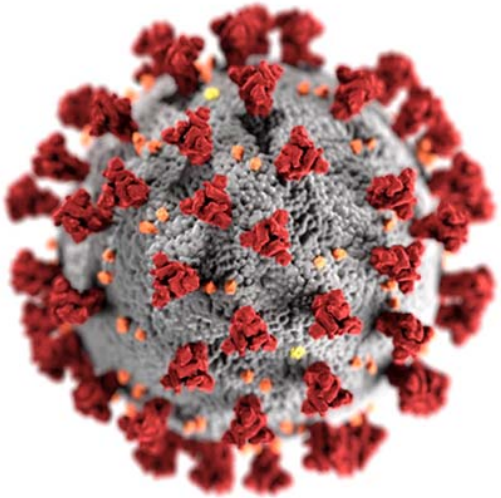
COVID-19: Neutralizing Antibodies



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Columbia University

ProHealth Care

Global Research & Development UnitedHealth Group

Parasites without Borders

COVID-19 Neutralizing Antibodies Talk outline

1. What is an Antibody?

2. Antibodies in COVID-19 Natural Infection

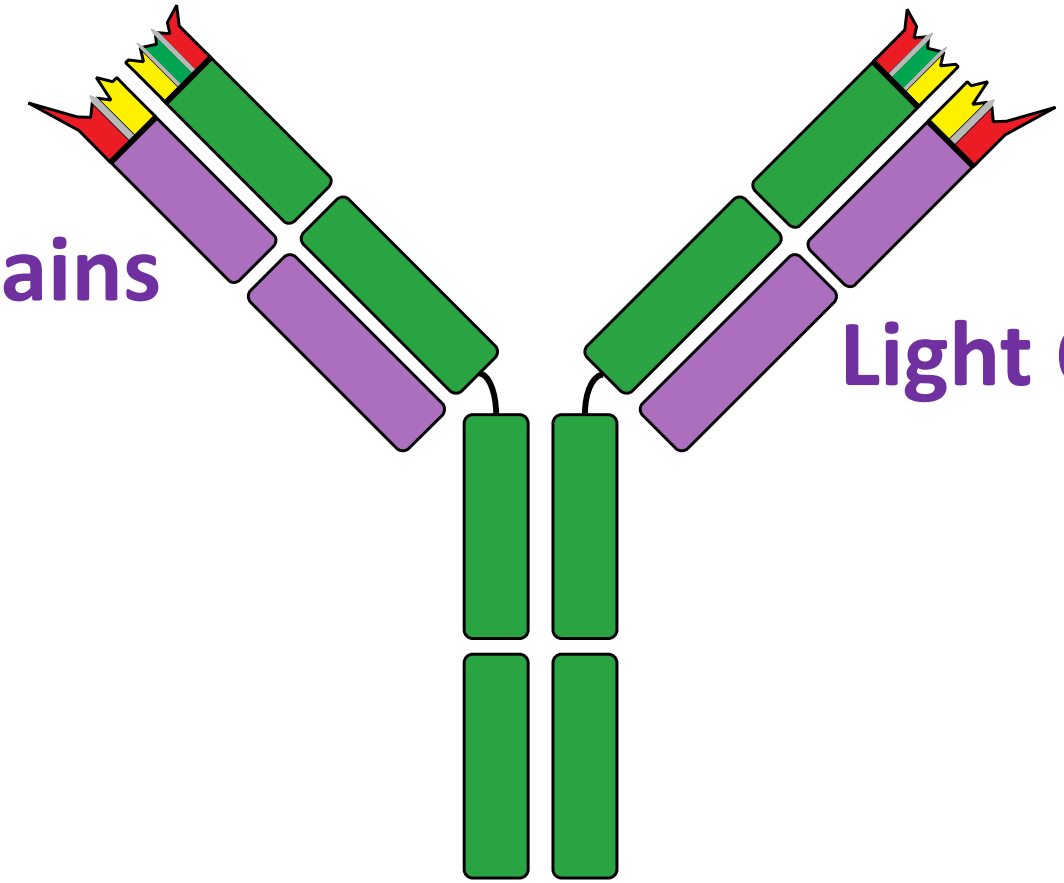
3. Monoclonal Antibodies as Therapeutics
    1. Neutralization is probably critical
    2. Timing is likely critical

4. Monoclonal Antibody Therapies Under Investigation

What is an Antibody?

Antibodies or Immunoglobulins

(the same thing, different names)

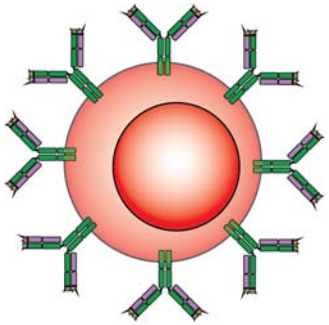


Light Chains

Light Chains

Heavy Chains

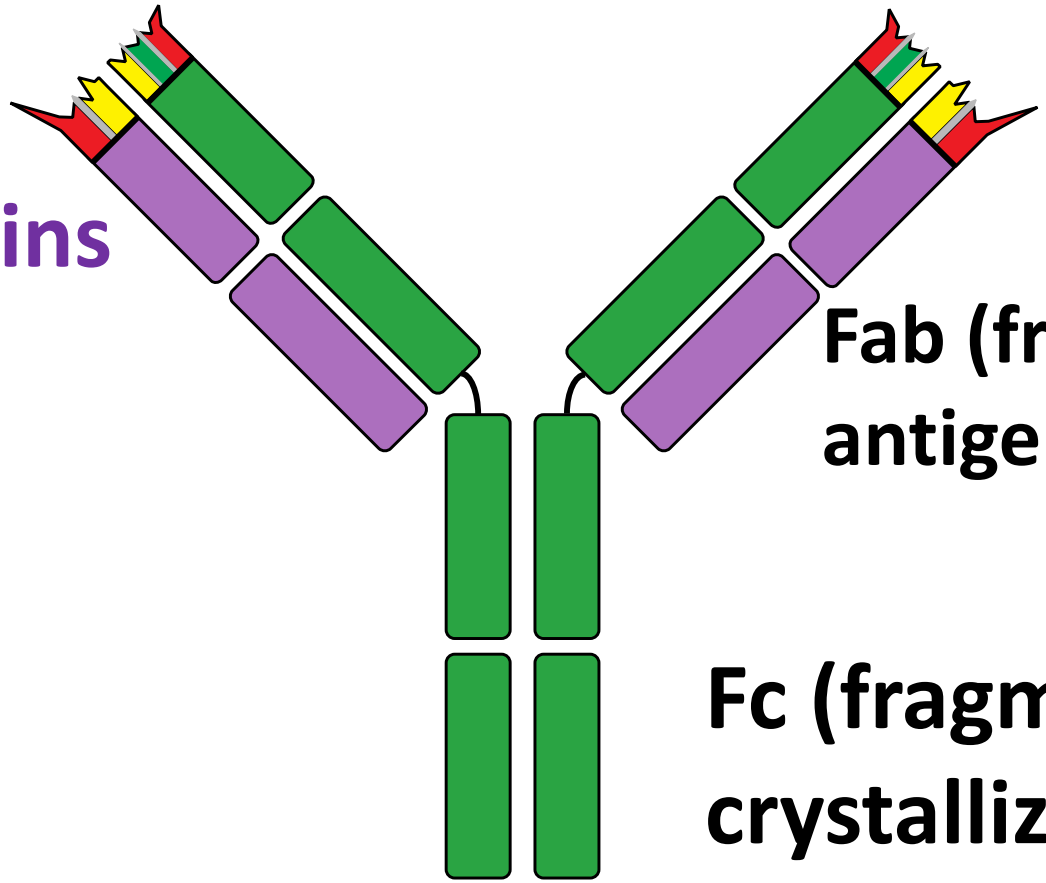
B cell with membrane bound antibodies



Complex protein with an ability to bind an ‘antigen’ at various affinities

Antibodies or Immunoglobulins

(the same thing, different names)



