The Complexity of Developing Re-purposed Therapeutics for COVID-19

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Infections Caused by the Coronavirus Family
SARS, MERS and now COVID-19 - What will it be in the future?

4 Coronavirus genera: α, β, δ, γ. α and β infect humans - Large, enveloped + strand RNA viruses
Four endemic strains: HCoVs (HCoV 229E, NL63, OC43, HKU1) - cause 10-30% of URIs
Immunity lasts for ~8 months, re-infections possible

Coronavirus are found in wild animals, bats most common, harbor many varieties
Wild/domestic animals - intermediate hosts, reservoirs, allow recombination, mutations to expand genetic diversity

2002: β HCoV. Named SARS – Severe Acute Respiratory Syndrome - originated in bats in China
SARS symptoms: Fever, cough, dyspnea, sometimes watery diarrhea. 20% needed mechanical ventilation, 10% fatal
- Few upper respiratory tract symptoms (unlike Influenza). Receptor is ACE2
- Peak shedding was 10 days- patient already hospitalized
- 8098 infected worldwide, 774 died

2012: β HCoV. MERS Middle-East Respiratory Syndrome, spread from bats to camels to humans. Saudi Arabia.
- Similar to SARS but severe GI symptoms, acute kidney failure. 50-89% needed Mechanical ventilation, 36% fatal
- Receptor in lung, GI, kidneys DPP4 (Dipeptidyl peptidase 4). 2494 cases, 858 deaths.

2017: SARS and MERS placed on WHO’s Priority pathogen list

2019: Wuhan, China: SARS CoV-2 : Spike glycoprotein binds human ACE2 receptor like SARS. Half a million deaths so far....
Differences in Spread of SARS-CoV-2 Vs. SARS and MERS

SARS and MERS were severe infections, no mild cases, patients hospitalized and contained spread.

SARS-CoV-2, Mostly subclinical and mild cases - not detected. Highly infectious. Spread rapidly. SARS-CoV-2 replicates in nasal tract in mild cases. (SARS and MERS in Lung)
Each “silently” infected person unknowingly infects many exposed individuals.

2-week incubation period before symptoms become apparent to quarantine

Once the infection is severe, the fatality rate for SARS-CoV-2 is similar to SARS and MERS.
Multiple Faces of COVID-19 - Understand the Host

- 80% no-symptoms or mild symptoms. Infectious and spread while in community.
- Multisystem inflammatory Syndrome (MIS) in children.
- Co-morbidities: Age, diabetes, hypertension, obesity*

Who, How and When to Treat?

1. **Prophylaxis:**
   - Vaccine is preferred but if not available...

2. **Prophylaxis to prevent infection in exposed individuals:**
   - *Safety, oral, low cost*
   - Pediatrics

3. **Moderate disease:** Antivirals

4. **Moderate disease in patients with comorbidities:**
   - Antivirals/immunomodulators and antibiotics

5. **Severe disease:**
   - Antivirals, Immunomodulators/ anticoagulants, anti-complement factors and antibiotics
Therapeutic Targets

Viral targets - Viral-cell interaction, various viral replication steps
Host targets - Immunomodulators, Coagulation and Complement pathway

Considerations for Use of Above

Combinations of the above - Depending on the stage of the disease
Combinations of the above drugs + antidiabetic, antihypertensive, anti-cancer and other medications

Drug-Drug Interaction

Delivery route/formulation
COVID-19: Developing Drugs and Biological Products for Treatment or Prevention- Guidance for Industry


Guidance focuses on the development of all the type of drugs:
Drugs with direct antiviral activity, immunomodulatory activity or with other mechanisms of action

The mechanism of action of the drug is likely to impact study design (e.g., population, endpoints, safety assessments, duration of follow-up).

