All Hands on Deck as Scientists Revive SARS Protease Inhibitor to Attempt to Fight COVID-19

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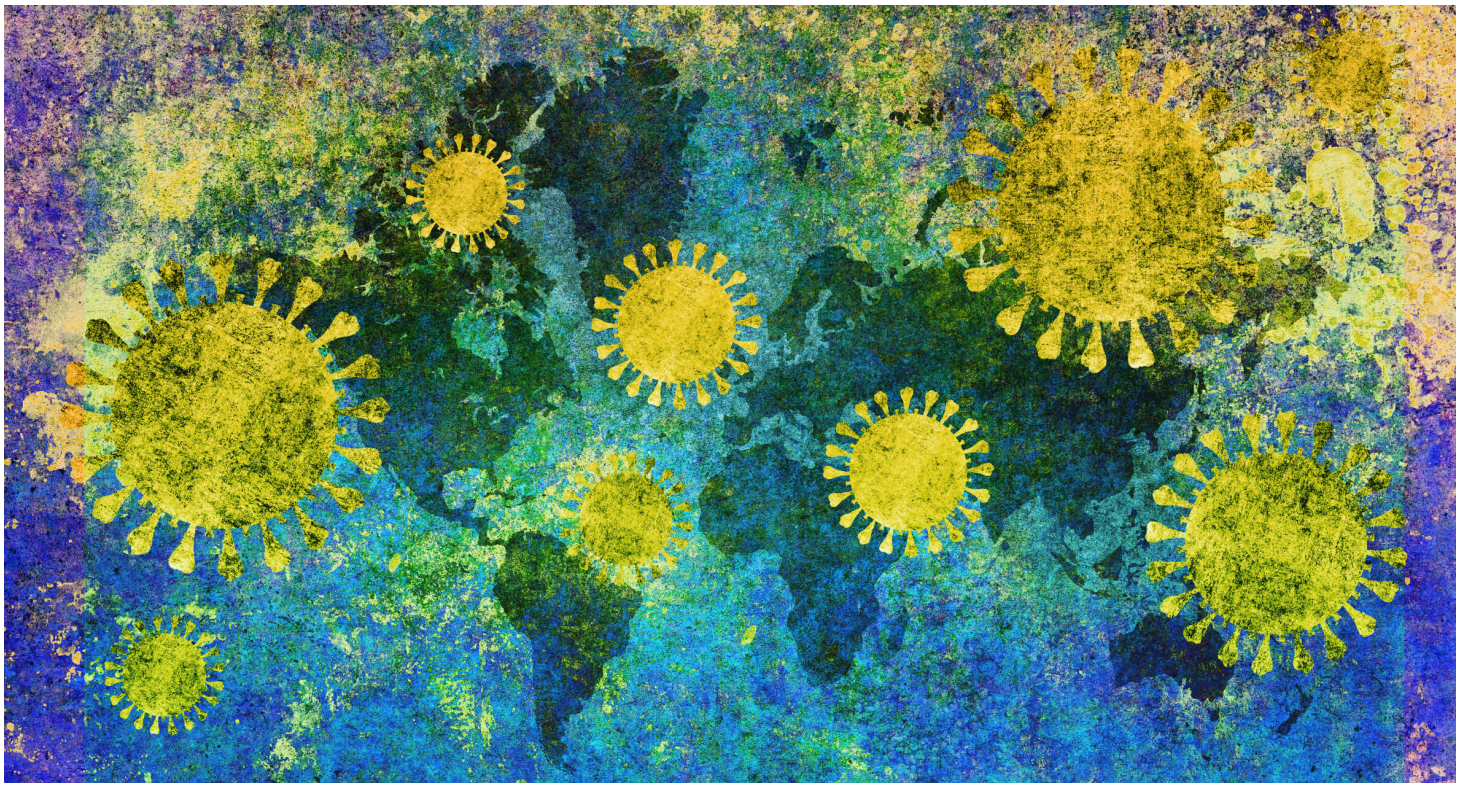

As scientists around the globe race to find ways to treat COVID-19, the fastest approach to finding a treatment may be to repurpose existing drugs in the hopes of avoiding having to start from “square one” on the drug development pathway. There are dozens of existing drugs currently being evaluated for treating COVID-19 and its symptoms, ranging from a failed Ebola treatment to arthritis and diabetes medications.

