A promising therapeutic modality against the coronavirus

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Since the emergence of the novel coronavirus in late 2019, multiple approaches for treating COVID-19 have been considered, from the use of repurposed medicines such as the antimalarial drug,

hydroxychloroquine, to the Ebola antiviral drug, remdesivir.

Many of these therapeutic strategies have fallen short in terms of their clinical effectiveness, which has propelled scientists to come up with more targeted pharmaceuticals to help COVID-19 patients.

Amidst the frantic race to find ways of stopping this tiny killer, a team of researchers at A*STAR's Singapore Immunology Network (SIgN), led by Senior Principal Investigator Wang Cheng-I, has made a tremendous breakthrough in identifying antibodies that block the SARS-CoV-2 virus from entering human cells, thus thwarting the symptoms of COVID-19.

The team recently established a partnership with Japanese pharmaceutical company Chugai Pharmabody Research and is currently working at full tilt to bring these antibody candidate drugs to the clinic.

Targeting the viral crown

Over the past six months, a wealth of information around the structure and biology of the coronavirus has been uncovered. Named for its "crown"—a halo of roughly a hundred sugar-coated protein protrusions on the virus' surface called spike proteins—SARS-CoV-2 uses these spike proteins to bind to receptors on human cells, allowing it to gain entry and initiate infection.

Therapies tailored towards disrupting this binding sequence are thought to be the best way for preventing the virus from harming its host, and antibodies are nature's answer to doing just that. These Y-shaped proteins, produced by immune cells in response to foreign invaders, latch onto specific sites on the viruses, rendering them unable to wreak havoc in the lungs and other organs.

Over the last two decades, the evolution of sophisticated technologies have enabled drug developers to harness antibodies' exquisite target-binding properties, turning them into a safe and reliable therapeutic modality. There are already more than 80 approved antibody drugs on the market, including several blockbusters for treating cancer and inflammatory conditions.

Mining for antibody candidate drugs

Natural immune systems are a rich source of antibody-producing cells that protect us from environmental hazards. This immune landscape is incredibly vast and complex; it has been estimated that humans make around ten billion different antibodies, each with the ability to bind to a specific antigen on a disease-causing agent.

The challenge in COVID-19 drug development is traversing this immense immune universe and finding the handful of antibodies that will strongly latch on to the SARS-CoV-2 spike protein. Even if they do successfully identify these antibodies, only a much smaller subset of these will have the biophysical characteristics required for an effective drug.

To solve the COVID-19 antibody puzzle, Wang and colleagues used a discovery method that involved "mining" for potential lead candidates from a library of synthetic human antibodies. Instead of searching through naturally-occurring antibody sources, the team panned through a large collection of diverse, pre-constructed antibodies, a sophisticated means of fishing out specific molecules for therapeutic applications rapidly.

"Our antibody discovery team consists of scientists specializing in antibody discovery and engineering. They have deep capabilities in these research areas, having worked on diseases such as chikungunya and

dengue fever previously," said Wang, expressing confidence in his team's chances of finding a suitable antibody candidate drug. Wang is currently Head of SIgN's human monoclonal antibody technology platform.

A race from bench to bedside

Using their in vitro antibody discovery platform, Wang's team was successful in singling out antibody molecules that attach strongly to the SARS-CoV-2 spike protein and prevent the virus from interacting with the host cell receptors. In another big win, they found that these antibodies could effectively neutralize live SARS-CoV-2 under experimental conditions, and reduce viral replication in human airway epithelial cells by over 10,000-fold, a functional property that makes these clinical candidates well-poised to perform therapeutically.

"By binding to the crown, the antibody prevents the virus from attaching to human cells, and hence prevents infection," Wang explained. There is a two-fold application potential for this antibody—prevention and treatment. Preventive or prophylactic use of the antibody can provide temporary protection for those at high risk of infection, such as healthcare workers and the families of infected patients, or those for whom COVID-19 vaccines cannot be used, such as in those who are already sick, the immunocompromised, the elderly or young children. The antibody could also be used to treat infected patients, Wang added. "We believe that the neutralizing antibody treatment can slow down the replication of the virus and assist clearing virus from the infected patients, hence allowing the patients a good chance to fight off the disease," he said.

A joint research collaboration between Wang's group and Chugai Pharmaceutical's Singapore-based research center has been established since May 2020, with the goal of promptly bringing this experimental

drug to the clinic. To date, A*STAR and Chugai already have a history of fruitful collaborations, including several Global Health Innovative Technology Fund initiatives to create antibody countermeasures against other threats to global health like dengue.

In this partnership, Chugai has committed to leveraging its proprietary antibody engineering technology to further optimize the lead panel selected by Wang's team. This engineering process involves modifying antibody sequences or structures to enhance their clinical functionality such as enhancing their potency, improving their safety profile or extending their circulation half-life in humans, for example.

"The outbreak of novel coronavirus is the most devastating threat that people around the world have faced in decades," said Osamu Okuda, Chugai's President and Chief Operating Officer. "I am thrilled that Chugai can join forces with A*STAR in the global effort to help address this threat, and hope that together, we can open the possibility of clinical use as soon as possible."

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