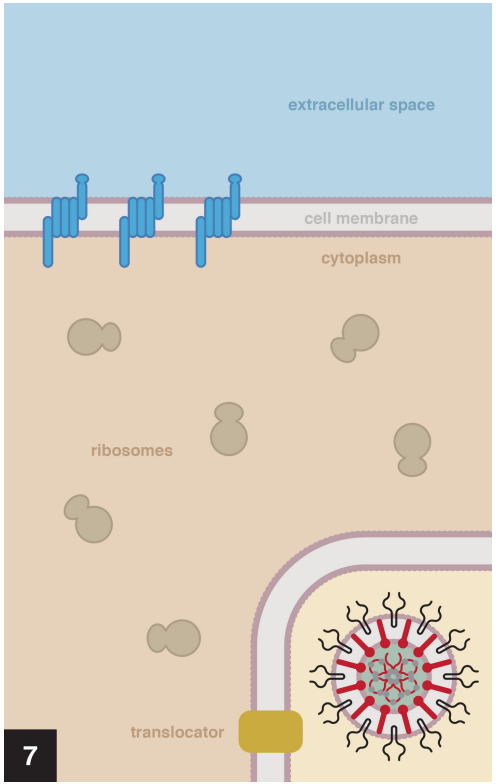
Bound virus enters cell and is uncoated, genetic material enters cytoplasm, viral RNA attaches to cell's ribosome and is translated to produce virus proteins

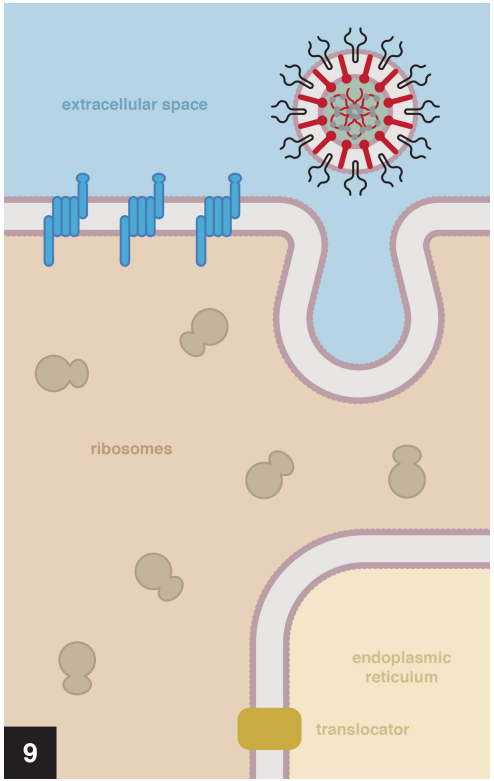


Virus polymerase copies genetic instructions needed to produce new virus particles

Step 3

New virus particles are produced inside the host cell…

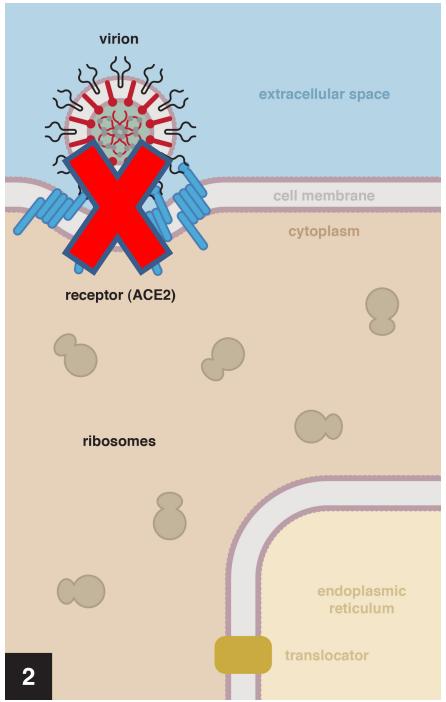




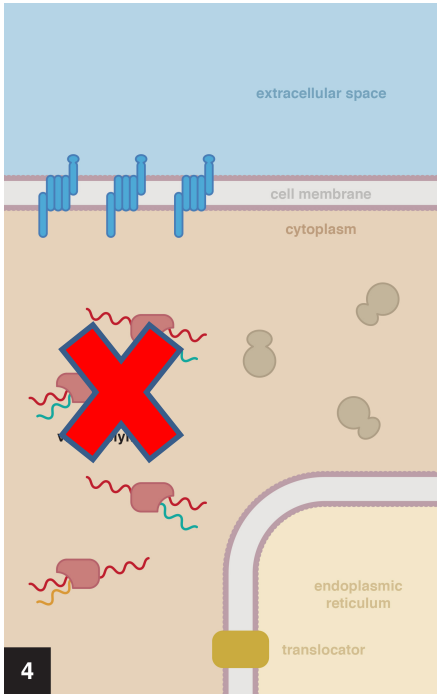
…And are released to go on to infect new cells

Disrupting SARS-CoV-2: Molecular targets

The goal is to interfere at the molecular level with the virus' ability to bind to cells or to reproduce



