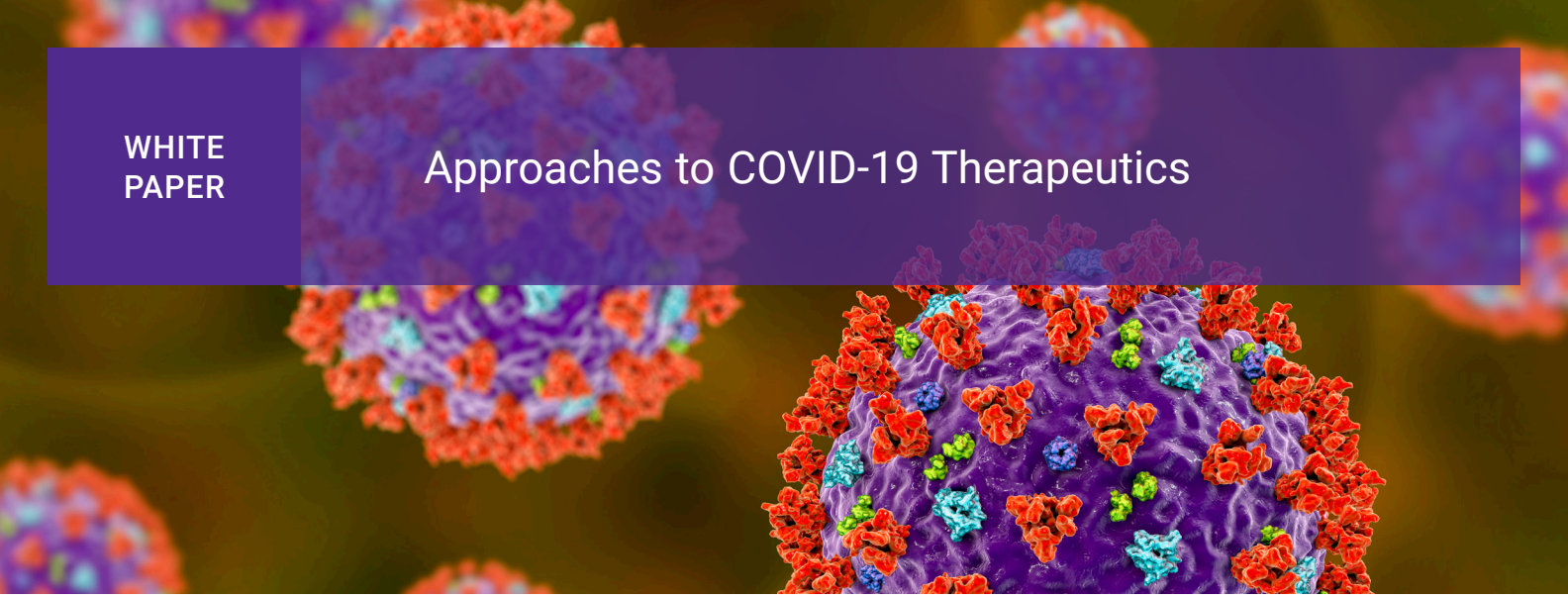
WHITE PAPER

Approaches to COVID-19 Therapeutics



COVID-19 Therapeutics: Demand, Challenges, and the Future

In a recent panel discussion, Dr. Kevin Coombs, Dr. Randal Ketchem, Dr. Mansoor Amiji, and Dr. Seyoum Ayehunie provided insights into why developing effective COVID-19 treatments will play a significant role in controlling the pandemic. They also explored the therapeutic approaches currently being pursued by the research community, and the hurdles scientists face when trying to bring such a treatment to the clinic. This whitepaper highlights the key discussion points addressed during the session.

Is a Therapeutic Really Needed?

