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Developing Therapeutic Monoclonal Antibodies at Pandemic Pace

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Biopharmaceutical Product Development

Overview

Potential sources of drugs for COVID-19

Regulation during a pandemic

- EUA, CTAP

SARS-CoV-2

- Biology of infection

Accelerating mAb development

- Pre-pandemic timelines
- Opportunities for faster timelines to make mAbs

Leading new therapeutics

- Current anti-SARS-CoV-2 mAb programs in the clinic

Pre-reads

1. Jon Cohen, “Antibodies May Curb Pandemic Before Vaccines”, *Science*, 14 Aug 2020
2. Brian Kelley, “Developing Therapeutic Monoclonal Antibodies at Pandemic Pace”, *Nature Biotechnology* vol. 38, May 2020
3. Paul Tullis, “How a Potential Treatment for the Coronavirus Turned Up in a Scientist’s Freezer”, *New Yorker*, 20 Jul 2020

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

Type	Description	Regulatory Pathway
Repurposed therapeutic or vaccine	Existing and marketed for another clinical indication or disease	EUA
Convalescent therapy	Processed blood from recovered COVID-19 patients	EUA
New drug or vaccine [new chemical entity]	Newly developed, never before tested	CTAP

Regulation during a pandemic

Medical Countermeasures (MCMs) - EUA

Related legislation

- Health Security and Bioterrorism Preparedness and Response Act of 2002 (Bioterrorism Act)
  - Provision to strengthen the nation's ability to respond to public health emergencies
  - Addressed the accelerated approval of priority MCMs; developed final rule on animal models when human efficacy studies are not feasible or ethical
- Project BioShield Act of 2004
  - Gave FDA Commissioner the authority to issue EUAs
- Pandemic and All-Hazards Preparedness Act of 2006 (PAHPA)
  - Amended Public Health Service Act to establish within HHS a new Assistant Secretary for Preparedness and Response
- Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA)
  - Provisions that further FDA's mission in development and availability of MCMs
- 21st Century Cures Act (2016): Facilitates the development of MCMs
- Public Law 115-92 (2017):
  - Amendment to authorize additional emergency uses of medical products
- Pandemic and All-Hazards Preparedness and Advancing Innovation Act of 2019 (PAHPAIA)

EUA = Emergency Use Authorization

Emergency Use Authorization (EUA)

- Emergency Use Authorization of Medical Products and Related Authorities: Guidance for Industry and Other Stakeholders, Procedural, January 2017
  - Purpose: Explain FDA's current thinking on the authorization (general recommendations and procedures) of the emergency use of certain medical products under certain sections of the Food, Drug and Cosmetic Act (FD&C Act) Sections 564, 564A and 564B
    - Added as a result of Pandemic and All-Hazards Preparedness Reauthorization Act (PAHPRA) of 2013
      - Key legal authorities to strengthen and sustain preparedness for public health, military, and domestic emergencies involving chemical, biological, radiological, and nuclear (CBRN) agents, including emerging infectious disease threats such as pandemic influenza.
    - Clarifies and enhances FDA's authority to support emergency preparedness and response and foster the development and availability of medical products for use in these emergencies.
      - These medical products, also referred to as "medical countermeasures" or "MCMs," include drugs (e.g., antivirals and antidotes), biological products (e.g., vaccines, blood products, and biological therapeutics), and devices (e.g., *in vitro* diagnostics and personal protective equipment).

What is EUA?

- Authorization to introduce a medical product into interstate commerce when the product is intended for use during an actual or potential emergency
  - EUA candidate products include medical products and uses that are not approved, cleared, or licensed, or unapproved use of an approved medical product
- Four statutory criteria
  - Serious or Life-Threatening Disease of Condition
  - Evidence of Effectiveness : “may be effective”
  - Risk-Benefit Analysis
  - No Alternatives
- EUA authority is separate and distinct from use of a medical product under an Investigational New Drug Application (IND) or Investigational Device Exemption (IDE)
  - Submission of an IND or IDE is not required for potential EUA products
- Contact FDA before submitting a formal request for an EUA - “pre-EUA” activities

COVID-19 Therapy Accelerated Program (CTAP)

May 2020

- FDA has created a special emergency program for possible coronavirus therapies, the Coronavirus Treatment Acceleration Program (CTAP)
  - The program uses every available method to move new treatments to patients as quickly as possible, while at the same time finding out whether they are helpful or harmful.
  - Key References
    - COVID-19: Developing Drugs and Biological Products for Treatment of Prevention, May 2020
    - COVID-19 Public Health Emergency: General Considerations for Pre-IND meeting Requests for COVID-19 Related Drugs and Biological Product, May 2020
    - Manufacturing, Supply Chain, and Drug Inspections during COVID-19 Public Health Emergency; Questions and Answers, August 2020
    - Recommendations for Investigational COVID-19 Convalescent Plasma, August 23, 2020
    - FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic: Guidance for Industry, Investigators and Institutional Review Boards, March 2020

CTAP Dashboard*

570+

Drug development programs in planning stages[1]

270+

Trials reviewed by FDA[2]

