QUINTO PANEL VIRTUAL COVID-19:
Estrategias de tratamiento, vacunas y antivirales

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**Drug Discovery and Development Process**

**Exploratory Early Discovery**
- Lead Identification
- Lead Optimization
- Preclinical Transition

**Lead Identification**
- Assay Development
- Screening
- Medicinal Chemistry

**Lead Optimization**
- SAR – Improve potency
- In vivo testing
- Pharmacokinetics
- Metabolism
- Pre-Tox

**Preclinical Transition**
- Complete Tox
- Safety studies
- Process Chemistry
- Scale-up
- Formulation
- IND

**Basic Sciences:**
- Target Identification and Validation
Drug Discovery and Development Process

Exploratory Early Discovery
- Lead Identification
- Lead Optimization
- Preclinical Transition

Phase I
- 20-80 volunteers
- Safety and Dosage
- Several months
- Possible side effects
- Early efficacy
- ~70% to next phase

Phase II
- Up to 100’s volunteers
- Efficacy and side effects
- Several months – 2 years
- Additional safety data
- Help design Phase III
- ~33% to next phase

Phase III
- 300-3,000 volunteers
- Treatment Benefit
- Safety Data/rare side effects
- 1– 4 years
- ~25-30% to next phase

Registration
- Drug Approved
- Post-market safety monitoring
Clinical Trial Standard:
Randomized Double-blind Placebo-controlled (multi-center)

Diseased population

Representative Group:
Inclusion/Exclusion criteria
- Age
- Stage of disease
- Laboratory results
- Other
Clinical Trial Standard:
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Diseased population

Standard treatment + Placebo

Randomize:
Blind to
- Patient
- Physician

Standard treatment + Drug
Clinical Trial Standard:
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**Representative Group:**
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**Diseased population**

**Randomize:**
Blind to
- Patient
- Physician

**Outcome:**
Statistical analysis on whether drug achieves expected outcome significantly compared with placebo

Standard treatment + **Placebo**
Standard treatment + **Drug**
Drug Discovery and Development Process

FDA timeline

- 100’s to 1000’s of drug candidates
- 9.5 to 13 years for only ONE approved drug
- HOW CAN WE REDUCE THE TIMELINE?
FASTEST SOLUTION: DRUG REPURPOSING

Investigate whether an already approved drug can be used to treat COVID-19:

- Already tested in humans
- Detailed information is available on
  - pharmacology
  - formulation
  - potential toxicity
- Reduces time frame
- Decreases costs
- Improves success rates

Repurposed candidate therapies can be:

- Ready for clinical trials quickly
- Quickly reviewed by the Food and Drug Administration
- If approved, rapidly integrated into health care.

Also consider potential drugs in development for SARS or MERS
FASTEST SOLUTION: DRUG REPURPOSING


795 Studies found for: COVID-19
Also searched for SARS-CoV-2. See Search Details

Your search included: COVID-19
Learn more about clinical studies related to COVID-19:
- ClinicalTrials.gov: Federally-funded clinical trials
- WHO Trial Registry Network: COVID-19 trials
- CDC: Information for Clinicians on Therapeutic Trials

Showing: 1-100 of 795 studies 100 studies per page
We already know a lot...

...There are pictures:
This transmission electron microscope image of SARS-CoV-2 isolated from a patient in the U.S., emerging from the surface of cells cultured in the lab.

Credit: NIAID-RML
We already know a lot...

...the virus life cycle

The life cycle of SARS-CoV
We already know a lot...

Four human coronaviruses produce symptoms that are generally mild:
- HCoV-OC43, HCoV-HKU1, HCoV-229E, HCoV-NL63

...experience with previous infections

Three human coronaviruses produce symptoms that are potentially severe:
- Severe acute respiratory syndrome coronavirus (SARS-CoV)
  Year: 2002  confirmed cases: 8096  Deaths: 774

- Middle East respiratory syndrome-related coronavirus (MERS-CoV)
  Year: 2012  confirmed cases: 2494  Deaths: 858

- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
  Year: 2020  confirmed cases: >2,500,000  Deaths: >170,000

...Drugs available against other viruses

- HIV virus
- Hepatitis C virus
- Influenza virus
- Herpes virus
Strategy 1: Block virus entry

Entry at plasma membrane

Antibodies to the virus
- Our own immune system
- Convalescent plasma
- Hyperimmune therapy
  - Pooled concentrated plasma
- Monoclonal antibodies
Strategy 1: Block virus entry

Entry at plasma membrane

**TMPRSS2:** Cleaves Spike Protein in S1 and S2
- **Camostat:** Blocks TMPRSS2
- Entry of virus blocked

*Approved in Japan for Pancreatitis*
Strategy 1: Block virus entry

rhACE2: Previously tested in clinical trials

Deficiency of ACE2 implicated in acute respiratory distress syndrome

Infusion of rhACE2 hypothesized to address this

Small clinical trial:
- rhACE2 appears safe
- rhACE2 catalyzes hydrolysis of AT-II to angiotensin (1-7)
- No significant clinical improvements

Recombinant human angiotensin converting enzyme 2 (rhACE2):

- Binds to Spike Protein
- Traps virus
- Entry of virus blocked
Strategy 1: Block virus entry