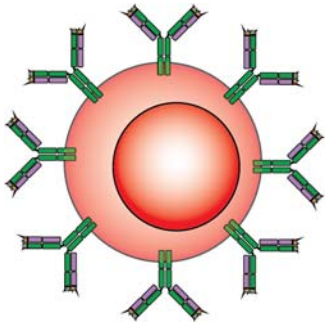
Light Chains

Fab (fragment antigen binding)

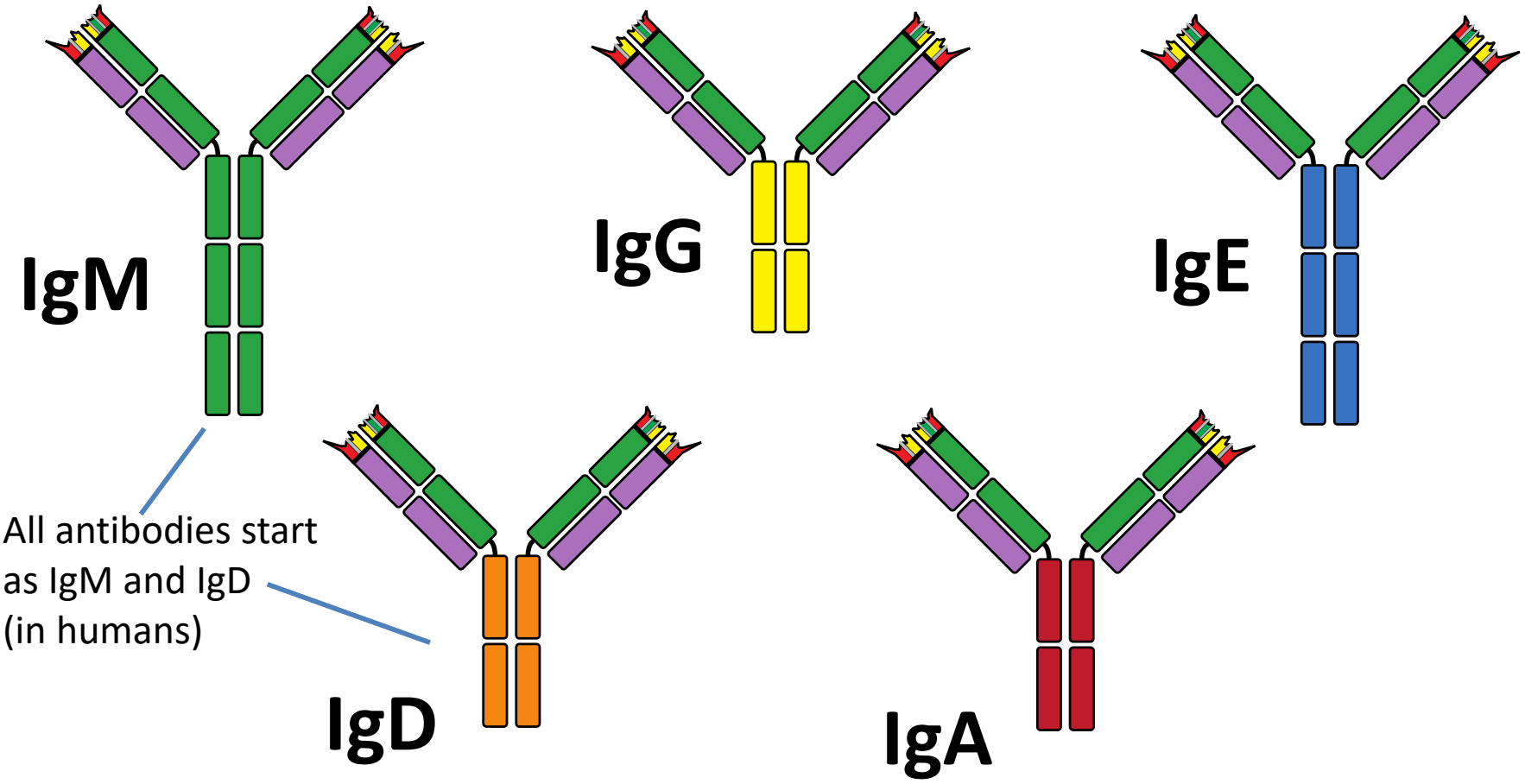
Fc (fragment crystallizable)

