PANDEMIC
Supermind Activation

Therapies & Vaccines

MilliporeSigma

MIT CENTER FOR COLLECTIVE INTELLIGENCE

community biotechnology

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For effective therapy and vaccine discovery and development, it is critical to understand the molecular basis of COVID-19 pathogenesis in terms of mechanisms of viral entry, replication, and host responses. The Supermind proposed approaches in computer-aided rational design and development of safe and effective broad-spectrum antivirals or repurposing known drugs with antiviral activity to combat the next pandemic, and development of antivirals to families of viruses that jump species. The Supermind also focused on various aspects of vaccine development including utilizing adjuvants that lower vaccine doses, inhalation-based vaccines, and approaches to fast track vaccine safety and efficacy evaluation and new ways to conduct clinical trials. Finally, the Supermind proposed ways to create more resilient supply chains for the various reagents and materials critical for manufacturing therapeutics and vaccines.

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Advances in patient treatment

Since March 2020, physicians' tools have improved considerably with significant advances in treating COVID-19 patients with multiple treatment regimens. These include:

- The antiviral drug Remdesivir, which has become a standard of care, and other repurposed antiviral drugs such as Kaletra (liponavir/ritonavir) and Tamiflu;
- Dexamethasone, a common corticosteroid used in autoimmune conditions and allergic reactions;
- Transfusion of convalescent plasma from recovered patients with high antibody content to treat active coronavirus infection;
- Acterma (Tocilizumab), a drug approved for rheumatoid arthritis which works by blocking interleukin-6 (IL-6), a protein involved in causing overactive immune system that could result in a cytokine storm, a potentially fatal problem where the immune system malfunctions and inflammation goes out of control;
- Monoclonal antibodies generated against portions of spike proteins, which are currently in clinical trials to see if they could provide short-term protection (until vaccines become available) from SARS-CoV-2 by binding directly to portions of the virus that are used to attach and enter host cells, preventing them from initiating the infection cycle.

Antivirals to families of viruses that jump species

Viruses like parvoviruses, coronaviruses, influenza viruses, parainfluenza viruses and arthropod transmitted viruses have shown a propensity to jump species, also known as zoonosis. Viruses jump species in two ways: the first is as a spillover event when humans become exposed to zoonotic viruses that they normally do not encounter. Forest clearances and dam building are examples of these events as they affect vector populations. In the second type, viruses mutate or undergo recombination or re-assortment, altering their ability to infect a variety of hosts.

Each of these virus families have points in their replication cycle that are targets for antivirals. For instance, for influenza viruses, the "M2 protein" has been a main target, but resistance has been developed to a class of antiviral medications known as "adamantanes." Combination therapy is required to reduce establishment of resistant mutants, ideally via rational design based on the 3D crystal

viruses that have jumped species, followed by in vitro selection with selected molecules to predict escape mutants and then designing drugs for escape mutants and combination therapy to reduce their establishment.

Search for broad-spectrum antiviral drugs

Unlike broad-spectrum antibiotics such as penicillin, available to treat multiple bacterial infections, we currently do not have any broad-spectrum antivirals to treat respiratory track diseases arising from various viral infections. The Supermind proposed screening novel molecules through computer-created virtual libraries and the libraries of known drug compounds for their ability to inhibit viral replication through either viral protease or polymerase inhibitors or by preventing viral entry into the host cells by specific host enzyme inhibitors. This approach has potential for pan-pathogenic applications to develop broad-spectrum antivirals to combat future pandemics.

Next-generation adjuvants for scalable vaccine production

While the United States Food and Drug Administration (FDA) has traditionally been cautious around the adjuvants used in vaccines, the Supermind proposed utilization of novel, next-generation protein-based adjuvants that may reduce the effective dose of the vaccine by a factor of 10–100, and vastly accelerate manufacturing and scale-up. Additionally, long-term protection may require a more powerful immune response than can be achieved using traditional vectors. The fastest vaccine modalities are nucleic acids (DNA and mRNA) which are traditionally not very immunogenic—but they also make it very easy to co-deliver adjuvants in gene-encoded form.

Designing an inhalation-based vaccine

The Supermind proposed novel methods for improving delivery of a mRNA vaccine for SARS-COV2 to the lungs. Through the design of an efficient and rapid process to generate biomolecule-carrying aerosols with minimum disruption to their internal structure, this concept could provide a method that minimizes waste of important vaccine biomolecules. While other nebulization processes can destroy biomolecules, a major breakthrough for biomolecule delivery could be deliverings directly to the lungs. If successful, it would provide validated technology to produce an optimized mRNA vaccine for SARS-CoV2 for delivery to the lungs. As such, this inhalation-based vaccine technology could offer several advantages including being non-invasive, direct delivery and reduced cost, resulting in improved access to potentially life-saving formulations.

Approaches to fast track vaccine safety and efficacy evaluation and new ways to conduct clinical trials

Vaccine trials often take a long time to uncover serious adverse effects. The Supermind has suggested the application of modern biotechnology tools to detect the adverse events early, to allow vaccine trials to proceed more quickly and safely with tools like modern proteomics.