2

COVID 19 treatments currently authorized for Emergency Use

0

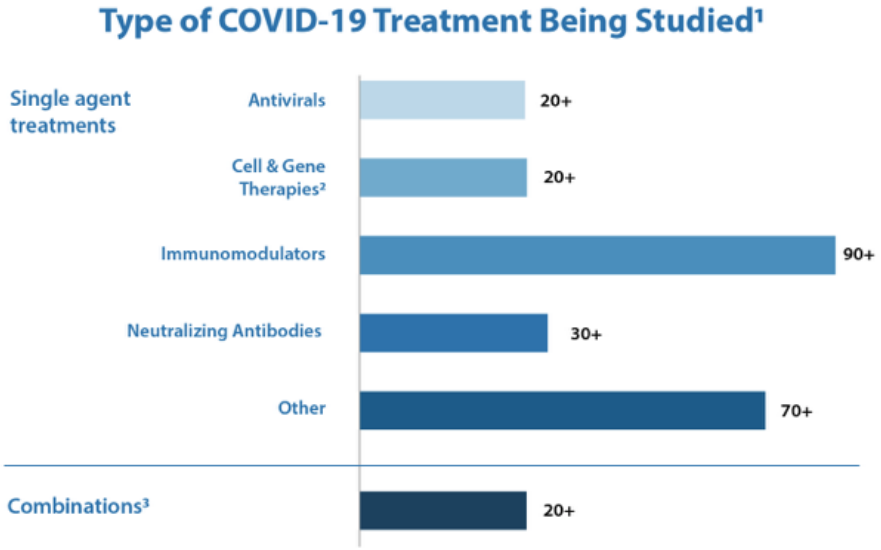
Treatments currently approved by FDA for use in COVID-19

[1]Active Pre-INDs. Excludes vaccines.

[2]Safe to proceed INDs. Excludes vaccines.

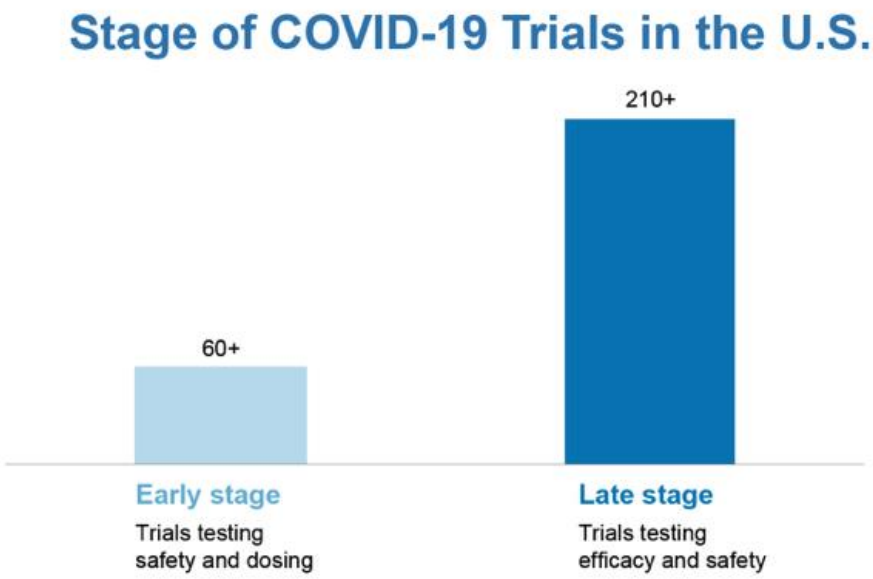
*As of July 31, 2020 FDA.gov/CTAP

COVID-19 Treatments Under Investigation



[1] Corresponds to number of safe to proceed INDs. Excludes INDs related to vaccines
[2] For additional information, please see Cellular & Gene Therapy Products
[3] Includes INDs with more than one product

COVID-19 US Trials by Clinical Stage



[1] Early stage = phase 0, 1, and 1/2; Late stage = phase 2, 2/3, 3, 4.

Examples of repurposed and convalescent therapies

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.
- Authorized 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%
- Authorized in the UK; EUA status in US unknown

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.
- Prior human experience, animal models (hamsters and mice), S&E from EAP by Mayo Clinic, and risk-benefit analysis
- Authorized by FDA under EUA on 23 Aug 2020 for the treatment of hospitalized patients