Repurposed approved drugs:
Already have a complete safety, PK/PD and efficacy data against the target, but not against COVID-19. May need PK/PD, in vitro cell culture data, animal models, target defined

When there is compelling preclinical or preliminary clinical evidence, one could move directly to conduct a trial of sufficient size/design. Small Phase 2, followed by larger controlled trial is recommended

Primary and Secondary endpoints, Safety monitoring board, Data Analysis, etc. are described in guidance
Protease inhibitors
Understanding the Complex Enemy

Positive strand RNA
~30,000 bases

**NSPs: Help in replication, or interfere in host response**

- **NSP1**: Cellular saboteur - redirects cellular machinery, degrades cellular mRNA, inhibits interferon
- **NSP2**: Binds to proteins that move in endosome
- **NSP3**: Protease Untagging/ cutting viral /host proteins –blocks host immune response, promotes cytokine expression
- **NSP4**: forms vesicle for new viral constructs
- **NSP5**: 3CLpro, Mpro, polypeptide cleaving, Cuts most of the viral proteins to do their task
- **NSP6**: Works with NSP3 and 4
- **NSP7 and 8 with NSP12**: Copies of viral RNA (NSP12: RNA polymerase. Remdesivir target
- **NSP9**: Makes nuclear membrane pore
- **NSP10**: works with NSP14 and 16: Masks viral RNA from host enzymes
- **NSP11**: Involved in RNA replication
- **NSP13**: Unwinds RNA – RNA helicase 5”triphosphatase
- **NSP14**: Proofreading during RNA synthesis. Exoribonuclease
- **NSP15**: Chops up any left over viral RNA- Endoribonuclease
- **NSP16**: RNA cap 2′-O-methyltransferase nsp10/nsp16 complex, avoids innate immunity

**SPs: Envelope layer S, E, M, N**

- **S**: Spike, binds ACE2
- **E**: Ion channel
- **M**: Transmembrane, major protein, morphogenesis and assembly
- **N**: Nucleocapsid protein

**Accessory proteins- Helps replication.**

- **ORF3a**: pokes holes in cell membrane to allow new virus. *Triggers inflammation*
- **ORF6**: Signal blocker from cell to immune system
- **ORF7a**: Liberates virus/ cuts host Tethrein, also induces epithelial cell death
- **ORF8 and 10**: Different from other CoVs
  Unknown functions

Chen Y, J med Virology. [https://doi.org/10.1002/jmv.25681](https://doi.org/10.1002/jmv.25681)
## Direct Antivirals

<table>
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<td>Entry Inhibitors</td>
<td>Attachment inhibitors: rhACE2, Spike antibodies</td>
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<td>Spike protein activation inhibitors – TMPRSS2 Protease, Camostat, Nafamostat</td>
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<td>Transcription</td>
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<tr>
<td>N Protein</td>
<td>Nitazoxanide</td>
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<tr>
<td>Assembly &amp; Release</td>
<td>No inhibitors known</td>
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ACE2 - Spike Protein Binding and Key Role in COVID-19 Pathology

ACE2 is expressed primarily in alveolar epithelial type II cells in human lung - viral entry
- ACE2 is also expressed in other organs - heart, kidneys, blood vessels, and intestine
- Explains the multi-organ effects and dysfunction observed in patients

Hypertension is a risk factor strongly associated with ARDS and with death in COVID-19 patients

Increasing ACE2 could decrease Angiotensin II levels
Decrease lung damage
**rACE2 is in clinical trial – decoy for virus to bind**

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ACE is a dipeptidyl peptidase- cleaving 2 aminoacids - ACEIs mimic dipeptidyl C-terminal end of ACE

ACE2

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Angiotensinogen -> Renin -> Angiotensin I -> ACEs -> Angiotensin II

**ACE2**

- Carboxypeptidase – cleaves single AA at carboxyterminal end
- Decreases inflammation and fibrosis

**SARS-CoV-2**

**Spike protein**

**rACE2** is in clinical trial – decoy for virus to bind

**ARB’s could increase ACE2 (found in animal urine)**

**Patel et al. JAMA Published online March 24, 2020**

**Mackey et al., Ann Int Med, 15 May 2020**

**Mas receptor - British Journal of Pharmacology (2013)** **169** 477–492
Antibodies as Therapeutics - SARS CoV and SARS CoV2

Spike Protein

Both are related Coronaviruses that have spike protein that bind ACE2 receptor in lung, GI, kidneys, other organs and endothelial cells.

