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THE RACE TO FIND DRUGS TO FIGHT COVID-19

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WHAT IS THE CURRENT PANDEMIC SITUATION?

As of 26 May there were more than 5.5 million cases of severe acute respiratory syndrome coronavirus 2 disease (COVID-19) recorded across 188 countries/territories, leading to more than 347,800 deaths. Over 2.2 million people have been documented to have recovered. As the cases and death toll continue to rise so has the pressure to both prevent and treat the condition. The scientific community is working at an unprecedented pace to develop vaccines and gather evidence for treatments that can flatten the curve and improve outcomes for those most vulnerable.

WHAT WOULD BE INVOLVED IN A TYPICAL COVID-19 DRUG DISCOVERY PROCESS?

In short, scientists need to develop a new prescription therapeutic drug or a new preventative vaccine with an aim to reduce the impact of the disease. Typically, once a lead compound has been identified, there is a period of laboratory research on microorganisms and animals, ideally leading to clinical trials in humans. This process can be a lengthy, taking more than a decade to reach a drug/vaccine that reaches regulatory approval for use.

There are typically four phases of trials; Phase I – determines safety and dosing in healthy volunteers; Phase II – establishes how effective and safe the drug may be in a small number of people with COVID-19; Phase III – seeks to establish efficacy and safety in a large number of people with COVID-19; Phase IV – occurs post-approval and involves reporting by the manufacturer of any adverse events related to the drug while in use amongst the general population.

In the past few years there have been major initiatives to stimulate and streamline vaccine and antiviral drug development through partnerships between government organizations and the industry to expedite public access to life-saving preventative and treatment options.

HOW CLOSELY IS THE DRUG DISCOVERY PROCESS BEING FOLLOWED IN THE CASE OF COVID-19?

Unprecedented times warrant unconventional solutions. The race to find a solution for COVID-19 is anything but typical. In fact, a COVID-19 Clinical Research Coalition has been formed, which has the following goals:

1) Facilitate rapid reviews of clinical trial proposals.

2) Fast-track approvals for the lead therapeutic compounds.

3) Ensure standardized and rapid analysis of efficacy and safety data.

4) Promote sharing of clinical trial outcomes before publication. The coalition is synergizing with existing initiatives such as the COVID-19 Therapeutics Accelerator (led by the Bill and Melinda Gates Foundation), the Coalition for Epidemic Preparedness Innovations (CEPI) and the SARS-CoV-2 Diagnostic Pipeline to facilitate researchers to identify, assess, develop and scale up potential drug treatments.

In March 2020, several US government departments and organizations pooled resources with industry and universities to expedite drug development of COVID-19 through computer-assisted research by accessing supercomputers from IBM combined with cloud computing resources from HP, Amazon, Microsoft and Google. This High Performance Computing Consortium has been applying these resources to screen thousands of chemical compounds in the hope of identifying some potential candidates for the drug/vaccine discovery process.

Some high-profile clinical trials that have been in the media, including the Solidarity trial (launched by the WHO and partners) and European Discovery trials. These studies, conducted in hospital on people suffering from severe COVID-19 infections, are applying adaptive design principles. This is to allow modification of the trials early insights to influence trial parameters and optimize use of trial resources and get the best possible results. While randomized clinical trials (considered to be the gold-standard) normally take years to design and conduct, the Solidarity trial design enabled an impressive 80% reduction in the time taken despite the complexity of 100+ countries participating.

WHAT ARE THE MOST PROMISING THERAPEUTIC STRATEGIES ON THE PATH TO A SOLUTION FOR COVID-19?

There are four major therapeutic approaches to identifying compounds worthy of inserting into the current drug discovery/trial process:

1) Drug repositioning (i.e. repurposing) – investigating existing drugs for new therapeutic application to accelerate the identification of safe and effective COVID-19 treatments. These treatments include previously developed drugs for SARS, MERS, HIV/AIDS and malaria.

2) Early stage drug candidates – drugs involved in, or expected to enter, any one of 36 Phase II trials as of April 2020.