SARS-CoV-2

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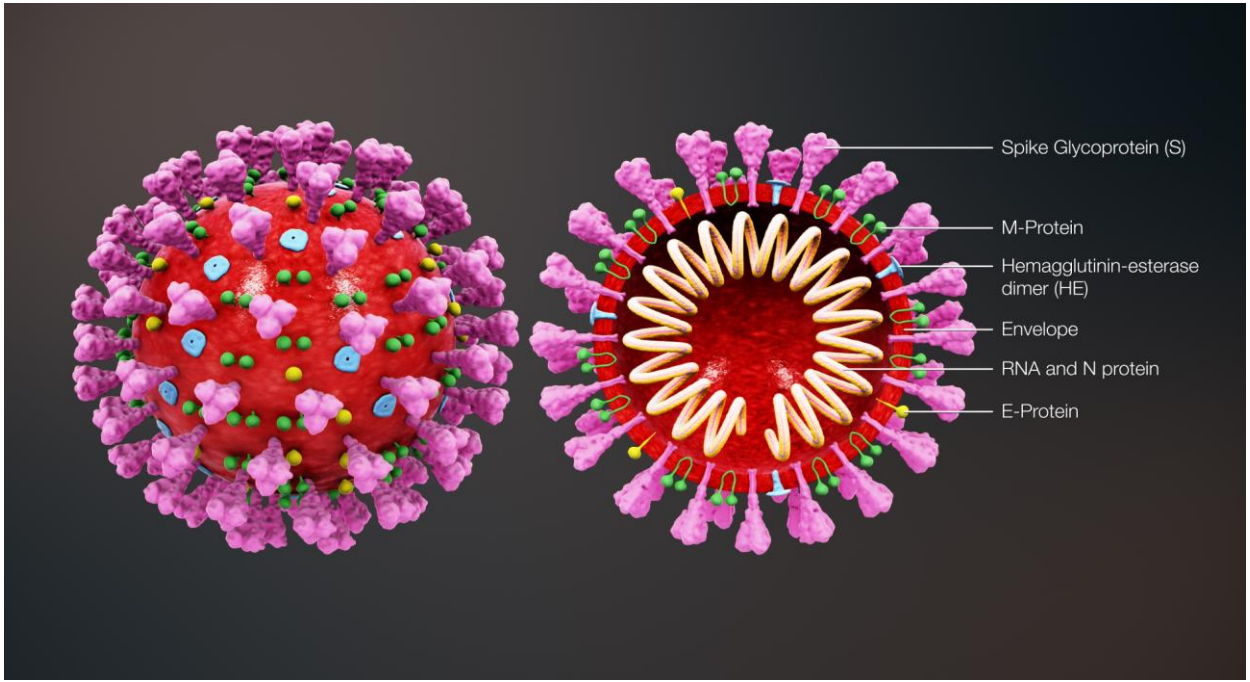
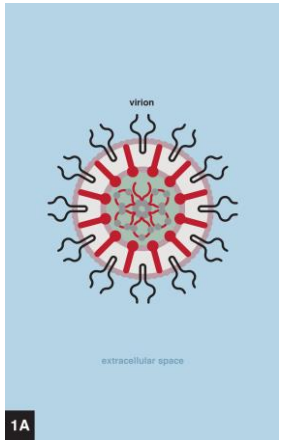
Structure of SARS-CoV-2



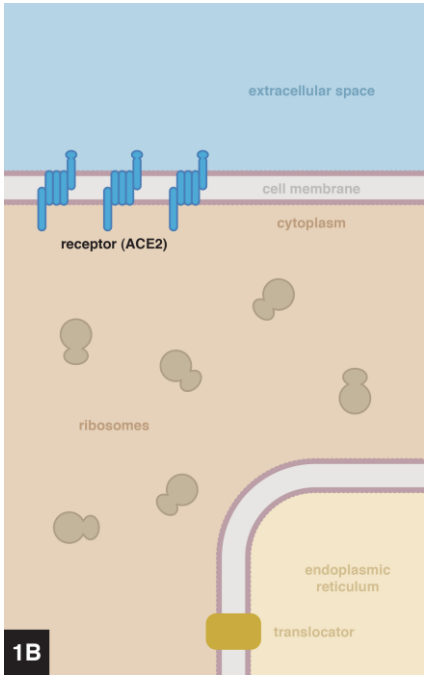
What happens when SARS-CoV-2 infects a human lung cell?