The safety risks for SARS-CoV-2 vaccines fall under three broad categories: 1) *Acute anaphylaxis* in response to the antigen or the adjuvant; 2) *Vaccine-induced allergies* or *autoimmune diseases*; and 3) *Antibody-dependent enhancement* (ADE) effects that can make future SARS-CoV-2 infections worse.

Acute issues typically occur within minutes of vaccination, and therefore can be rapidly identified in Phase I and Phase II trials. Determining adverse reactions due to allergies and autoimmune disorders are the main reason that trials take a long time. However, it should be possible to detect warning signs of adverse immune response without actually causing them in people. For instance, allergen tests can be carried out before and after vaccination to identify unexpected shifts in allergen profiles. Proteome protein arrays and mass spectrometry methods can be used to detect the development of autoantibodies, allowing potential autoimmune issues to be identified in early vaccine subjects who do not go on to develop any diseases. These data can then be used to build custom assays for early diagnosis of potential side-effects in Phase III trials, eliminating the potentially lengthy follow-up period.

Antibody-dependent Enhancement (ADE) has been observed in Severe Acute Respiratory Syndrome (SARS) and Middle Eastern Respiratory Syndrome (MERS). In cats, for example, a feline coronavirus produces a mild disease, but if re-infected with a variant virus a fatal autoimmune disease can occur which, in part, is associated with ADE (Vennemma et al. 1990; Vennemma et al. 1998; Corapi et al. 1992; Hohdatsu et al. 1998). The Supermind proposed an assay to test ADE by comparing virus entry in three engineered cell types, all based on a common parental cell. These cell types would be designed to have variations of the "FC receptor," a protein found on immune cells, and the "angiotensin-converting enzyme 2" (ACE2) receptor, which is utilized by the SARS-CoV-2 virus to infect cells. By infecting these cell lines and testing their responses, one could identify an ideal vaccine candidate that elicits high neutralizing activity while having no or little infectivity on a cell line expressing FC receptors but not ACE2 receptors.

Accelerating and improving clinical trials

The Supermind also proposed a novel approach to speed up Phase III clinical trials for vaccines, using population-level statistics. One could capitalize on the high prevalence of SARS-CoV-2 in many American communities, such that an effective vaccine would be expected to shift the dynamics of local spread. The vaccinated subjects may develop a strong Immunoglobulin G (IgG) response within a few days, enabling efficacy measurements as early as five weeks into a clinical trial. In contrast, traditional clinical trials rely on measuring the protection conferred to each clinical trial subject, which may require more than one year of observation to obtain sufficient statistical validity.

In a pandemic crisis situation, traditional processes must be accelerated. There is a need to implement new thinking in clinical trial processes—like real-world trials, Bayesian Statistics, etc.—on an emergency basis, in parallel with the traditional Randomized Clinical Trial (RCT) approach to collect data very broadly across candidates, by removing competitive barriers, both geopolitical and institutional.

The Supermind noted pros and cons regarding the ethical dilemma of accelerating vaccine trials by infecting healthy volunteers with SARS-CoV-2 virus following vaccine administration. Instead of vaccinating hundreds to thousands of people and waiting to see if they naturally catch the virus and whether the vaccine would be effective in neutralizing the virus, the idea would be to purposely infect a smaller number of healthy vaccinated volunteers with the virus in a controlled setting to see if a vaccine offered protection (Lambert, 2020). If successful, such studies could fast-track vaccine evaluation, as well as our understanding of COVID-19 immunity. Arguments for and against this "human challenge trial" approach need to be evaluated and a decision would need to be made by regulatory authorities.

Finally, the Supermind noted that communities of color have historically been excluding from pharmaceutical clinical trials. Given the disproportionate impact the virus is having on communities of colors, the clinical trial programs for promising therapies must include adequate representation from those communities to ensure we are developing treatments that are efficacious for those hardest hit by COVID-19 (CDC, 2020).

Creating resilient supply chains

The Supermind noted that the development of therapies and vaccines will only make a significant impact if sufficient manufacturing capacity exists and can be rapidly deployed. For example, when the antiviral drug Remdesivir was approved by the FDA for "emergency use authorization," there were only enough doses to treat 5,000 patients and the pharmaceutical supply chain was not equipped to deliver the drug in sufficient quantity (Gilead, 2020). Similarly, raw materials for the SARS-CoV-2 diagnostic kit manufacturing were also in short supply, resulting in large delays in viral RNA testing.

The push for vaccine development on an accelerated timeline has resulted in multiple modalities being pursued simultaneously, including RNA vaccines and antigen (recombinant) based vaccines, each of which has different manufacturing requirements. The Supermind proposed ways to improve supply chain resiliency by increasing local capacity to produce some of the most commonly used reagents and ingredients in a selected number of regional hubs. The Supermind also proposed the development of "innovation teams" that could be assembled under emergency conditions that could be connected to existing "maker" or grassroots innovation communities to aid in local production. Existing manufacturing capacity could also potentially be re-purposed, if relevant standards could be made available along with operating procedures and expertise. This type of flexible and decentralized manufacturing, along with manufacturing redundancy with multiple factories for critical reagents and ingredients, could significantly increase supply chain resiliency for therapeutic and vaccine deployment.

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