Heavy Chains

B cell with membrane bound antibodies

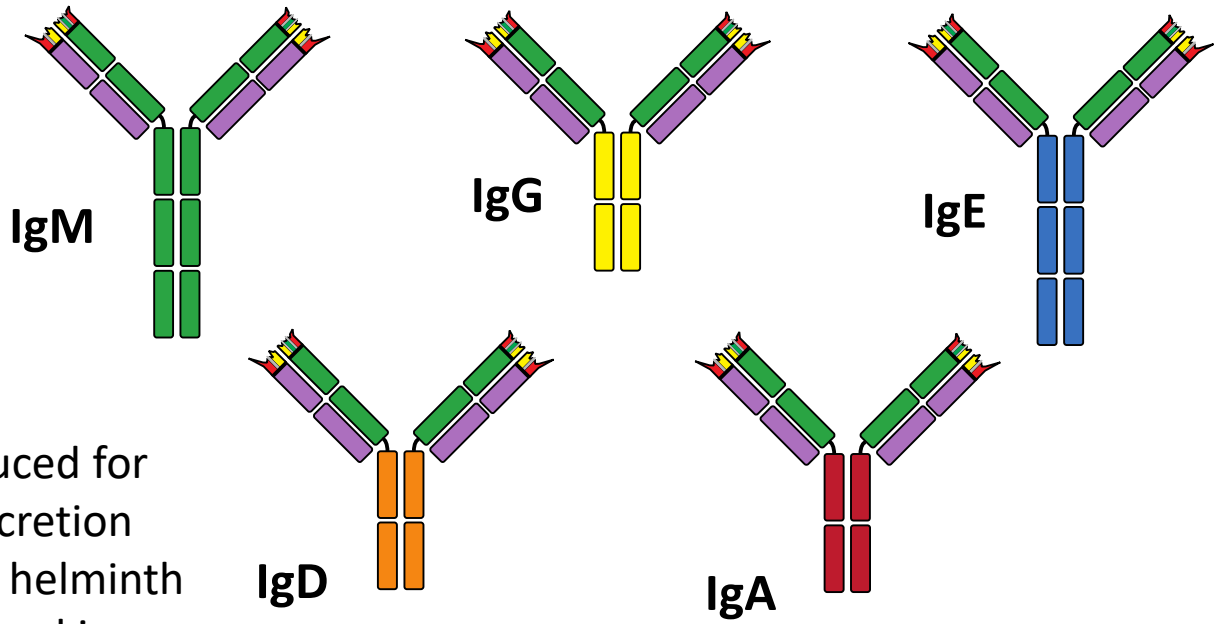


Change the Fc and you get IgM, IgD, IgG, IgA, IgE



Class switching is the change to the other antibody types

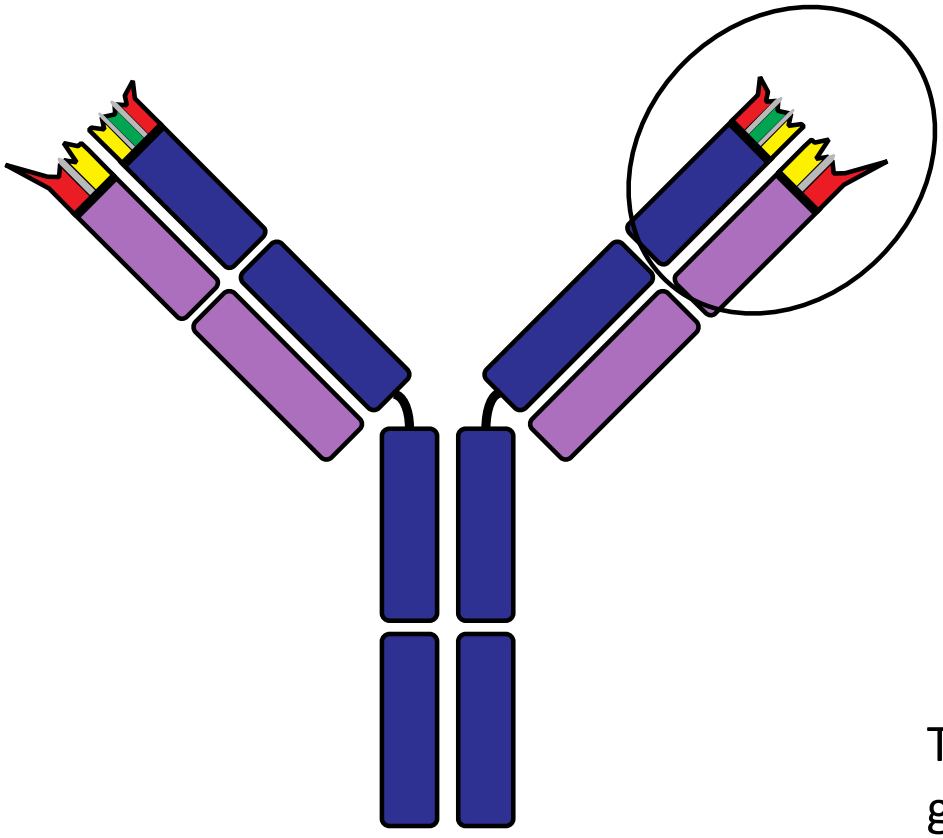
Changing the Fc portion changes the function but also the half life

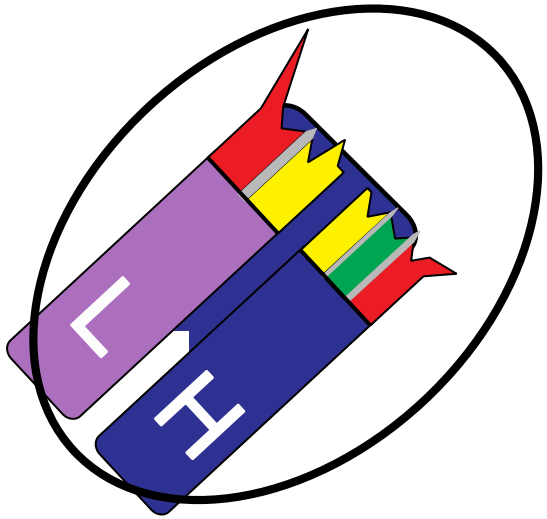


IgA is predominantly produced for mucosal protection and secretion
IgE seems to have a role in helminth protection but also is involved in allergies
IgM and **IgA** can form pentamers and dimers
IgG is the works horse of the antibodies

No Discussion of Immunology is Complete without the words "It is complicated"

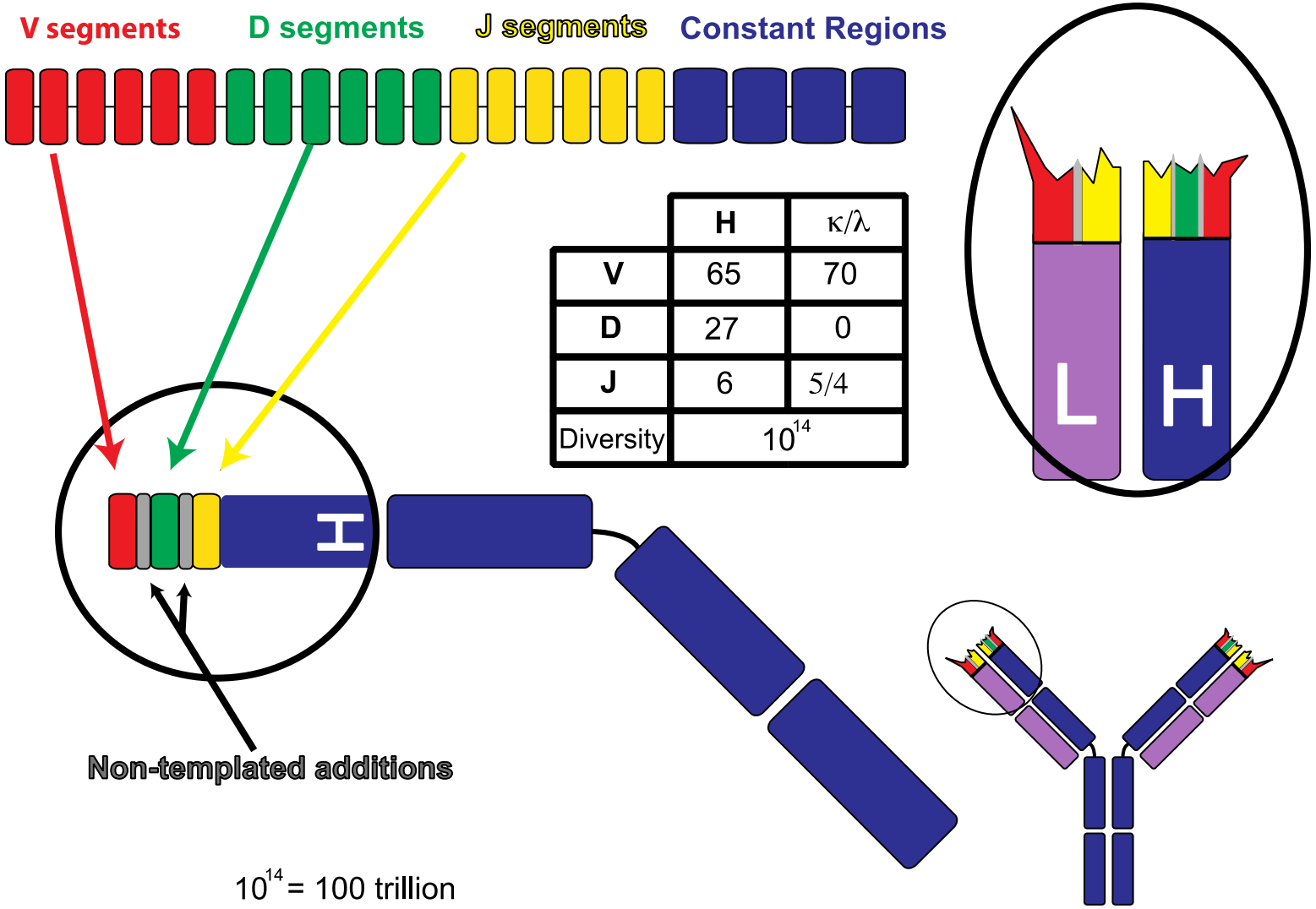
The end of the Y's is where the binding specificity is found





To be honest, the mechanics of getting that ideal antigen binding is complicated.