Step 1-Bind



Step 2-Reproduce

New therapeutic design approaches

NCE type*	What is it?	How does it act?	Where does is act?	How would it be administered?
Synthetic chemical	An enzyme inhibitor, made using medicinal chemistry	Interferes with viral polymerase enzyme required for virus to reproduce	Outside or inside the cell	Oral pill or capsule
Biologic	Monoclonal antibody, made using genetic engineering technology	Interferes with binding of spike protein to host cell receptor	Outside the cell	Injection

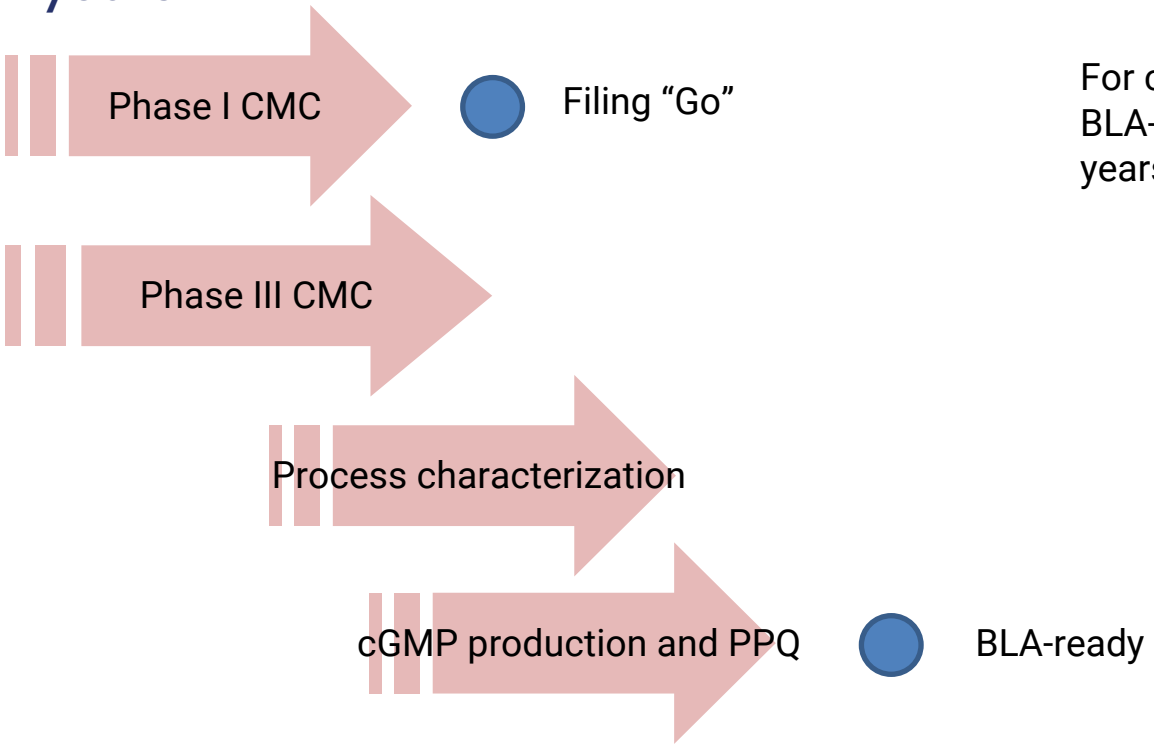
*Each requires all 4 stages of development:
Discovery research - laboratory testing - animal testing - human clinical testing

Leading new therapeutics ready for testing

Name	What is it?	Molecular target	Sponsor	Status
LY-CoV555	Monoclonal antibody	Spike protein of SARS-CoV-2 (Blocks viral attachment and entry into human cells)	Eli Lilly/AbCellera	• Genetically engineered from the blood of a recovered patient • Required <3 mo from screen to first-in-human clinical trials • 1 Jun 2020 dosed first patients in Ph1 trial
REGN-COV2	Cocktail of 2 monoclonal antibodies	Spike protein of SARS-CoV-2	Regeneron	• Genetically engineered from the blood of a recovered patient • Started Ph1 trial this month
VIR-7831 and/or VIR-7832	Monoclonal antibody	Spike protein of SARS-CoV-2	GSK/Vir Biotechnology	• Collaboration announced in Apr • Genetically engineered from the blood of a recovered patient • Expects to move directly into Ph2 in Jul-Sep
TBD	Cocktail of 2 monoclonal antibodies	Spike protein of SARS-CoV-2	AstraZeneca/Vanderbilt Universty/DARPA	• Genetically engineered from the blood of a recovered patient and to be more stable *in vivo* • Expects to start Ph1 in Aug

CMC: Monoclonal antibody development for pandemics

2 years



For comparison, Filing “Go” to BLA-ready duration is normally >5 years

Redrawn from Kelley, *Nature Biotechnology* **38**, 540-545 (2020)

Summary

- SARS-CoV-2 (COVID-19) is an RNA virus
- Because it is novel, we have had no tools to detect or treat it
  - Without adequate testing kits or effective drugs, our only defense right now is to slow the rate of transmission
- Any treatment for this disease will require FDA approval, likely under an EUA
- The fastest path to a drug or vaccine is to repurpose an existing one
- New treatments will require a year or more to complete the key stages of clinical and CMC development

Questions and Discussion