12 bases change from bats to human virus (ccucggcgggca) - a new insert in Spike protein that helps bind tightly to ACE-2

Target for vaccine

Antibodies to SARS spike blocks CoV-2 binding to ACE2 receptor (Sorrento, Vir biotech, Abcellera (Lilly), Regeneron)
Focus on Spike Protein for Therapeutics and Vaccines

The spike protein ectodomain has S1 and S2 domains - As in SARS, MERS and CoV2

The S1 domain has the receptor binding domain - recognition and host receptor binding

CoV and CoV-2 Spike glycoproteins are activated by cleavage between S1 and S2 – Cleaved by a furin (a serine protease called TMPRSS2) in Golgi membrane

The cleavage site is important - Four amino acid residue insertion (681-684) at cleavage site is not found in endemic CoVs. Important for transmissibility and pathogenicity.

The S2 domain, contains the fusion peptide (blue), and also has transmembrane domain (purple) and 2 heptad repeats HR1, HR2 (orange, brown).
Differences between SARS CoV and SARS CoV2 Spike Protein

CoV-2 sequence has a single insert at 483 – not found in CoV. COV-2 Spike binding to ACE2 is higher than CoV

14 AA in spike needed for ACE2 binding is shown with *

The S1 part of spike protein, organized as trimers, binds ACE2 - One of the three spikes changes conformation as it binds
Viral Entry – Spike Protein Activation by TMPRSS2

S protein is cleaved at two sites - S1/S2 and S2’, by cellular serine protease, TMPRSS2. The cleavage allows fusion of viral and cellular membranes.

There are several arginine residues at the S1/S2 site in CoV-2 which is not in CoV. While the S2’ cleavage site of COV-2 is similar to that of CoV.

Endosomal cysteine proteases cathepsin B and L (CatB/L) can also process S protein, and inhibition of both proteases is required for complete blockade of viral entry.

Proteolytic processing of the Spike protein can be studied in human cells (like 293T cells).

**Camostat mesylate** is active against TMPRSS2 and partially blocks SARS-2-S-driven entry into Caco-2 and Vero-TMPRSS2 cells.

Full inhibition is attained with camostat mesylate and **E-64d**, an inhibitor of CatB/L.

**Camostat**

*Used for Chronic Pancreatitis*

**Nafomostat**

**E-64 D**

*Cathepsin inhibitor*

*Being tested in brain injury*
Viral 3CL protease (Mpro) and Inhibitors
HIV Protease Inhibitors as CoV-2 Mpro inhibitors

The large viral polypeptide is proteolytically processed at 11 sites to many functional proteins by a viral protease called 3C-like protease (3CL protease), also called main protease (Mpro)

Mpro is an attractive target - essential in the viral life cycle, with no human homologs

Protease inhibitors have been successful in treating HIV

Ritonavir/Lopinavir has not been effective in COVID-19 trials

Nelfinavir (Torii pharmaceutical Co. Ltd) inhibits SARS CoV and SARS CoV-2 virus replication in cells. Does not inhibit viral cell entry

The EC90 of nelfinavir was 1.76 μM, the lowest of nine HIV-1 protease inhibitors

The trough and peak serum concentrations of nelfinavir are 3-6 times higher than the EC50

Yamamoto et al. bioRxiv doi: https://doi.org/10.1101/2020.04.06.026476 April 2020
Other Viral 3CL Protease (Mpro) Inhibitors