Interactions between SARS-CoV-2-RBD and ACE2

Arbidol
Approved in Russia for influenza

*Science* 27 Mar 2020:
Vol. 367, Issue 6485, pp. 1444-1448
Strategy 2: Inhibit replication/transcription

**RdRP**: RNA dependent RNA Polymerase

If inhibited:
- Inhibition of replication of RNA
- Inhibition of transcription of RNA
- Inhibition of formation of proteins
- Inhibition of viral replication
Strategy 2: Inhibit replication/transcription

**Remdesivir**
- No approval
- Developed for Ebola
- Active in SARS and MERS

**Favipiravir**
- Approved in Japan
- Treatment of influenza

**Ribavirin**
- Approved in US/worldwide
- In combination with interferon for treatment of hepatitis C
Strategy 2: Inhibit replication/transcription

RNA strand

Template RNA strand

A
U
G
C
A
U
G
C
Strategy 2: Inhibit replication/transcription

Template RNA strand

A
U
G
C
A
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Template RNA strand
Strategy 2: Inhibit replication/transcription

Remdesivir
\[ \text{ACTIVATION} \]
Activated Remdesivir

Faviparivir
\[ \text{ACTIVATION} \]

Ribavirin
\[ \text{ACTIVATION} \]
Strategy 2: Inhibit replication/transcription

Template RNA strand

Activated Remdesivir
Strategy 2: Inhibit replication/transcription

Activated Remdesivir
Strategy 2: Inhibit replication/transcription

Template RNA strand

Activated Remdesivir
Strategy 2: Inhibit replication/transcription

[Diagram showing RNA strand and activated Remdesivir]
Strategy 2: Inhibit replication/transcription

Template RNA strand

BLOCKED
Stop Viral replication

Activated Remdesivir
Strategy 2: Inhibit replication/transcription

Fig. 4 Incorporation model of remdesivir in COVID-19 virus nsp12.

Yan Gao et al. Science 2020;science.abb7498
Strategy 3: Block Protease Activity

Cleaved by Papain Like Protease (PL$^{PRO}$)
Cleaved by 3C-like protease (3-CL$^{PRO}$) = Main protease (M$^{PRO}$)

Strategy: Inhibit a Protease
- Polyprotein does not get cleaved
- Relevant proteins do not get formed
- Virus can not replicate
Strategy 3: Block Protease Activity

APPROVED HIV-DRUGS CURRENTLY IN CLINICAL TRIALS FOR COVID-19

HIV-Protease Inhibitor

Lopinavir-Ritonavir

Darunavir-Cobicistat

Use of these protease inhibitors debatable:
- 2019-nCoV proteases PLA<sub>2</sub> and M<sub>PR</sub> are cysteine proteases
- HIV protease is an aspartic protease
- HIV protease inhibitors optimized to fit in the catalytic site of HIV protease dimer
- Potency remains a concern
Strategy 3: Block Protease Activity

13a: Developed to inhibit $M^{\text{PRO}}$ of SARS coronavirus – Not brought to clinic
13b: Modified to inhibit $M^{\text{PRO}}$ of SARS-Cov-2

Need to perform toxicity studies
Strategy 4: Block Inflammatory Response

- Hospitalized SARS-CoV-2 patients – can enter severe phase of the disease
- Hyper-inflammation - immune system overactive - cytokine storm
- Increased levels of interferons α and β and **IL-6**

**Actemra® (tocilizumab) approved in 2010**
Blocks Interleukin-6 (**IL-6**) receptor
- Arthritic diseases
- Cytokine release syndrome

**Kevzara® (sarilumab) approved in 2017**
Blocks Interleukin-6 (**IL-6**) receptor
- Moderately to severely active rheumatoid arthritis
Strategy 4: Block Inflammatory Response

- Both inhibit Janus kinase (JAK1/JAK2)
  - Reduces cytokine storm
- Also inhibit enzymes related to viral entry
- **Concern:** Inhibit response of immune system to virus

**FDA approved**
- 2018
  - Moderate to severe arthritis

**FDA approved**
- 2011
  - myelofibrosis
Chloroquine and Hydroxychloroquine

**Hypothesized mechanisms:**
- Raise endosomal pH slightly, which prevents fusion of virus to enter the cell.
- Block enzymes involved in the fusion between the virus and lung cells
- Block viral replication process
- Reduce inflammation

**Issues:**
- Side effects – cardiotoxicity
- Availability
- Efficacy not proven

**FDA: Emergency use authorization for COVID-19 (March 28, 2020)**

Chloroquine
Approved as anti-malarial drug

Hydroxychloroquine
Approved for treatment of
- systemic lupus erythematosus
- rheumatoid arthritis
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WHO global megatrial – SOLIDARITY (March 18, 2020)

Four Drugs
• Remdesivir
• Chloroquine and hydroxychloroquine
• Lopinavir – ritonavir
• Lopinavir - ritonavir plus interferon-beta

Patient with confirmed COVID-19
• Physician enters patient’s data into a WHO website, including any underlying condition, such as diabetes or HIV infection.
• Patient signs informed consent form - scanned and sent to WHO electronically
• Physician states which drugs are available at hospital
• Website randomizes the patient to one of the drugs available or to the local standard care for COVID-19.

Obtained data (>100 countries)
• Physician will record the day the patient left the hospital or died
• Duration of the hospital stay
• Whether the patient required oxygen or ventilation

Adaptive – Other drugs can be included