Step 1

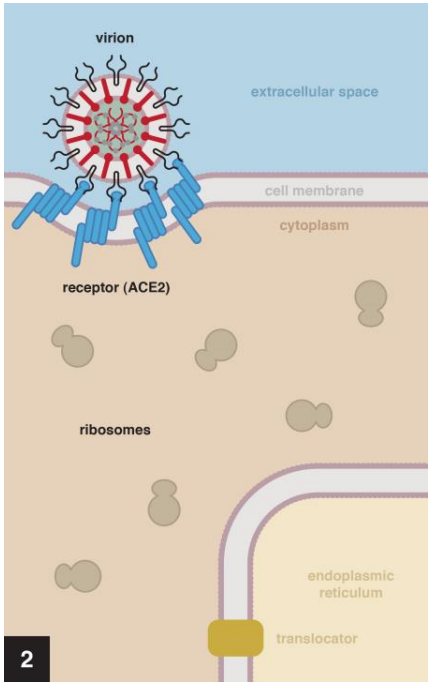
SARS-CoV-2



Human lung cell

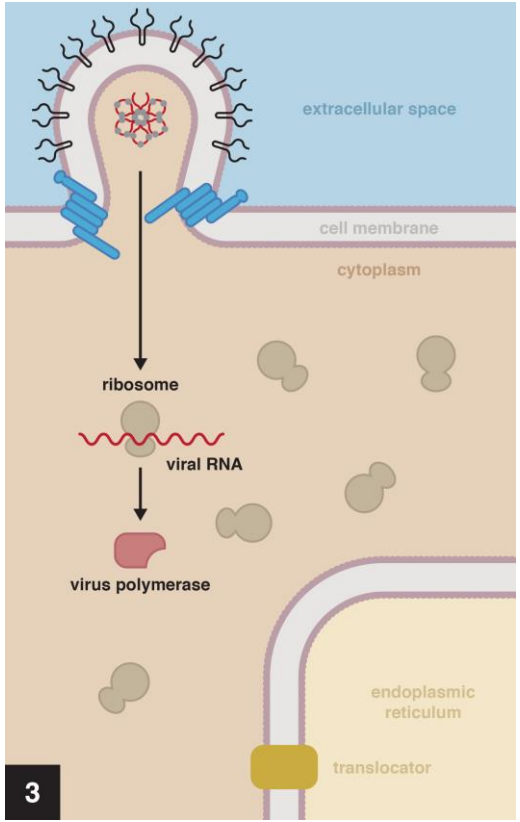


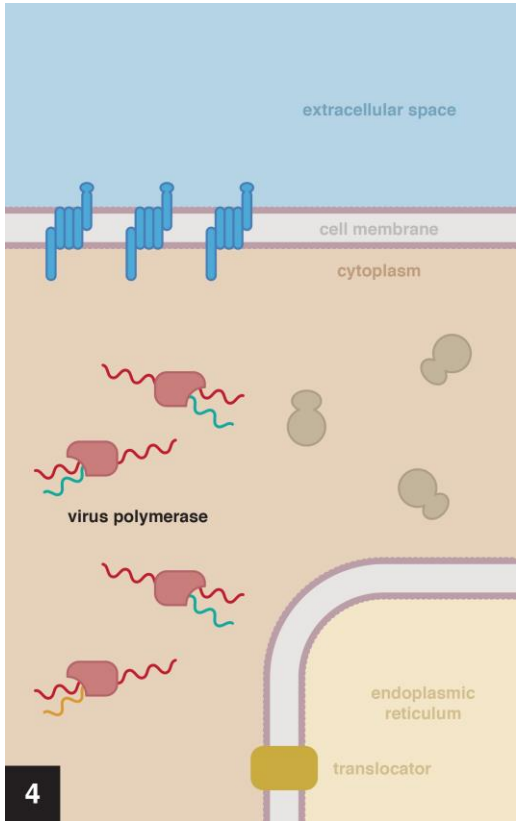
SARS-CoV-2 recognizes and binds to specific receptors on surface of cell



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

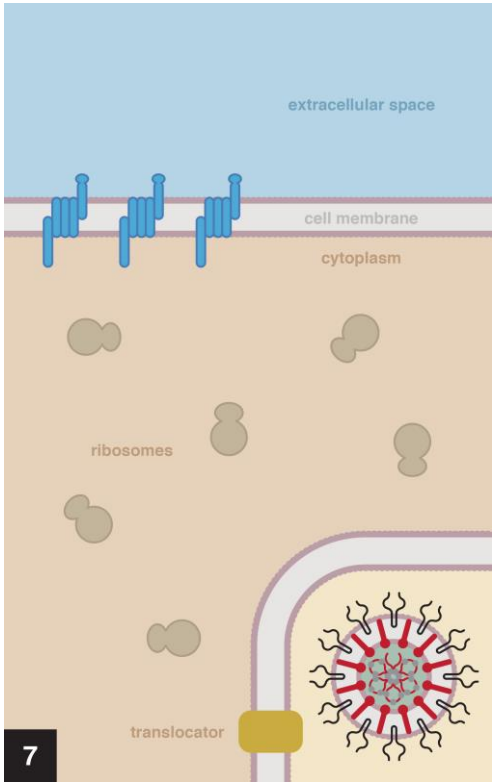


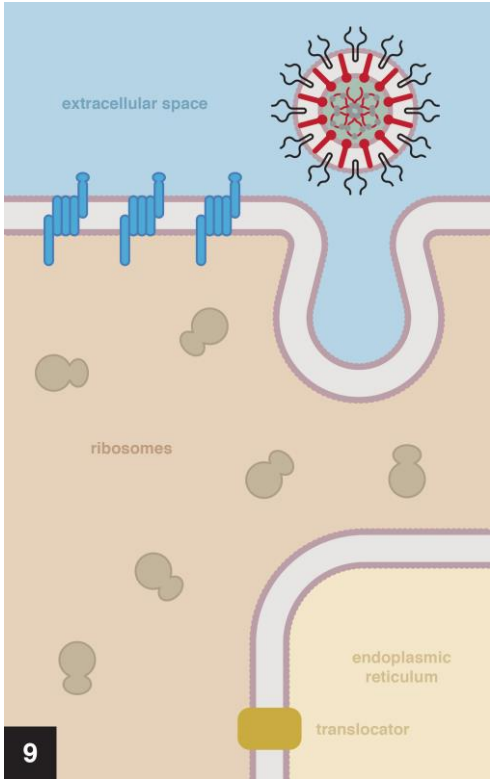


Virus polymerase copies genetic instructions needed to produce new virus particles