The Nobel Prize-winning biologist Joshua Lederberg once warned: "The single biggest threat to man's continued dominance on the planet is the virus." Over the last two years, SARS-CoV-2 has been evidence of this, spreading at an alarming pace between and within countries. In response, scientists were mobilized into action and vaccines were subsequently developed, tested in clinical trials, and approved for use at accelerated speed. To date, three COVID-19 vaccines have been authorized or approved for use in the US[1] and five have been given conditional marketing authorization in the EU.[2]

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While vaccines have significantly transformed the trajectory of the pandemic by reducing an individual's risk of getting and spreading the virus, and preventing serious illness and mortality, other strategies are needed to complement this approach. The rationale is that viruses have evolved a wide variety of immune evasion strategies to survive and thrive which need to be addressed to continue controlling the pandemic.

Vaccines exploit the ability of the human immune system to induce protective neutralizing antibodies against a pathogen, a method which has proved highly effective in controlling infectious diseases such as Polio. However, in the case of SARS-CoV-2, the emergence of new variants raises fears that mutations in the virus could make existing vaccines less effective. "We've already seen a few variants of concern, which is an evolutionary way that viruses respond to being under pressure," explained Dr. Coombs, who is a Professor in Virology at the University of Manitoba. "It's like an arms race – we are developing vaccines and the virus is constantly undergoing mutations. The ones that can escape current therapies take over, so we have to develop new approaches and the challenge continues." The emergence of new variants can have a significant impact on disease severity or lead to enhanced transmission of the virus in the population. A recent example of this is the Omicron variant, which spreads more easily but causes less severe disease than infection with prior variants.[3] While current vaccines proved to be effective at preventing severe disease from Omicron, it brought to light the potential threat that novel variants pose and the need for alternative treatment strategies.

For individuals at high risk, such as those with co-morbidities, the elderly, and healthcare workers, the development of prophylactic treatments could help prevent infection and substantially reduce the burden on healthcare systems. Dr. Ketchem, Senior Vice President of Biotherapeutic Discovery and Molecular Design at Just-Evotec Biologics, explained: "We need to have therapies on hand, such as biologics, that have a long half-life and can load up a person's immune system so that they are pre-protected from the virus."

Another reason for developing therapeutics is that antibody titers can wane over time, and some individuals may not develop a sufficient immune response following vaccination. "One of the advantages of therapeutics is that we can think of other mechanisms that are susceptible as targets for attacking the virus," explained Distinguished Professor Dr. Amiji, who is based at Northeastern University. "We can also ensure that patients who develop the infection have an effective treatment strategy in place, so it doesn't create a burden on the healthcare system." He added that therapeutics can also be used to address the issue of 'long haulers' – people who are living with persistent aftereffects of infection such as CNS and cardiovascular conditions – and not just for treating initial infection.

Therapeutic Strategies Being Explored

Due to the complexity of the disease, researchers are investigating multiple mechanisms to target SARS-CoV-2. There are currently over 300 therapeutics for COVID-19 at various phases of development – either new medicines or repurposed therapeutics that were previously approved to treat other diseases.[4]

Therapeutic options broadly fall into one of three categories:

- Antivirals – designed to inhibit SARS-CoV-2 replication
- Antibodies – designed to bind the virus for inhibition or neutralization
- Protein-protein interaction inhibitors – designed to inhibit essential virus protein interactions with human proteins, thereby inhibiting the viral life cycle.

Alternative approaches, including treating the symptoms of COVID-19 rather than the viral infection itself, are also being explored. So far, Pfizer's Paxlovid and Merck's molnupiravir are the only antiviral COVID-19 drugs authorized for emergency use by the FDA.[5,6]

There are two main targeting strategies that drug developers are adopting for SARS-CoV-2: either developing virus-targeted drugs which target a virus protein, or host-targeted drugs which target a host cell protein . "Different modalities work better for different strategies," noted Dr. Amiji. "For example, neutralizing antibodies might prevent the virus from entering the cell, but drugs like remdesivir and other antivirals are more targeted towards viral replication." He also believes that different strategies will be more effective at specific stages of infection. "To treat initial infection, I think the ideal therapeutic would be a small molecule. But as you get to the clinical stage of disease where patients have a high viral load, a significant number of comorbidities, and are potentially in a life-threatening situation, I think antibodies are the best way we can neutralize the virus before it enters the cell in a rapid and efficient manner."