In addition to evaluating its current portfolio of therapeutics for a compound that can treat COVID-19 and/or its symptoms, Pfizer scientists are working to revive a compound

that they identified in 2003 as a potential treatment for the Severe Acute Respiratory Syndrome (SARS) epidemic in China. The Pfizer compound was developed to inhibit an enzyme called a protease. The revived compound is specific to the proteases produced by coronaviruses, which are responsible for causing SARS in 2003 and COVID-19 today.

Since the 2003 and 2019 strains are very similar, scientists have reason to believe that this compound can be developed to treat the current pandemic, and they recently shared that preliminary data confirm the compound shows antiviral activity against SARS-CoV-2. “This is a critical enzyme that a coronavirus needs to replicate and we had discovered a very potent inhibitor against it for SARS,” says Rob Kania, Senior Director, Design Chemistry based at Pfizer’s La Jolla, California, research site. “With the advances we made back in 2003, we’re at a very good starting point to apply learnings to the current outbreak,” adds Kania, who led the team of scientists that identified the compound in 2003.

While not starting at “square one,” there are still months of work ahead before the compound will potentially be ready for testing in humans. “The fact that we already have a compound with a mechanism that seems to have the potential to treat COVID-19 is fantastic,” says Annaliesa Anderson, Chief Scientific Officer of Bacterial Vaccines and Hospital at Pfizer. “We're definitely much further ahead than we would be if we were starting from scratch. A key piece of this is the people involved; we have such a talented group of scientists working on this effort, and everyone has the same goal in mind: to help patients now and to prevent this situation from taking foothold in the future.”

Going after protein-cutting enzymes

When a virus invades our cells, it takes over the cell’s internal machinery in order to produce viral proteins to make more copies of itself. Initially, the infected cell forms a single viral protein chain like a long string that is mostly non-functional. The protease enzyme cuts the protein chain in specific areas to produce fully functional working sub-units that are critical for the virus to replicate.

Protease inhibitors are a class of antiviral drugs that shut down this protein-cutting process, and thus stop a virus from multiplying. Several protease inhibitors are widely used to treat HIV and the hepatitis C virus. “Protease inhibitors were one of the very first highly active drugs that were approved for HIV,” says Jennifer Hammond, Global Medical Affairs Product Lead based in Pfizer’s Collegeville, Pennsylvania, site. “There's a long history of their use and they have a very good safety profile.”

Scientists are hopeful that the SARS protease inhibitor will be effective against the current novel coronavirus, because the two viruses have very similar protein-cutting enzymes where the drug binds. “The active binding sites of this essential enzyme are almost identical in the SARS virus and the COVID-19 coronavirus,” says Kania.

Developing the right puzzle piece

Back in 2003, scientists produced a 3D crystal structure of the SARS protease in order to develop a compound that could fit like a “puzzle piece” into the binding site and inhibit it. “It’s a very challenging class of proteins to inhibit,” says Kania. But ultimately, through an “iterative” process of designing, synthesizing, and testing thousands of prototype compounds, and tweaking chemical structure along the way, they developed their compound.

Given the urgency of the current epidemic, Kania says it is both rewarding and exciting to contribute his expertise to this antiviral program. “So many people are coming together to build on this previous work,” says Kania. “I feel proud to be working with such talented scientists to have the opportunity to bring something forward that would help patients.”

An urgent dynamic

In this all-hands-on-deck effort, scientists across industry, academia and government are collaborating at unprecedented speed. “We need to do a lot of pre-work before we can get it into patients, including manufacturing enough of the drug for clinical testing,” says Anderson. Even before confirming that the compound has potential to treat COVID-19, Pfizer has made investments in the materials that will be needed to move forward into the clinic as quickly as possible should the pre-clinical work support beginning a clinical trial. In addition, academic researchers and other experts in the field are collaborating with Pfizer to help accelerate the process. “To say that we are getting promising results within weeks of this project even existing is like nothing I’ve ever seen before,” says Anderson. “Clearly, the dynamic now is very urgent and we are driven by the goal to serve patients.”

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