Step 3

New virus particles are produced inside the host cell

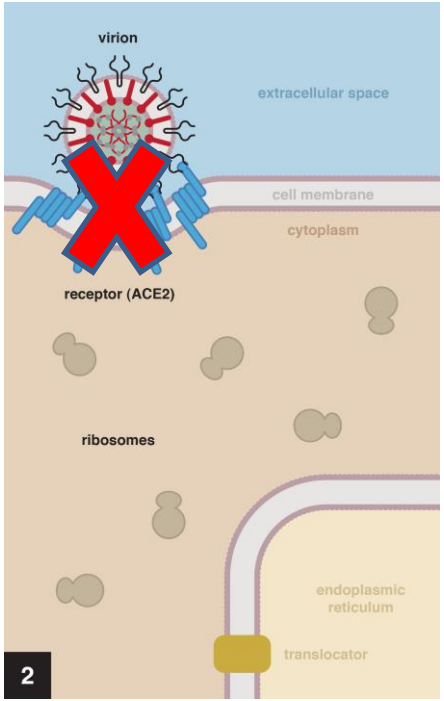




And are released to go on to infect new cells

Anti-SARS-CoV-2 mAbs inhibit infection

- The goal is to for a drug to interfere with the virus' ability to bind to lung cells to prevent infection.
- Anti-spike glycoprotein mAbs or mAb cocktails block the ability of virus to initiate infection of lung cells.



Accelerating mAb development

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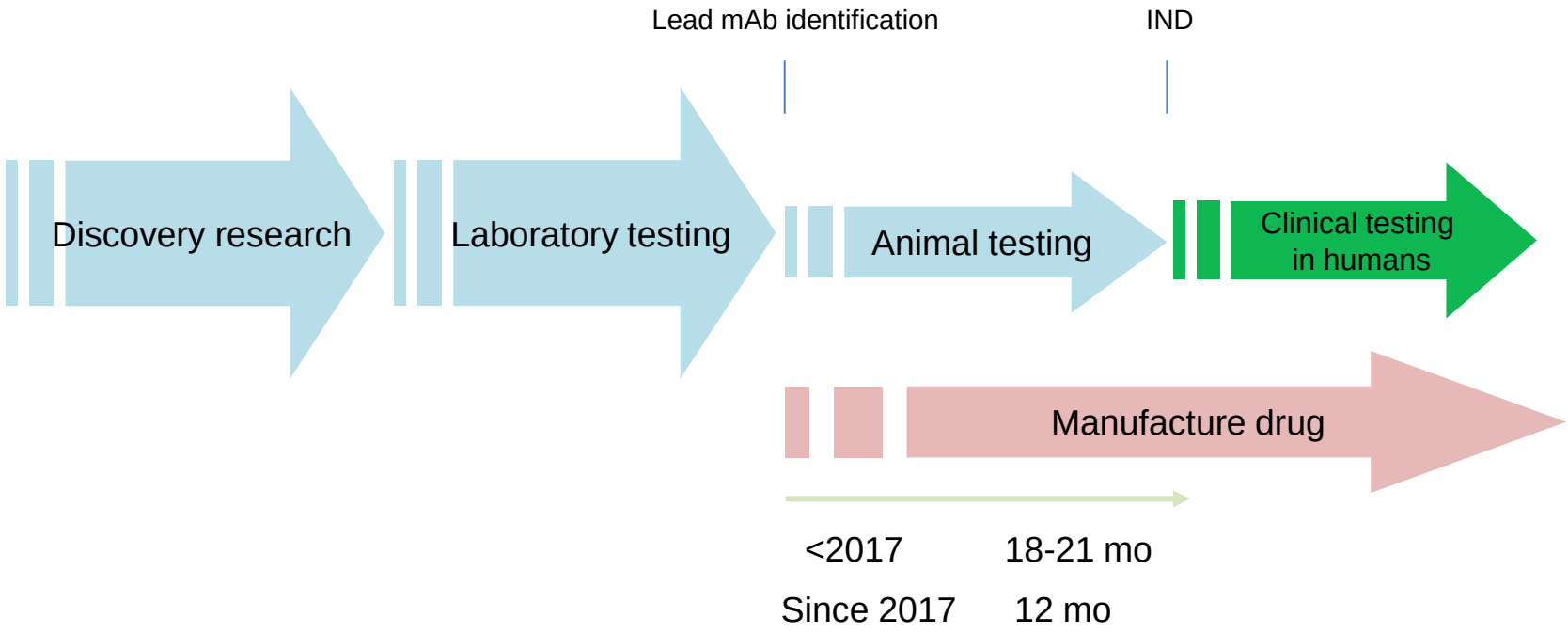
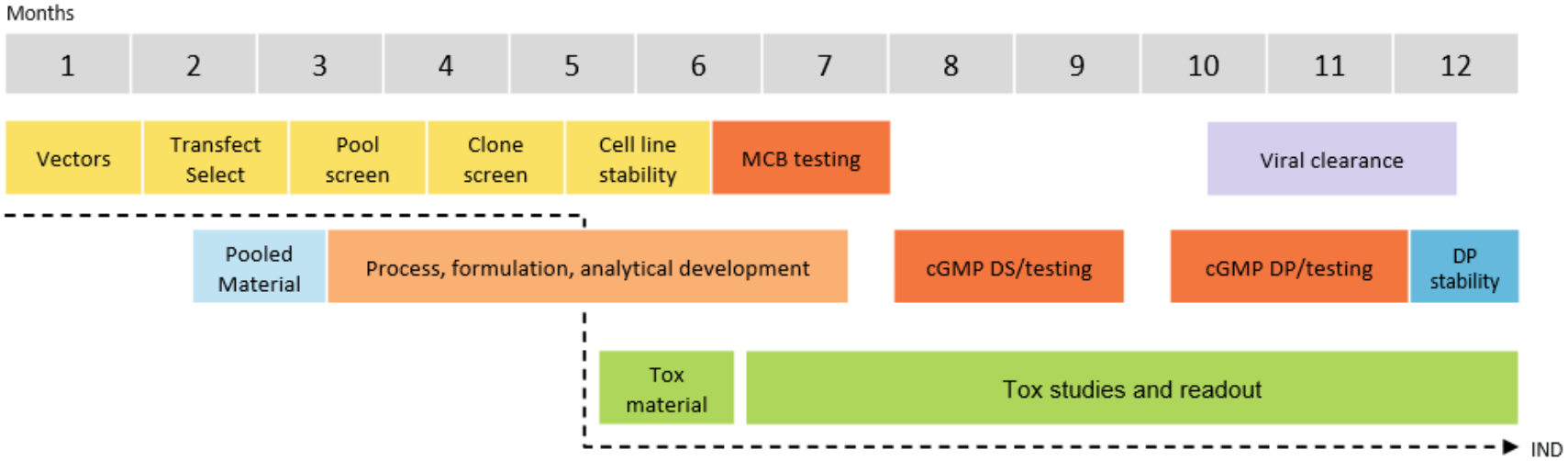
Stages in mAb product development