Whichever approach developers decide to take, they also need to consider the safety of their product before it reaches the patient. "Any approach that targets the virus is much safer," affirmed Dr. Coombs. But he notes that if the virus mutates, then the efficacy of such a virus-targeted therapeutic could be impacted. For this reason, many groups are focusing their efforts on targeting host cellular proteins such as angiotensin-converting enzyme 2 (ACE2), the cellular receptor for SARS-CoV-2. The challenge here is ACE2 is widely expressed in multiple organs including the liver, kidney, and the gut, which raises safety concerns about the risk of off-target effects and the potential impact on the biology of the patient. Dr. Amiji suggested this could be addressed by targeting drug delivery to specific sites of infection; however, this is a concept that still needs to be explored.

An effective strategy to fast-track the drug discovery process is to screen libraries of molecular compounds that already have some degree of safety and activity data for potential use against COVID-19. Successful hits could then move into *in vivo* trials in a rapid timeframe. This approach, known as drug repurposing, confers a reduced risk of failure as the safety and dosing profile of the drug will typically be well established. In addition, some researchers are using new technologies like artificial intelligence to use characteristics of the virus to find or design drugs that might successfully treat COVID-19.

Biologics – Opportunities and Challenges

Dr. Ketchem believes that developing a well-tolerated small molecule antiviral, which broadly neutralizes a viral class, will be the most cost effective and efficacious approach to treat COVID-19, and one that researchers should continue to pursue. But he also notes there are significant benefits of developing large molecule modalities. "The mechanism of viral escape is always a concern because as mutations arise, we need to think of strategies that can act broadly across viral species," he explained. "For example, some of the early antibody treatments proved to be highly curative in patients, but once the virus mutates past that antibody response it is extremely difficult to use that therapy anymore. If we can design a modality which has low affinity to a single variant, but high avidity across multiple viruses, we can be successfully prepared against a viral class and inhibit viral infectivity across mutations."

Another approach Dr. Ketchem believes has potential is the use of convalescent patient antibodies. "These are fantastic because the human has a polyclonal response, so we can identify antibodies that have the best possible targeting to stop infectivity of the virus." The limitation of this method is that convalescent antibodies have no selective pressure towards developability, which means they may not behave or express in the same way when developed outside of the body. "If you are developing an antibody therapeutic you have to balance the best efficacy with the best developability, which can be difficult and time consuming," he said.

Cost considerations are always key when working with large molecules, which are often very effective but a lot more expensive than small molecules. With this in mind, Dr Ketchem has developed an AI-driven antibody discovery library which has 'developability' built into the platform. "The aim of the platform is to quickly identify broadly neutralizing agents that block infection pathways, which can be developed at high capacity. We want to make biologics more affordable and more accessible, while increasing their capacity and decreasing their timeline," he said.

One of the biggest challenges with biologics, including mRNA vaccines, protein-based vaccines, and antibodies, is that they require a low temperature-controlled supply chain for distribution. "Cold chain issues limit accessibility to vaccines in many parts of the world," said Dr. Amiji. "Subsequently, a lot of effort is going into developing vaccine formulations that are thermostable, as well as those which can be administered non-invasively to improve accessibility."

Physiologically Relevant Disease Models

For all therapeutic pipelines, a major obstacle is the time it takes to get a therapy from bench to bedside. "In the case of SARS-CoV-2, we don't have enough time to go through the conventional drug development program, which usually takes about 12 years," said Dr. Ayehunie, Chief Scientific Officer at MatTek Corporation. He explained that one of the essential early requirements for COVID-19 was to understand the biological mechanism of infection and how drugs were going to interact with the virus and cell outside of the human body. "At the start of the pandemic there were no appropriate models available to conduct these studies in such a short period of time," he said.