Developing Ideal Antigen Binding Require a Complex Process but Someone Else is doing the Work



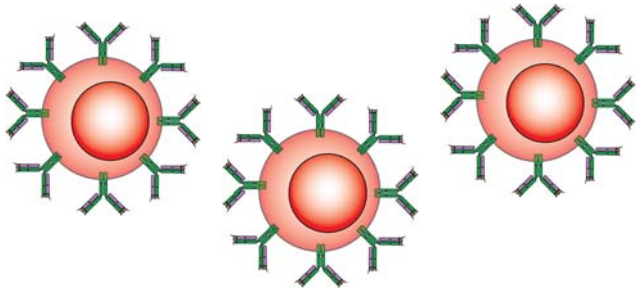
	H	κ/λ
V	65	70
D	27	0
J	6	5/4
Diversity	10^{14}	

10^{14} = 100 trillion

Developing an Antibody with the Antigen Binding You Want is a Complex Process

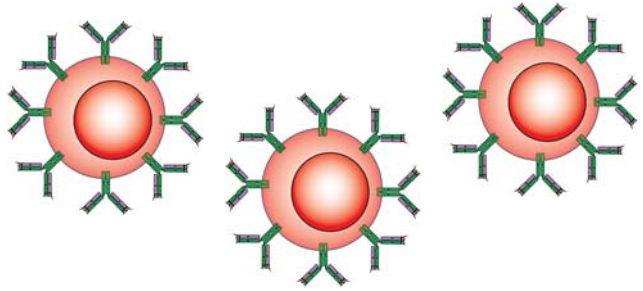
So We Let Someone Else is do the Work (A Mouse or a Person)

$120 million mouse



Mice with a human touch by Christopher Thomas Scott Nature Biotechnology 2007

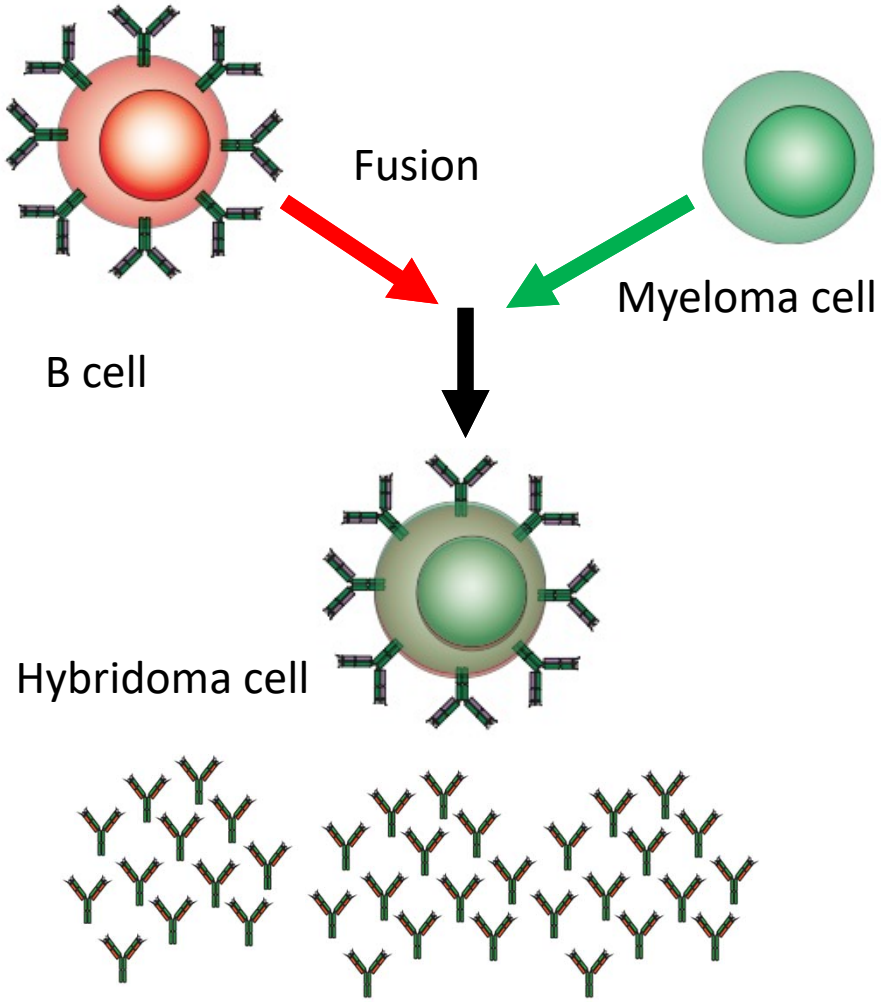
100 trillion B-cell People



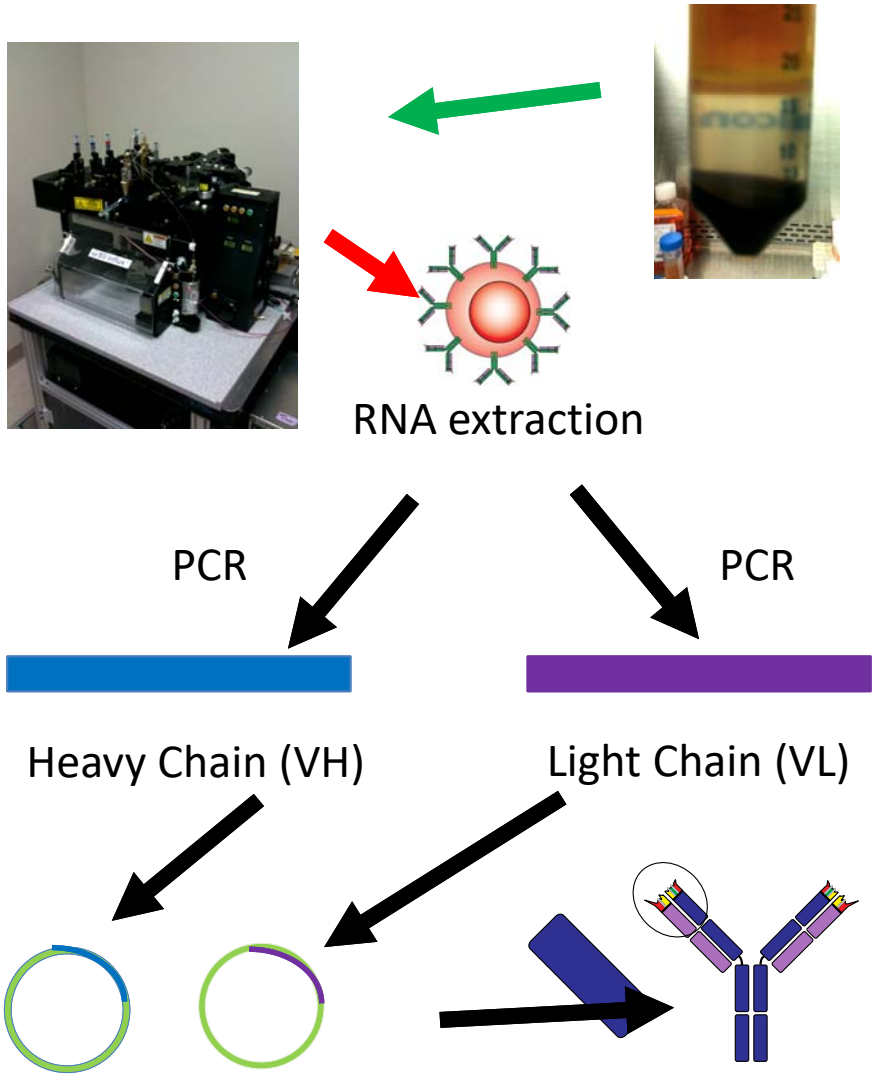
The Griffin Family Sands Point, NY 2017 Barnaby, Daniel, Daisy, Jessica, Eloise