Current lead mAb identification-to-IND is 12 mo



Current mAb development timeline

State-of-the-art technology applied to achieve 12 mo



---- Critical path to IND

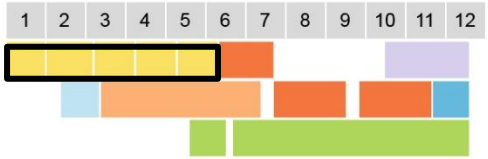
From Kelley, *Nature Biotechnol.* **38**, 540-545 (2020)

How can we move faster than 12 mo?

- Adopt latest technological advances
  - Highly productive cell lines
  - Large bioreactors using single-use technology
    - Enables production of thousands of doses from single batch of >5 kg
- Focus on platform approach
  - Human IgG1 expressed in CHO cells
    - Safety and quality risks are low
    - >50 have been commercialized
    - Substantial platform knowledge, cGMP production experience and facilities
- Accept higher business risk
  - Consider caveats, but…with no increased risk to patients in first clinical trials (risk/benefit)
- Why not after a pandemic?

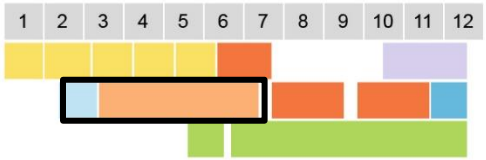
Faster cell lines

- Targeted integration of mAb expression vectors
  - More consistent expression
  - Integration of low copy numbers in highly active transcriptional hotspots
  - More high-expressing clones reduces time for screening cell pools or clones
  - Potential time savings—1 mo
- Clone screening
  - Incorporating imaging eliminates requirement for second round of cloning
  - Use of ambr15 vs 5L bioreactors eases evaluation of many clones or conditions
  - Potential time savings—1 mo
- Combined time savings—2 mo/low risk



Faster process development

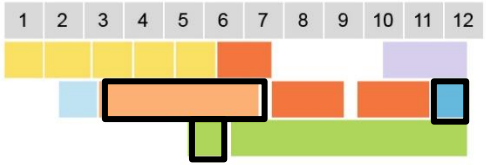
- Supply run for DSP, formulation and analytical development
  - Large scale (>100L) transient expression vs. stable transfected pool
    - More work than from stable transfected pool, but can be available 1 mo earlier



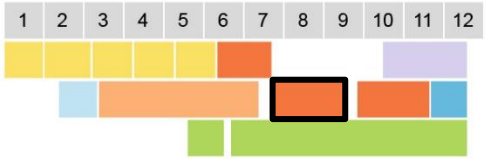
- Platform process
  - Restrict selection of raw materials to those already in inventory in cGMP warehouse
  - Platform applies to all unit ops
    - DSP polishing step is variable-this is a risk
  - Because of the use of material from transient culture, unit ops can be defined before final clone selection
  - No demonstration batch

Faster formulation development and stability

- DS/DP stability
  - Due to speed to cGMP production, assessing stability of tox material may be of little benefit
  - mAb stability profile under accelerated and stressed conditions could be compared with other mAbs. Product expiry dating would be extended by extrapolation based on real-time data



Faster scale up



- No demonstration batch
- No evaluation of process performance at pilot scale
- Rapid transfer to cGMP production scale following completion of cell line development
  - Caveats: Testing for bioburden, endotoxin needed, must allow for this time
- Platform process enables rapid scale up
- High business risk: Lack of process confirmation increases chance that operations will not scale well and process performance and product quality will vary from target.