To address this, Dr. Ayehunie has developed a 3D primary human nasal tissue model for respiratory disease modeling, including COVID-19 research, which is being tested and used in different academic laboratories. "We also developed a gut model which is being used for screening repurposed drugs," he said. "These models are critical because they are physiologically relevant to the human and so the results will predict what is going to happen in the human body."

Turning Potential into Success

Taken together, identifying and accelerating the development of potential therapeutics is going to be key to tackling the challenges of emerging variants, preventing severe infection, lowering the burden on healthcare systems, and treating patients suffering with post-infection complications. Dr. Coombs believes that the advent of high-throughput technologies will enable drugs to be developed at a much faster pace. "The days of taking decades to understand a particular agent and design the appropriate treatment has now been reduced down to months," he said. "A lot of the advances in technologies allow us to test for safety and toxicity much more rapidly than we used to."

Despite these advances, manufacturers still need to provide substantial evidence to demonstrate the safety and efficacy of any therapeutic they are developing. "We still have to go through the regulatory hurdles to get a drug to market, and this is very important," said Dr. Ketchem. "There's a lot of misinformation surrounding COVID-19 vaccines and how they were developed too quickly, whereas these technologies have been under investigation for the better part of a decade. The big question is how we can combat this misinformation and drive therapeutics to market faster, while maintaining rigor, safety, and effectiveness."

Concluding the session, Dr. Ayehunie said controlling the current pandemic will require a multifaceted approach. "We have to ensure access to vaccines so that we don't let the virus get out of control, and we need small molecules or neutralizing antibodies to complement vaccination and minimize the effect of infection," he said. "Unless we have these treatments in place, we will have a tough time controlling this pandemic."

Panelists

Dr. Kevin Coombs

Professor in Virology, Max Rady College of Medicine, Medical Microbiology and Infectious Diseases, University of Manitoba

Dr. Coombs' major research interests are to delineate the protein and nucleic acid interactions in nucleoprotein complexes, using a variety of RNA viruses as models. His lab studies how these interactions change as a result of, and in turn, are modulated by, conformational transitions that occur during macromolecular assembly and disassembly, how these processes can be attenuated by anti-viral compounds, and how they contribute to pathogenesis in the host.

Dr. Mansoor Amiji

University Distinguished Professor, Professor of Pharmaceutical Sciences and Professor of Chemical Engineering Director, Laboratory of Biomaterials and Advanced Nano-Delivery Systems (BANDS) Northeastern University

As a distinguished professor, some of Dr. Amiji's current research interests include: target-specific drug and vaccine delivery systems for gastrointestinal tract infections; localized delivery of cytotoxic and anti-angiogenic drugs for solid tumors in novel biodegradable polymeric nanoparticles; intracellular delivery systems for drugs and genes using target-specific, long-circulating, biodegradable polymeric nanoparticles; gold and iron-gold core-shell nanoparticles for biosensing, imaging and delivery applications. Dr. Amiji has received several awards and is a Fellow of AAPS and the Controlled Release Society.

Dr. Randal R. Ketchem

Senior Vice President of Biotherapeutic Discovery and Molecular Design, Just-Evotec Biologics

Dr. Ketchem has focused his career on the application of computational structural biology toward the design of biotherapeutics for both efficacy and developability. At Just-Evotec Biologics he has built a team of software engineers, data scientists, biologics designers, and antibody discovery scientists to drive integrated technology development to optimize therapeutics for developability and manufacturability.

Dr. Seyoum Ayehunie

Chief Scientific Officer, MatTek Corporation, a BICO company

Dr. Ayehunie is currently the lead scientist responsible for the incorporation of immune cells into MatTek's different organotypic tissue models. He has developed a new *in vitro* primary human cell-based organotypic small intestinal (SMI) microtissues for predicting pathogenicity, intestinal drug absorption, metabolism, and drug-drug interaction that can be used to predict drug toxicity and efficacy. Recently, Dr. Ayehunie developed a nasal tissue model for respiratory disease modeling including COVID-19 research and nasal drug screening which is being tested in different academic laboratories. He has more than 40 publications in refereed journals to his credit.

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