Monoclonal Antibody Production

Hybridoma Process

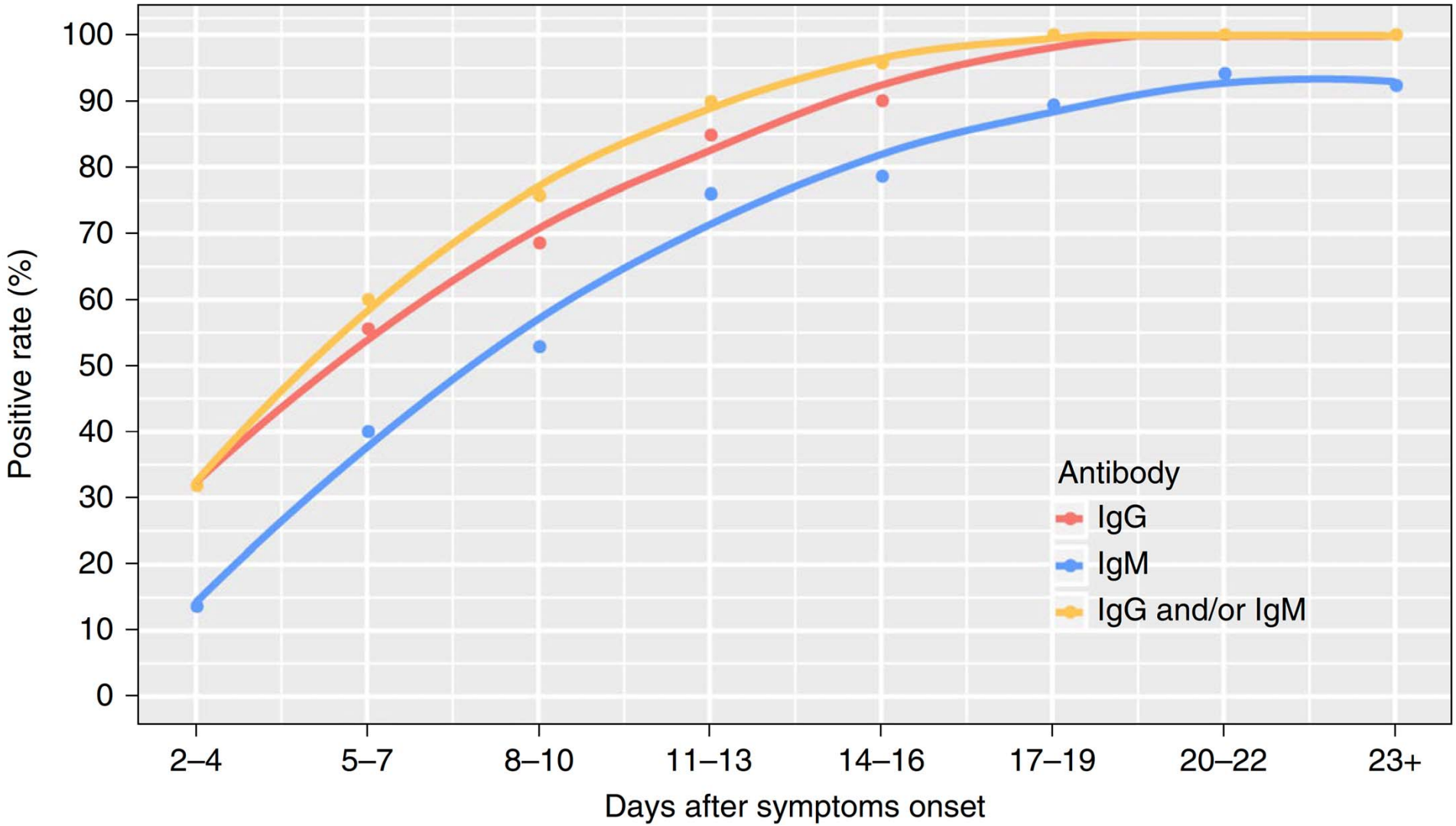


Single B cell cloning



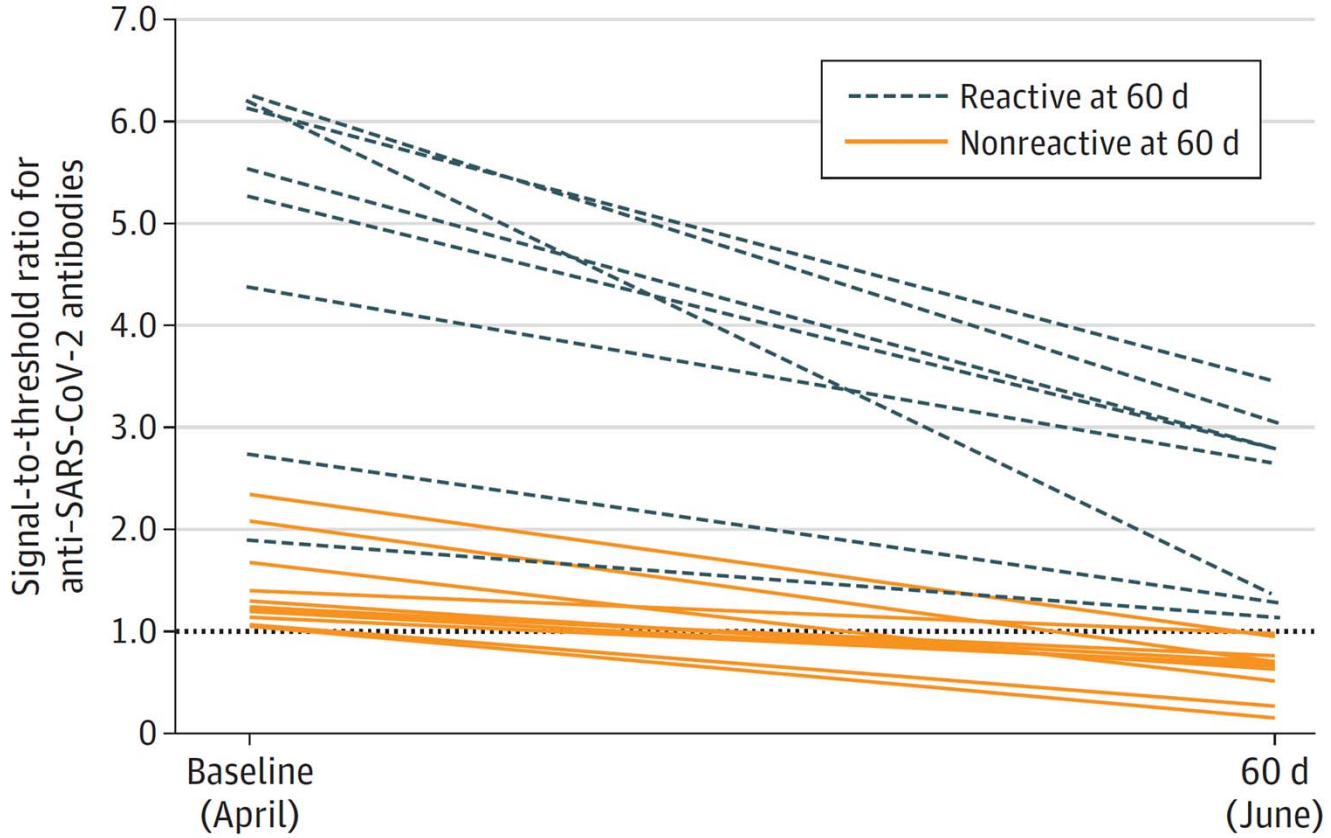
Antibodies in COVID-19 Natural Infection