Faster drug product

- Assume
  - Relatively large dose >0.5 g for infectious disease indication
  - Route of administration is intramuscular or intravenous injection
- 50-75 mg/mL liquid, stored cold or frozen
  - Only proven formulations and excipients would be evaluated
  - Container closure should be standard components
  - While long-term stability (>12 mo) not required for early stage
    - Cost is low, benefit is high to set up for longer stability (24 mo)

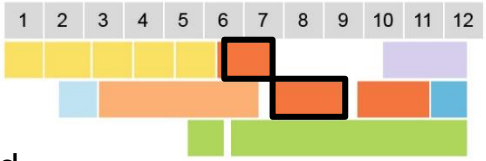
Faster toxicology

- Goal is to remove pivotal tox studies from the critical path
  - Several companies have successfully performed

  tox studies using material from transfected cell pools or minipools
  - Accelerates initiation of appropriate tox studies
    - *In-vitro* AMES
    - *In-vitro* tissue cross-reactivity study
    - *In-vivo* efficacy in appropriate species

Faster cGMP production

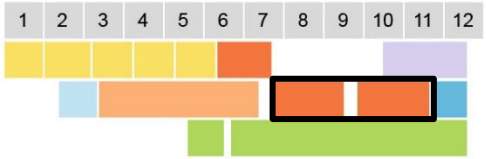
- Use of MCB prior to completing full panel of testing
  - Business risk-using an unreleased MCB in a cGMP facility
  - Full MCB testing would be completed before any product is distributed

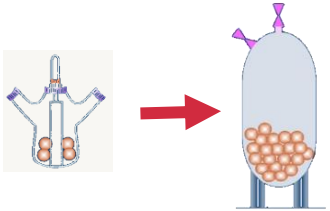


- Derive seed culture for cGMP production from expansion of selected clone during MCB manufacture (e.g., no RCB established)
  - First batch not derived from MCB vial
  - Saves 1-2 weeks
- Perform initial cGMP production at smaller scale (200L vs. 2000L)
  - Shorter inoculum train
  - Lower risk of scale up without pilot batch

cGMP production and analytics (cont'd.)

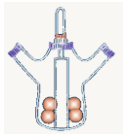
- Co-location of DS and DP
  - More efficient operation and time savings associated with shipping DS between sites
- DP fill-finish
  - Disposable fill lines, robotic operation in isolators to facilitate rapid product changeover
  - 200L batch with 3-4 g/L titer would yield 300-500 1-g doses
- DP release testing
  - Qualify platform analytics for IgG1 mAbs
  - ELISA may be qualified and performed as "confirmatory" during IND review
- Resupply batches could be further scaled (10-20x)
  - 1000-2000L (several manufacturers)



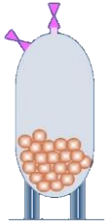


Cell line 200L bioreactor

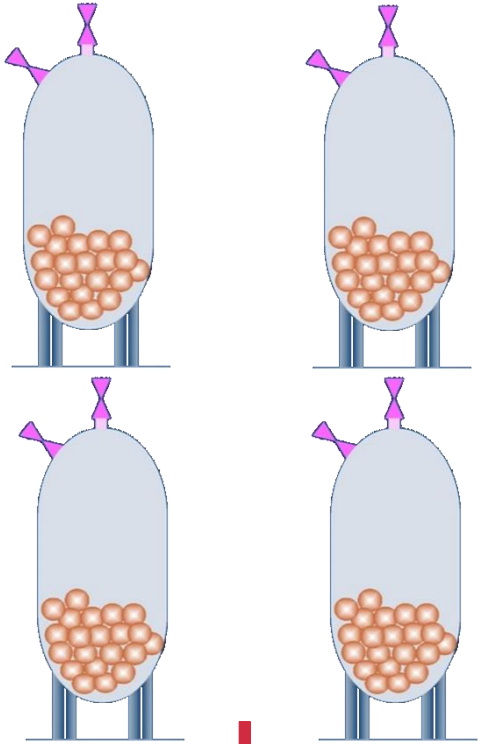
Scale up from first cGMP batches



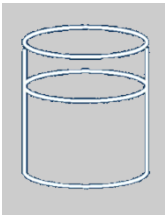
Cell line



200L bioreactor



Multiple 1-2kL production bioreactors



Downstream process

Formulation and testing

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Faster quality

- Conditional release of DS, DP
  - Safety testing (sterility, identification, endotoxin) performed before further processing (for DS to DP)
  - Release testing completed while subsequent processing underway (for DP to labeling/packaging)
- Viral clearance studies
  - Use of platform DSP steps enables modular claims of viral clearance, obviating the need for product-specific viral clearance studies
    - Low-pH inactivation
    - Virus filtration
    - Protein A
    - AEX chromatography