**Ebselen** found after screening 10,000 compounds. Active in cell culture viral infectivity assays

Peptidomimetic α- *ketoamides* inhibit Mpro and also have broad spectrum RNA virus activity [https://dx.doi.org/10.1021/acs.jmedchem.9b01828](https://dx.doi.org/10.1021/acs.jmedchem.9b01828)

X-ray structures of the SARS-CoV-2 Mpro and its complex with an α-ketoamide are published
Zhang et al., Science 368, 409–412 (2020)
Antacid- Famotidine (Pepcid) Mpro inhibitor

Histamine-2 receptor antagonists, including famotidine, inhibits HIV replication \textit{in vitro}, whereas the histamine-1 receptor antagonists (diphenhydramine and cyproheptadine) had no effect (Bourinbaiar and Fruhstorfer, 1990s).

**Famotidine** inhibits Mpro

It is one of the highest-ranked matches for drugs that could potentially target Mpro.

Promising results were noted in a NY study

Famotidine was significantly associated with reduced risk of death or intubation compared to the control arm

Freedberg, DE et al.
https://doi.org/10.1101/2020.05.01.20086694

A controlled clinical trial is underway

Oral and IV available. Already used in China

45-50% absorbed orally
Repurposed Veterinary Drugs – Mpro Inhibitor

**GC376** - Broad spectrum Coronavirus and Norovirus inhibitor being developed by Anivive for feline coronavirus peritonitis

An Mpro inhibitor with a high therapeutic index > 200

Recommended dosage of **GC376** for cats with FIP is 4 mg/kg, SC, once a day, for 12 weeks. Cats with neurological FIP may require a progressively higher dosage of 5-10 mg/kg

Human clinical trials being initiated

Am. Pharma Rev. May 28, 2020
Kim Y, J Virology May 2015 Volume 89
RNA Polymerase Inhibitors

Ribavirin – First RNA polymerase inhibitor. Approved for polio and other virus infections but has notable adverse events

Guanosine analog, converted to triphosphate. Mimics purines in RNA synthesis

Some general properties of viral RNA polymerase inhibitors:

All are nucleosides

Chemical modifications may be needed to gain cell entry

Once intracellular, they are phosphorylated and act as substrate for viral RNA polymerase

Result: Incorrect RNA synthesis – non-viable mutants, chain termination
RNA Polymerase Inhibitors

**Favipiravir** – Approved for Flu and Ebola in Japan (Avigan), Approved in China for COVID-19, Phase 3 trial in Japan, US. Oral and IV formulations. Teratogenic, embryotoxic

**Remdesivir** - EUA approval - IV only. Cannot be used in renal insufficiency
Crosses the cell membrane, converted to an alanine intermediate, a phosphoramidase – before conversion to a nucleoside triphosphate. Mimics Adenosine

**BCX4430** - an Adenosine nucleoside analog.

All are converted to a nucleoside triphosphate intracellularly. After pyrophosphate cleavage, they mimic nucleosides and are incorporation as nucleotide-monophosphate into nascent viral RNA
Result: Lethal mutations. Strand extension is blocked, Non-viable virus


In-vitro-to-in-vivo extrapolation of EC50’s in cell culture assumes similar in vivo cellular drug conversion and accumulation as those seen in in vitro experiments
**RNA Polymerase Inhibitor - EIDD-2801**

**EIDD-2801** – iso-propylester prodrug of β-d-N^4^-hydroxycytidine (EIDD-1931)

Improved oral bioavailability

Prodrug converted intracellularly to the active triphosphate.