Antibody Take Time to Rise in COVID-19 Natural Infection



Antibody responses to SARS-CoV-2 in patients with COVID-19 by Quan-Xin Long et al in Nature Medicine June 2020

Antibody Levels Drop in COVID-19 Natural Infection



SARS-CoV-2 indicates severe acute respiratory syndrome coronavirus 2.
The dotted line at y = 1.0 indicates the threshold for seropositivity.

Change in Antibodies to SARS-CoV-2 Over 60 Days Among Health Care Personnel in Nashville, Tennessee by Patel, M et al in JAMA 9/2020

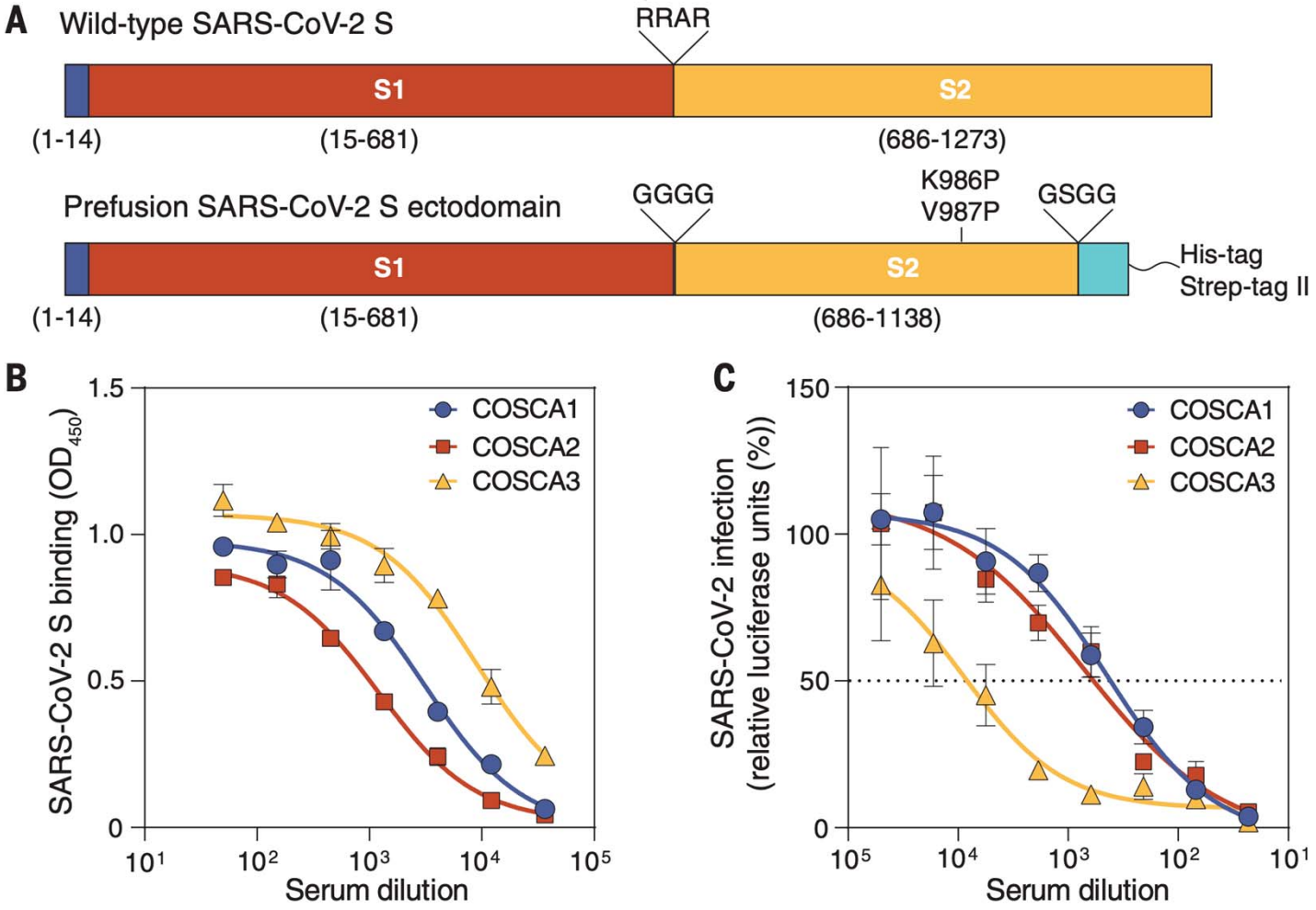
Monoclonal Antibodies as Therapeutics

- In 1986 the FDA approved the first monoclonal antibody treatment, muromab-CD3 for prevention of transplant rejection.
- There are now over 100 monoclonal antibodies approved for various fields such as oncology, rheumatology and osteoporosis.
- There are multiple monoclonal antibodies in clinical trials for CMV, HIV, Influenza, RSV and Ebola.
- There are now multiple monoclonal antibodies in clinical trials for COVID-19

What are the Risks with Monoclonal antibodies for Treating an Infectious Disease?