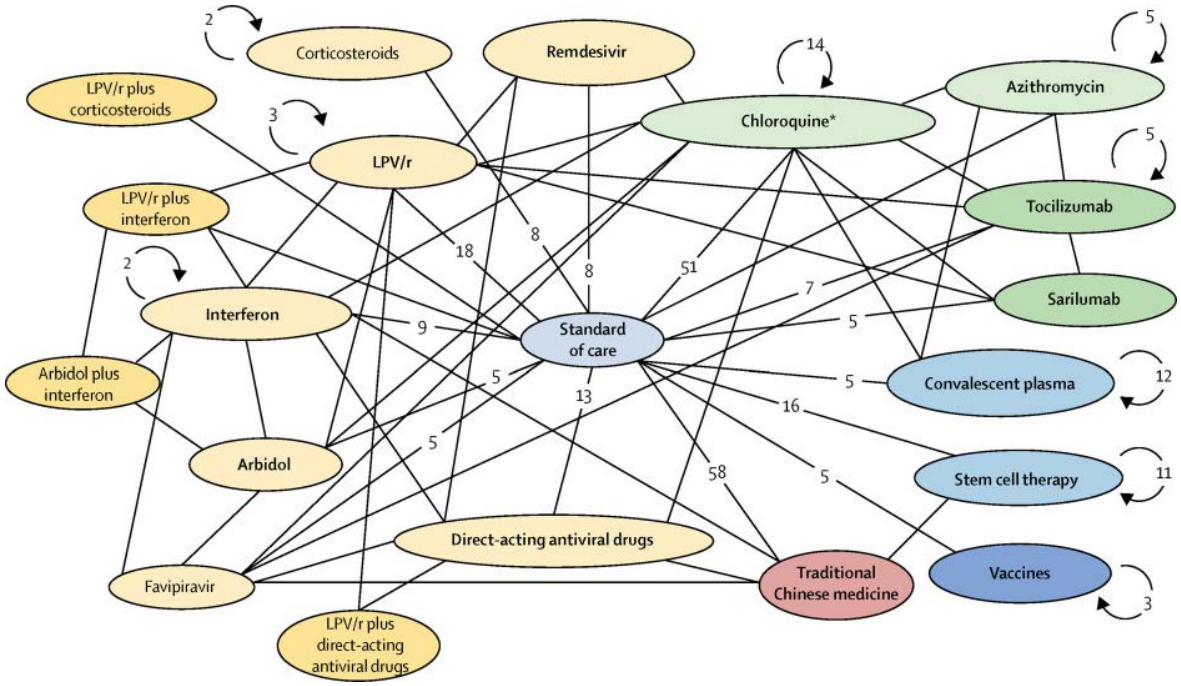
3) Preclinical research – a strategy that represents in vitro or in vivo laboratory studies to determine the effective dose and safety in animals occurring at the beginning stage for development of a vaccine or therapy. Unfortunately, this process is likely to take 1–2 years for COVID-19 according to many reports from early 2020.

4) Inhibitors – once the COVID-19 genome was released by Chinese researchers, the main enzyme (protease) that enables the host cell to reproduce the RNA of the virus was identified in March 2020. This discovery will serve as a key target of post-infection therapies.

ANY PROMISING COVID-19 THERAPIES SO FAR?

Potential therapies in preclinical or early stage clinical research span across many different therapeutic categories. An estimate of the number of candidates in each category are indicated in the table below and include 249 candidates for post-infection treatment (as of late April):

Category	Candidates
Antibodies (i.e. COVID-19 IG plasma derived)	58
Antivirals (i.e. remdesivir)	22
Cell-based compounds (i.e. placenta-based cell therapy)	14
RNA-based compounds (i.e. rintatolimod)	5
Scanning compounds to be repurposed (i.e. repurposing existing and new therapies)	15
Other specific categories: anti-inflammatory (i.e. hydroxychloroquine), antimalarial (i.e. chloroquine), interferon, protein-based, antibiotics, and receptor-modulating compounds	66
Miscellaneous other (i.e. extracorporeal blood purification devices)	69



The dashboard schematic has circles (nodes) showing interventions and or intervention categories. The lines between the circles are comparisons of the interventions in clinical trials. The numbers on the lines indicate the number of clinical trials making that specific comparison. Finally the circular arrows with numbers are referring to non-comparative trials that include a given intervention. Reproduced under a Creative Commons Attribution 4.0 International license, from Thorlund K, et al. Lancet Digital Health 2020;2:E286–7.

On 24 April 2020, a real-time dashboard of clinical trials for COVID-19 was published (as seen below) and demonstrates the complex web of candidates being researched and how they are being compared to one another. For example, a recent study published on 20 May explores the repurposing several disease-modifying anti-rheumatic drugs (DMARDS), including hydroxychloroquine, in targeting the 'cytokine-storm' in COVID-19 patients. In fact, as of 26 May 2020, over 1100 clinical trials have been registered at the various international and national clinical trial registry sites by drug companies, biotechnology firms, universities research teams and other health organizations.

WHAT IS THE BOTTOM LINE?

As with many aspects of life, COVID-19 has necessitated a tremendous amount of coordination and innovation amongst government, large and small organizations, researchers and clinicians to focus resources and energy towards finding both preventative and treatment solutions at a mind-boggling pace. Ideally, the unimaginable amount of data from the drug trials would benefit from being centralized and analyzed in real-time to truly assist researchers, policy makers and, ultimately, clinicians in making evidenced-based decisions. In addition, as early stage clinical trials will focus on testing drug therapies on the most seriously ill and where treatment regimens are most likely to fail, later trials may provide drugs earlier in the course of disease where antiviral therapies are most likely to succeed, e.g. Tamiflu for influenza. As we gradually resurface after a prolonged lockdown, you can rest assured that our scientific community continues to work feverishly towards proven solutions for COVID-19. In the meantime, you can't go wrong by continuing to practice social distancing, frequent handwashing and getting adequate rest if you feel ill!