Exists as Cytidine and Uridine - Tautomer. RNA polymerase reads it as Uridine instead of Cytidine - mismatches with Adenosine instead of inserting a Guanosine. Massive number of mutations that makes the virus non-functional

Broad-spectrum antiviral against various unrelated RNA viruses including influenza, Ebola, CoV, and Venezuelan equine encephalitis virus (VEEV)

EIDD-1931 is highly active against SARS-CoV-2, MERS-CoV, and SARS-CoV in primary Human airway epithelial cell cultures infected with clinical isolate SARS-CoV-2

**Remdesivir resistance mutations increase susceptibility to EIDD-1931**

EIDD-2801 has a low resistance rate

Good safety – not mutagenic or teratogenic

Available IV and Oral formulations

Nitazoxanide Repurposed Antiparasitic
Dual mechanism: N Protein, Host Cytokine Response

Nitazoxanide used orally for decades as an antiparasitic in adults and children
Nitazoxanide is a salicylamide prodrug of tizoxanide
It belongs to a class of drugs called thiazolides

Nitazoxanide inhibits replication of a broad range of other RNA and DNA viruses in culture assays, including RSV, rotavirus, norovirus, hepatitis B, hepatitis C, dengue, yellow fever, Japanese encephalitis virus, and HIV

Successful in a Phase 2b/3 clinical influenza trial (Lancet Infectious Diseases) – Oral nitazoxanide, reduced clinical symptom duration and viral shedding in patients with laboratory-confirmed influenza

Nitazoxanide inhibits SARS-CoV - EC50 value of less than 0.1 μM in Vero E6 cells. Nitazoxanide inhibits expression of the viral N protein

In addition, also inhibit the production of pro-inflammatory cytokines. TNF-a, IL-2, IL-4, I-5, IL-6, IL-8 and IL-10 from PBMCs inhibited in vitro

Rossignol J-F. https://doi.org/10.1016/j.jiph.2016.04.001
Screening Antivirals In Vitro

Primary screens: Vero E6 cells

Secondary Screens: Primary lung epithelial cells

Lung organoid model using human pluripotent stem cells (hPSCs) that could be adapted for drug screens. The lung organoids, particularly alveolar type II cells, express ACE2 and are permissive to SARS-CoV-2 infection.

Transcriptomic analysis following SARS-CoV-2 infection shows a robust induction of chemokines and cytokines with little type I/III interferon signaling, similar to that observed amongst human COVID-19 pulmonary infections. hPSC-derived lung organoids can be used for high throughput screen

Han, Y et al. ttps://www.biorxiv.org/content/10.1101/2020.05.05.079095v1

Non-Anti-Viral Therapeutics: Treating Overactive Host Factors
ARDS in COVID-19
Immune enhancement, Coagulation, Complement activation

SARS-CoV-2 enters alveolar epithelial cells via the ACE2 receptors damaging these cells resulting in:

1) Strong inflammatory response, in some cases a cytokine storm;

2) Damage to endothelial cells of small blood vessel leading to platelet aggregation and leading to **activation of coagulation pathway**. **Blood clots** are found in the small vessels of all organs, not only the lung but also the heart, the liver, and the kidneys.

3) Tissue damage and virus mediated proteases can **also activate the complement pathway**.

McGonagle et al. Lancet Rheumatol 2020 Published Online, May 7, 2020 https://doi.org/10.1016/S2665-9913(20)30121-1
Mediators of the Cytokine Storm Associated with COVID-19

Cytokine storm results from the enhanced immune response in severe COVID-19

Lymphocytopenia is an important indicator for diagnosis and severity in COVID-19 patients

Release of proinflammatory cytokines include: Interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), followed by IL-12 (11), IL-1β, and IL-8, IL-2, IL-7, IL-10, granulocyte-colony stimulating factor, IFN-γ, monocyte chemoattractant protein, macrophage inflammatory protein 1α.