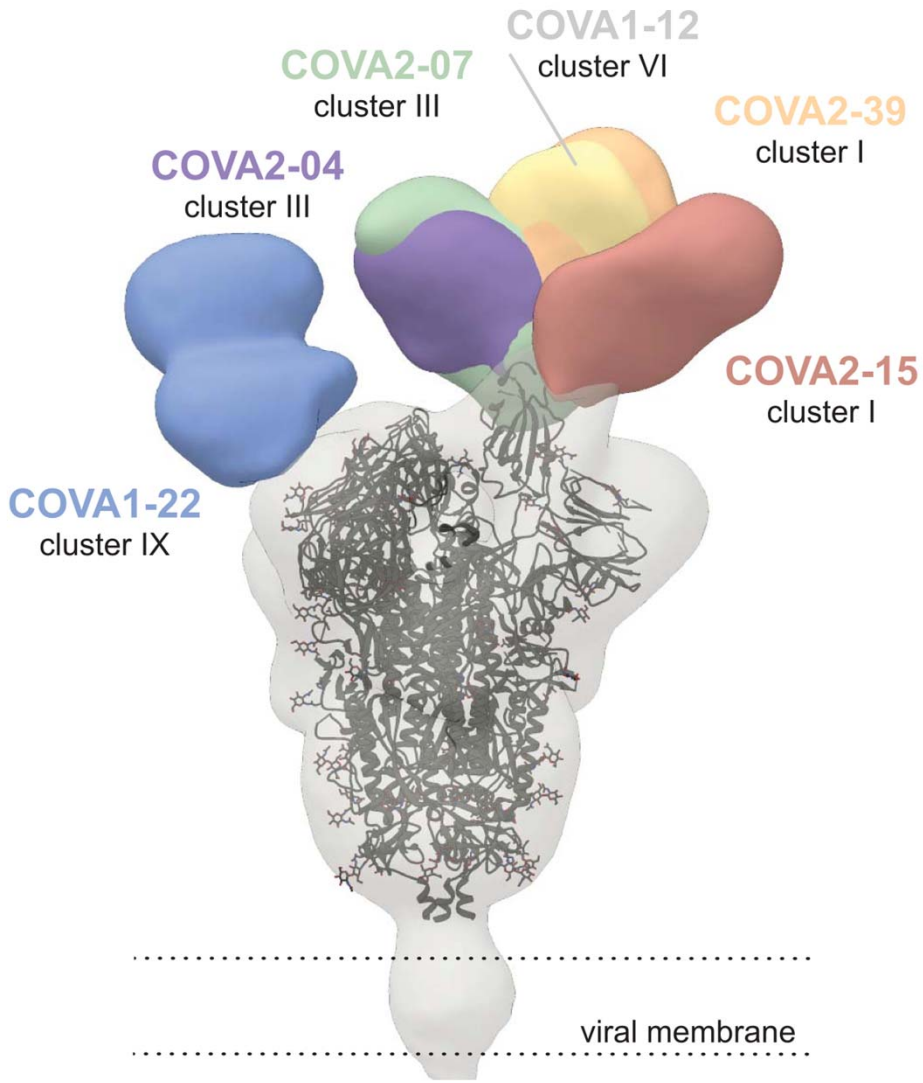
- No significant infectious risk as these are not prepared from human or animal plasma.
- Infusion reactions can occur rarely in the first 1-2 hours perhaps due to carbohydrate moieties on the heavy chain but more likely with repeat treatments.
- Off target effects due to binding of a different antigen.
- Development of host antibodies against the given monoclonal therapy.

Neutralization is Probably Critical



Potent neutralizing antibodies from COVID-19 patients define multiple targets of vulnerability by Brouwer P et al, Science August 2020

Neutralization is Probably Critical



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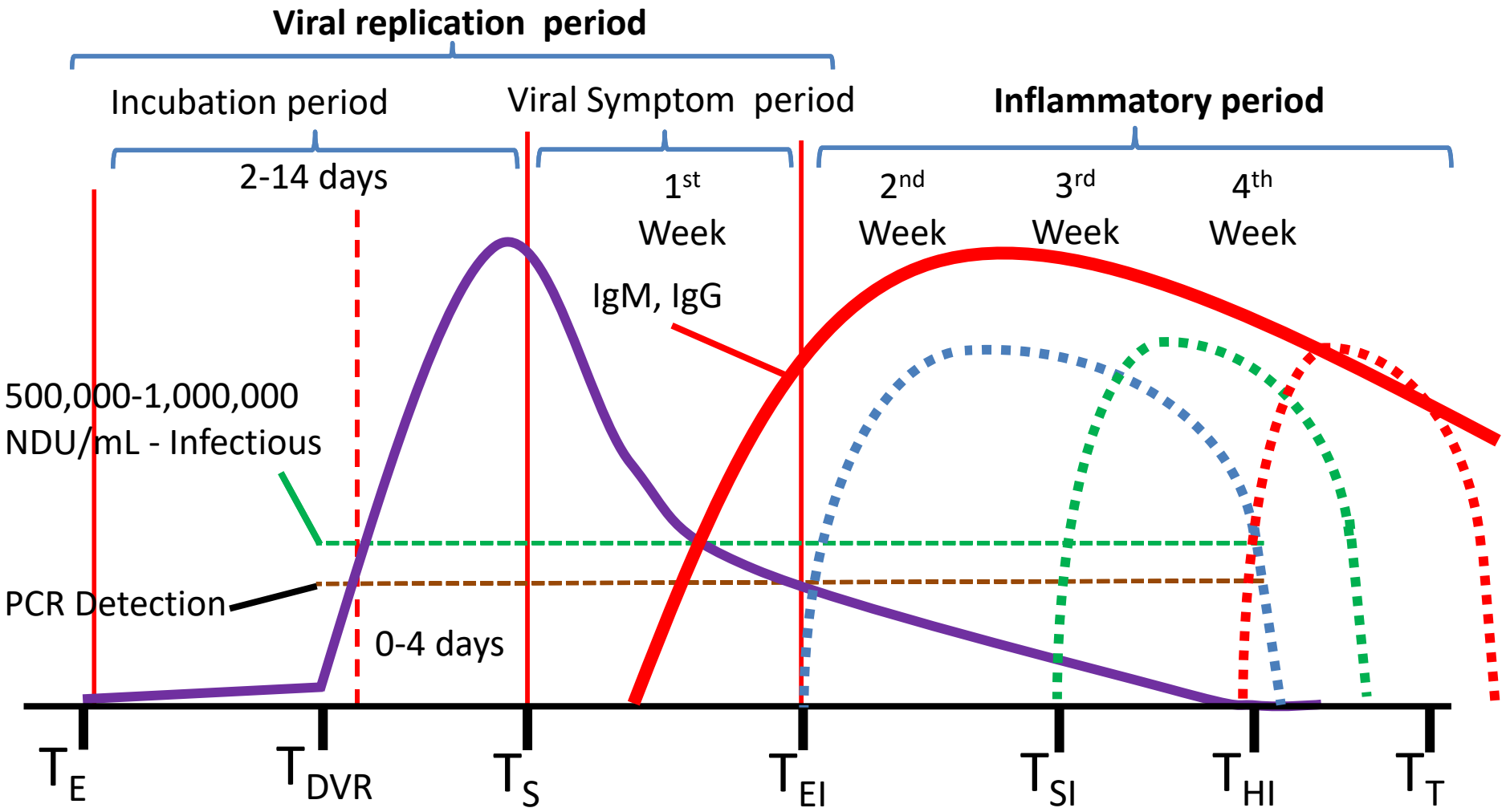
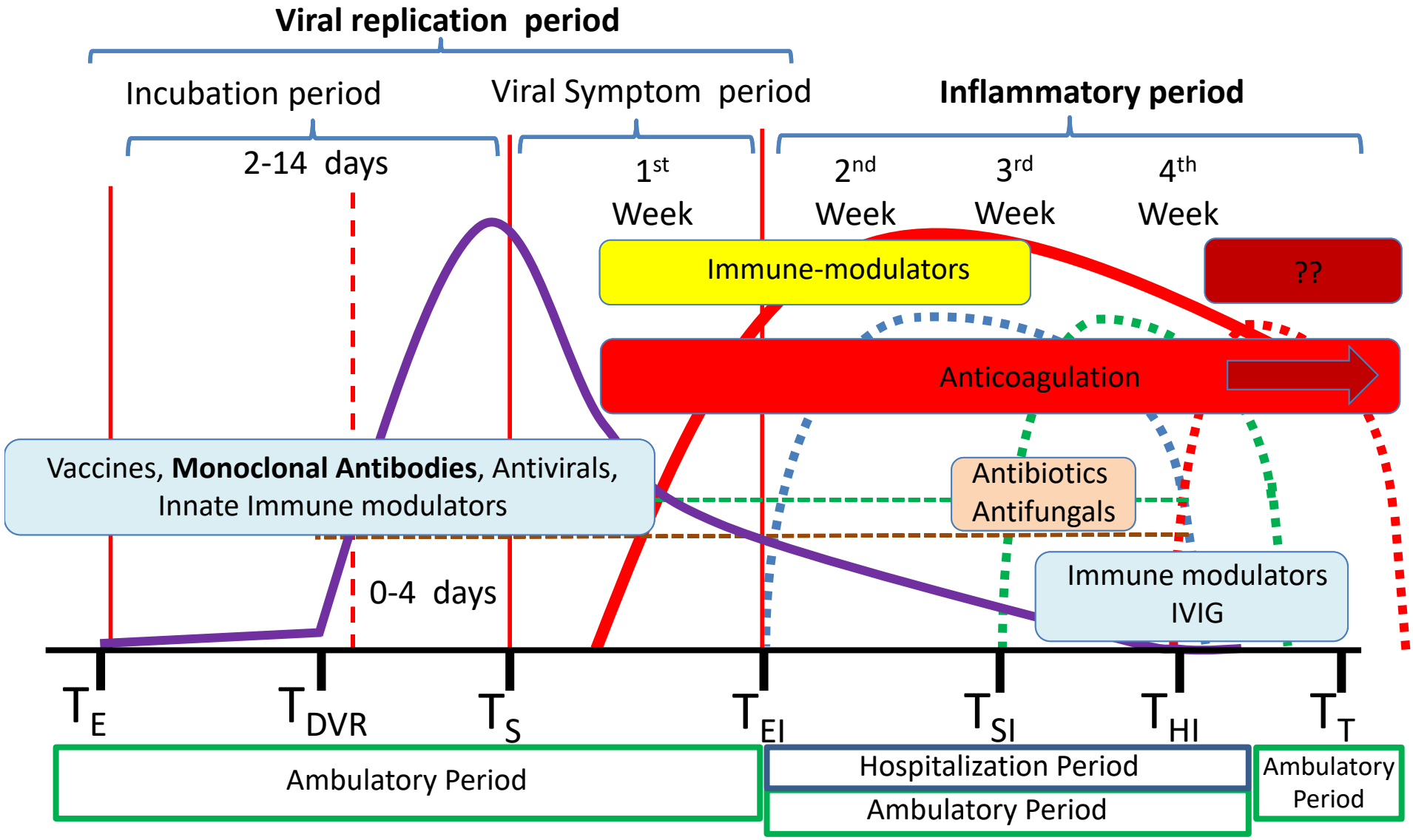
Timing is Probably Critical