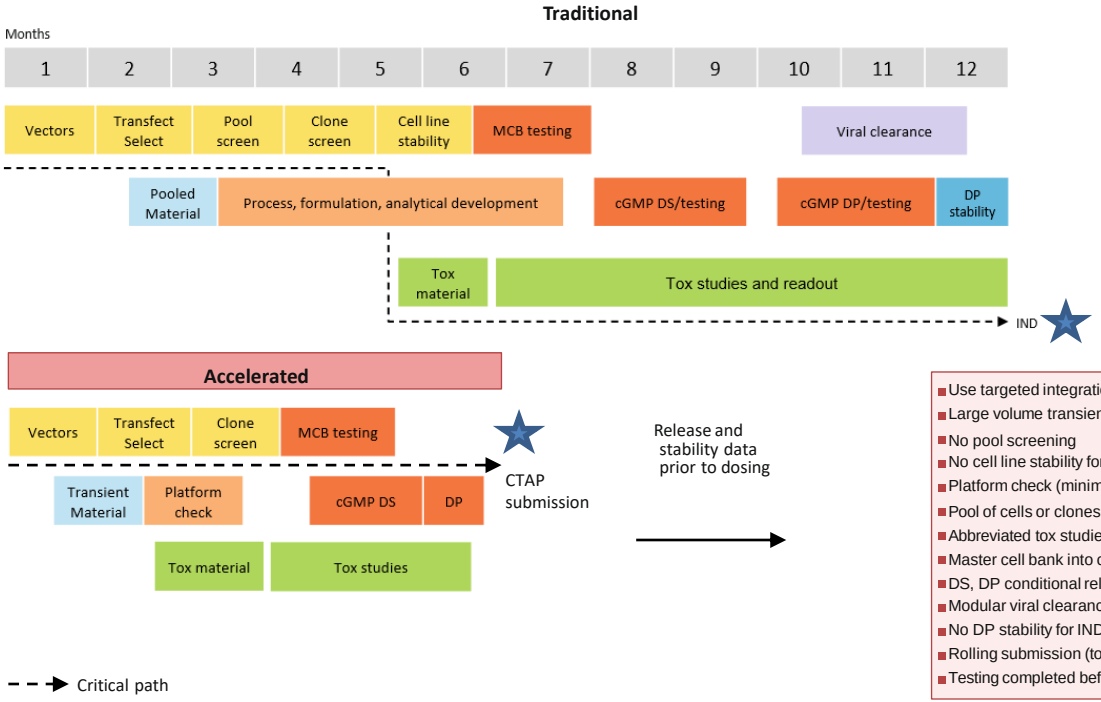
Faster (focused) regulatory

- Get and stay familiar with guidance, regulations, etc.
  - Early contact with FDA/regulatory bodies at soon as is feasible
  - Use Pre-EUA Activities for early discussion
    - Submit clear EUA requests
  - CTAP – Pre-IND meetings
    - Pre-IND meeting request and meeting information package submitted together
    - Clearly outline the science and plan

Think out of the box!!!!

Faster CMC development timeline for pandemic

Potential reduction from 12 mo to 6 mo



- Use targeted integration/high productivity host
- Large volume transient material supply
- No pool screening
- No cell line stability for clone selection
- Platform check (minimal PD/form/AD)
- Pool of cells or clones used for toxicology studies
- Abbreviated tox studies off critical path
- Master cell bank into cGMP production w/o testing
- DS, DP conditional release
- Modular viral clearance—no studies
- No DP stability for IND
- Rolling submission (tox, release, stability)
- Testing completed before first patient dosed

From Kelley, *Nature Biotechnol.* **38**, 540-545 (2020)

What's new here?

- Integration of innovative CMC methods with focus on speed
  - Targeted integration
  - Single round of cloning with imaging
  - Ambr15
  - Development supply run from large scale transient culture
  - Tox production from cell pool
  - No RCB--growth of production cell line concurrent with MCB manufacture
- Abbreviated tox studies
- Accepting higher business risk

Leading new mAb therapeutics

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Leading new mAbs in clinical 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 Clinical data expected in Q4	• Genetically engineered from the blood of a recovered patient • Required <3 mo from screen to first-in-human clinical trials • Ph1 trial completed; currently in Ph3
REGN-COV2	Cocktail of 2 monoclonal antibodies	Spike protein (different epitopes)	Regeneron Manufacturing agreement with Roche	• Genetically engineered from the blood of a recovered patient • Ph1 trial completed; currently in Ph3
VIR-7831	Monoclonal antibody	Spike protein	GSK/Vir Biotechnology Manufacturing agreements with WuXi, Samsung, Biogen	• Collaboration announced in Apr • Genetically engineered from the blood of a recovered patient and for increased stability *in vivo* • Expects to move into Ph2/3 in Aug
CT-P59	Monoclonal antibody	Spike protein Neutralizes virulent D614G variant.	Celltrion	• Clinical Ph1 began 17 Jul in Korea

Leading new mAbs in clinical testing

Name	What is it?	Molecular target	Sponsor	Status
TBD	Cocktail of two monoclonal antibodies	Spike protein (different epitopes)	AstraZeneca/Vanderbilt University/DARPA	• Genetically engineered from the blood of a recovered patient and for increased stability *in vivo* • Expects to start Ph1 in Aug

Summary

- Pre-pandemic mAb CMC development timeline is 12 mo from product development decision to IND filing
- Factors from several areas can be combined to shorten timelines
- The pandemic mAb CMC development timeline could be reduced to 6 mo
- The CTAP pathway involves frequent dialog and collaboration with FDA
- CMC should be ready when a COVID-19 therapeutic mAb is authorized

Questions?

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