Higher plasma levels of many of these cytokines are found in COVID-19 ICU patients - predicting severity and bad prognosis

Therapeutics repurposed for COVID-19

Enhanced immune response:

Drugs used to treat RA and other autoimmune diseases

Drugs developed to treat cytokine storm seen in CAR-T and stem cell transplant patients
Immunomodulators – Antibody to IL-6R

IL-6 likely plays a key role in the cytokine storm - blocking IL-6 could be a potentially therapeutic for severe COVID-19

IL-6 binds to soluble IL-6 receptor to form a complex, which then binds to gp130 on the cell membrane to complete signal transduction and plays a proinflammatory role

In observational trials, recombinant humanized anti-human IL-6 receptor monoclonal antibody, Tocilizumab (Actemra) effectively improve clinical symptoms of severe COVID-19 patients
Randomized controlled trials currently underway.

Xu, X, et al., PNAS 117: 10970–10975, May 19, 2020

Other IL-6 inhibitors include Sarilumab (Kevzara) and Olokizumab

Observational trials have tested TNFα inhibitors. Humira was not effective

Anakinra is a recombinant human IL-1 receptor antagonist. It is approved to treat rheumatoid arthritis and has shown promise in observational COVID-19 studies
Type 1 Interferons

Clinical studies of type I interferons, including interferon alfa and interferon beta, in the treatment of SARS-CoV has had variable results

Benefit was noted if treatment was started in a study where interferon beta-1b was used with HIV protease inhibitors and ribavirin.

Shalhoub S. Lancet June 8, 2020 https://doi.org/10.1016/

Baricitinib (Olumiant)- Janus Kinase inhibitor

Baricitinib is approved for second line treatment of rheumatoid arthritis in adults

Blocks Janus kinase, subtypes JAK1 and JAK2

Currently in a NIH trial in combination with Remdesivir

Concern: Could affect interferon production
**Immunomodulator: BTK Inhibitor - Ibrutinib**

**Ibrutinib** irreversible inhibitor of **Bruton's tyrosine kinase (BTK)** in B cells, used to treat B cell cancers, is an orally bioavailable small molecule.

Potent covalent inhibitor of BTK (IC50 0.5 nM) and a potent reversible inhibitor of HCK (IC50 49 nM).

![Ibrutinib](image)

Patients with chronic lymphocytic leukemia (CLL), WM, and cGVHD treated with ibrutinib showed marked reductions in proinflammatory and chemoattractant cytokines that are the same as seen in SARS-CoV-1 and SARS-CoV-2 patients.

BTK and its upstream activator HCK are involved in TLR-mediated signaling - in response to viruses/ bacteria.

The potential for ibrutinib to abrogate lung injury and death was also demonstrated in mouse Influenza.

Phase 2 COVID-19 trial has shown good improvement in patients.

Immunomodulator: Newer BTK inhibitors

Ibrutinib and Acalabrutinib are covalent inhibitors of a nucleophilic cysteine at position 481 - limited selectivity as they react with other kinases that bear a cysteine at the same position and also reversibly inhibit additional kinases, resulting in serious side effects.

Remibrutinib is a more selective BTK inhibitor Remibrutinib - currently in phase 2 clinical trials for treatment of chronic urticaria and Sjögren’s syndrome.

Gabison, R et al. https://dx.doi.org/10.1021/acs.jmedchem.0c00597
Inhibiting Thrombotic Complications - Coagulation

In addition to the bilateral diffuse alveolar edema, hyaline membranes, and proliferation of pneumocytes and fibroblasts, thrombi are frequently seen in small pulmonary arteries, most likely secondary to endothelial damage in all vessels of all organs.

Severe thrombocytopenia: 57.7% and 3-4 fold increase in D-Dimer 59.6% - Predictors of high mortality following multi-organ failure.