Griffin et al., Annals of Internal Medicine-under review

This is Viral Replication Phase Therapy



Griffin et al., Annals of Internal Medicine-under review

Monoclonal Antibodies Therapies Under Investigation

- Eli Lilly
- Regeneron
- Vir/GlaxoSmithKline

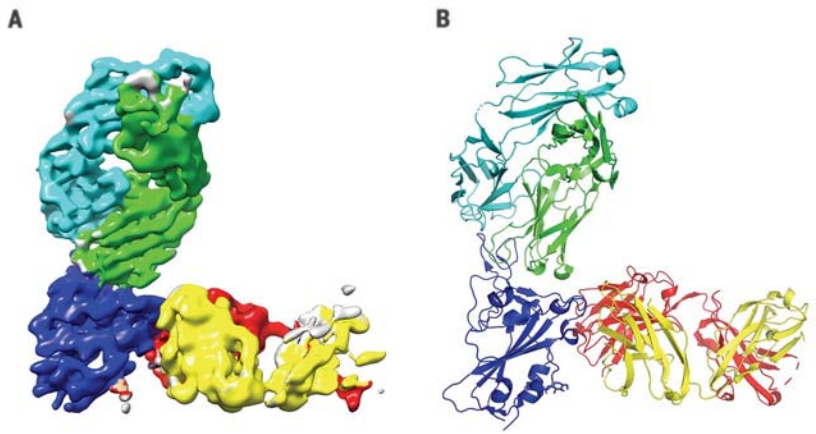
Eli Lilly Antibodies

- **Eli Lilly** is studying LY3819253 (LY-CoV555-bamlanivimab) and LY3832479 (LY-CoV016-etesevimab) separately and together.
- LY3819253 (LY-CoV555-bamlanivimab) is a human antibody from one of the first U.S. patients who recovered from COVID-19.
- LY3832479 (LY-CoV016-etesevimab) is a recombinant fully humanized monoclonal neutralizing antibody.

Regeneron Antibodies

- **Regeneron** – Currently studying a combination of two monoclonal antibodies REGN10933 and REGN10987 called *REGN-CoV2.*

3.9-Å cryo-EM map of the REGN10933-RBD-REGN10987 complex, colored according to the chains in the refined model (**B**). RBD is colored dark blue; REGN10933 heavy and light chains are green and cyan, respectively; and REGN10987 heavy and light chains are yellow and red, respectively.



Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody cocktail Hansen J, et al Science 8/2020

Vir/GlaxoSmithKline

- **Vir/GlaxoSmithKline** – is studying VIR-7831 (also known as GSK4182136), a fully human anti-SARS-CoV-2 (Severe Acute Respiratory Syndrome coronavirus-2) monoclonal antibody, for the early treatment of COVID-19. *This antibody has an Fc amino acid change that increases it half-life and it also may neutralize SARS-CoV-1*.

Are cocktails of mAbs likely to be preferable to antibody monotherapy?

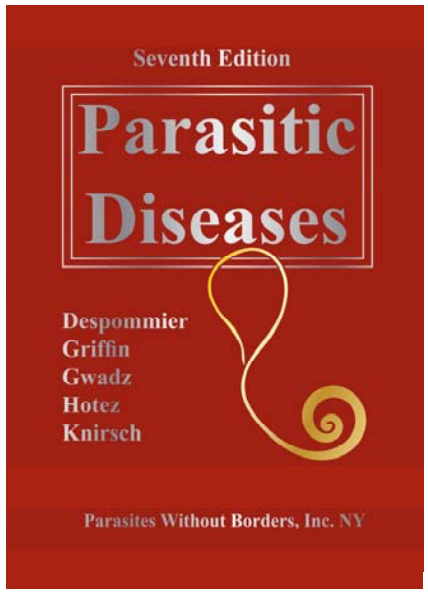
- While cocktails are purported to prevent escape mutants, SARS-CoV-2 is genetically less diverse and have a high-fidelity RNA proofreading enzyme making this less important. As a real life example a single anti-Ebola mAb (mAb114) worked as well as ZMapp's three-mAb cocktail (EB3).
- Cocktails ultimately double the cost and complexity of manufacturing.

FAQs about Monoclonal Antibodies?

- What is the difference between a monoclonal antibody and a polyclonal antibody?
  - Monoclonal from just B-cell all the same while polyclonal antibodies come from many different B-cells.
- Is it better to just give one antibody or a cocktail?
  - We do not know.
- Is the safety profile acceptable relative to the benefit? (Are they Safe?)
  - These tend to be some of our safest therapeutics.
- If given at the right time do these monoclonal antibodies work? (Are they efficacious?)
  - We need Phase 3 Efficacy trials.

Thank you!

- If you want more information visit:
- www.parasiteswithoutborders.com
- http://www.microbe.tv/twiv
- Dgriffin@ProHEALTHcare.com



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