Parallel increase in inflammation markers – CRP

Some differences from Classical DIC (Gram-negative sepsis) in that PTT (Partial Thromboplastin Time) elevation is less than PT (Prothrombin Time) elevation.
Coagulation Pathways

Heparin: Inhibits several Factors in Extrinsic and intrinsic pathways

Prothrombin Time Higher than PTT in COVID-19

Increased in COVID-19

Partial Thromboplastin Time

Rivaroxaban
Apixaban
Edoxaban

Dabigatran etixilate

Fibrinogen Monomers
Fibrinogen Polymers

Insoluble Fibrin

Plasminogen

α-2-ANTIPLASMIN

D-Dimer

Fragment E
Fragment D
Fragment Y
Fragment X

TAFI
(FDP)

α-2-ANTIPLASMIN

u-PA

PAI-1

t-PA

activation

inhibition

Intrinsic Pathway
Extrinsic Pathway

Anti-Coagulants in COVID-19

Low MW heparin and unfractionated heparin are used to treat severe COVID-19 and being tested in trials.

Direct Oral Anticoagulants (DOAC) therapy with edoxaban, apixaban, rivaroxaban, or dabigatran are being tested. The comparator is low molecular weight heparin (LMWH) alone or with warfarin. Potentially more effective. Safety is a concern.

Thrombin inhibition:
Glycosaminoglycan enhancer (odiparcil [SB-424323]), indirectly enhances thrombin inhibition via heparin cofactor II.

Serine protease inhibitors, Nafamosat (also blocks TMPSS2), can block coagulation.

Blood product transfusion is used in clinical bleeding. Patients who are not bleeding do not have improvement on blood product transfusion. Replacement could enhance thrombosis.
Dysregulation of Complement Can Go Hand-in-Hand with Thrombosis and Inflammation in COVID-19

Activated complement plays a crucial role in the phagocytosis of pathogens and cellular debris by C3b or C5b-mediated opsonization. The complement system is activated via:
- the classical pathway (CP),
- the lectin pathway (LP), or
- the alternative pathway (AP).

Platelets have sensors known as pathogen pattern recognition receptors for infectious agents or immunoglobulin Fc receptors and complement receptors.

The N protein of SARS-CoV2 bind and potentiate the Lectin Pathway.

Mechanism shared with MERS-CoV and SARS-CoV.
Proposed Mechanism of Complement Activation in COVID-19

MBLs (Mannan and N-acetylglucosamine Binding Lectins, also called ficolins) are in the blood, recognize and bind to residues on microorganisms or injured host cells, targeting MBL-Associated Serine Protease-2 (MASP-2), leading to their activation.

CoV2 N Protein (nucleocapsid protein) binds MBL and potentiates the activation of MASP-2 - leads to the uncontrolled activation of complement cascade

Complement cascade is characterized by enhanced C4 cleavage. Complement deposition and MASP-2 deposits are seen in lung tissue of COVID-19 patients

Further evidence of MASP-2’s role:
MBL binds to SARS-CoV-infected cells in a dose-dependent, calcium-dependent, and mannan-inhibitable manner in vitro, enhancing the deposition of complement C4 on SARS-CoV.

SARS-CoV N protein shown to regulate MASP-2 dimerization, activation and cleavage. Mutant protein that does not dimerize cannot activate MASP-2

Gao T et al. doi: https://doi.org/10.1101/2020.03.29.20041962
Complement Factor Activation Cascade and Inhibitors

Narsoplimab: Monoclonal IgG to MASP-2

Camostat
Nafamostat
Also inhibits TMPPS2

CoV2 N Protein → MASP-2

Commercially available reagents for each pathway and several factors can be used to screen inhibitors
Humanized mice are available if in vivo tests are needed
Challenges in COVID-19 Clinical Trials

Different treatments may be needed depending on the stage of COVID-19 - Be sure of the stage of the disease being treated in the trial

Both study arms will need to be matched for other drugs:
- ACE inhibitors or ARB’s,
- Diabetes treatments
- Balance heparins/L.M. wt. heparins, anticoagulants
- Antibiotics

Patients may have taken hydroxychloroquine, azithromycin (could have immunomodulatory activity)

Drug-drug interactions

More than one anti-viral may be needed to decrease resistance development

Is it possible for the patient to take an oral drug?

Very difficult circumstances – rigorous management may not be possible
Thank you for listening!

Questions?