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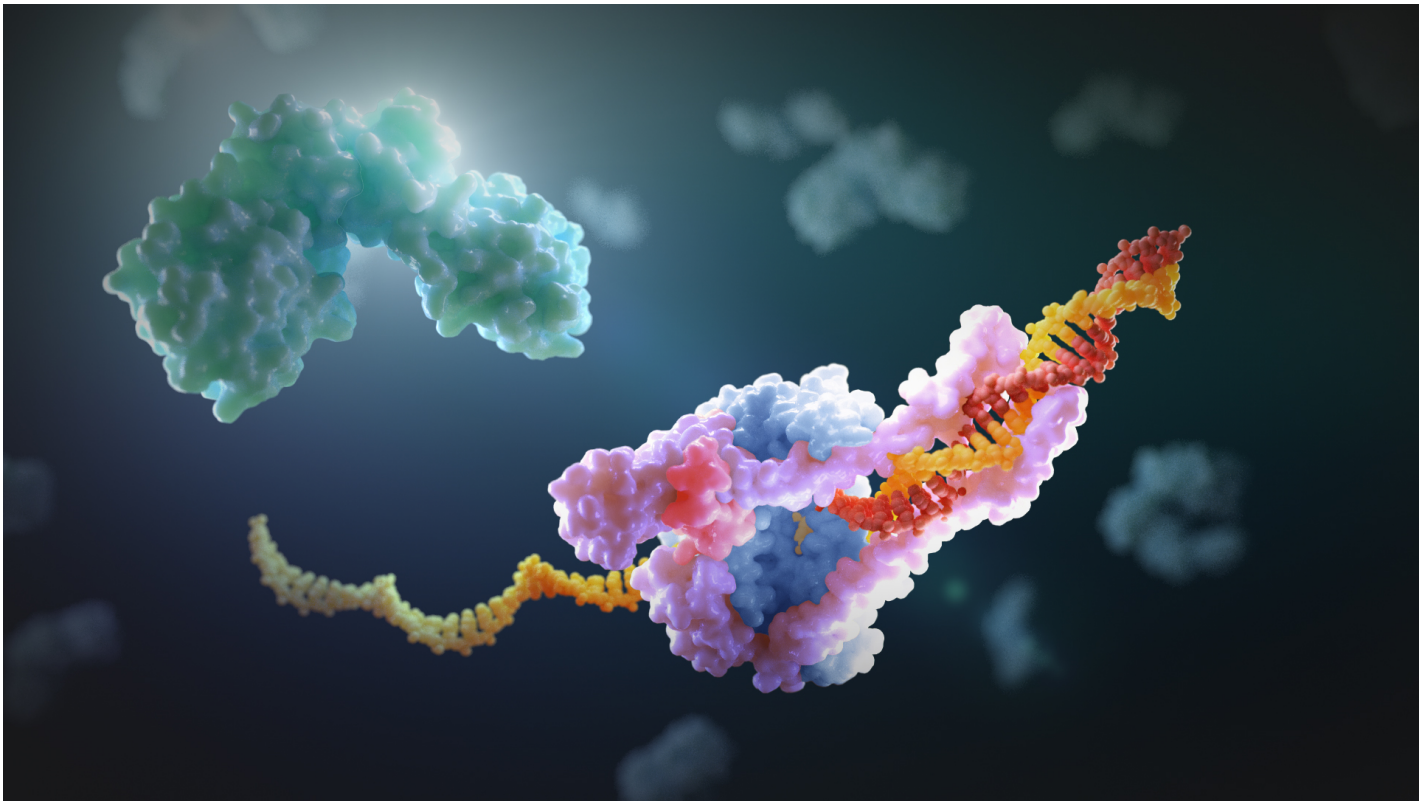
Stopping this coronavirus – and the next one



Inside the hunt for new antivirals to combat the current pandemic and to prepare for future ones.

By Kevin Jiang | Nov 12, 2021

The coronavirus that causes COVID-19 is mind-bogglingly tiny. Stacked end to end, a thousand of them could fit across the width of a human hair. How does something so small cause so much harm? More importantly, how do we stop it?

An answer to these questions, in part, could lie within a devious and complex...copy machine.

The search for new and better antivirals against the coronavirus that causes COVID-19 and its variants is one of the most urgent needs in medicine, one pursued by scientists around the world. And it's not the only need – other coronaviruses could also have pandemic potential. Coronaviruses are a family of viruses notorious for causing not only COVID-19 but also outbreaks such as SARS and MERS (in 2003 and 2012, respectively).

"The historic speed at which we have developed and rolled out COVID-19 vaccines shows how far science has come," says Stephanie Moquin, a virologist at Novartis. "But we still need effective coronavirus antivirals, not only to help patients who become infected, but also to have drugs that are ready to stop any other coronaviruses that may emerge in the future."

> We can't ever be caught off-guard again like we were with COVID-19.
>
> **John Tallarico**, Head, Chemical Biology and Therapeutics at Novartis

At Novartis, researchers are focused on the molecular machine that coronaviruses use to hijack human cells and replicate themselves. All coronaviruses depend on this machine, not just the one that causes COVID-19. So efforts to sabotage it may be a key to developing a new pan-coronavirus antiviral – one with the potential to help end the current pandemic, as well as prepare the world for future threats posed by other coronaviruses. This machine could even yield clues to a possible "cure" for some types of the common cold.

A pill for the pandemic

From the moment scientists first identified the novel coronavirus, they rallied to combat the disease, creating highly effective vaccines at an unprecedented pace.

However, not everyone can or will be vaccinated, and efforts to repurpose existing medicines – which were not designed with coronaviruses in mind – can yield limited results. There remains a critical need for antivirals that can slow or stop the course of coronavirus infections, especially as variants continue to emerge.

So even as vaccines are distributed globally, work on antivirals continues to accelerate. Researchers around the world, including at Novartis, are tackling the challenge by openly sharing knowledge and resources, and establishing new frameworks for collaboration. In this spirit, scientists across academia and industry have convened to discuss the latest research and strategies at virtual forums, including the inaugural Science of Therapeutics Symposium, hosted by the Novartis Institutes for BioMedical Research (NIBR).

Because antivirals stop viruses from replicating, they are most effective in the early stages of an infection. This means that, optimally, such drugs should be widely available and easily taken by anyone infected with the virus.

“The ideal antiviral against coronaviruses should be in pill form, so that people can take something at home to stop the virus as soon as they feel symptoms, test positive or even think that they’ve been exposed,” says Julien Papillon, a medicinal chemist at Novartis.

The coronavirus copy machine

To this end, Novartis scientists are going after key machinery that makes the virus so dangerous.
At a basic level, the coronavirus is a delivery package for its genome – a genetic blueprint for making more coronaviruses. Once inside a cell, the first thing this blueprint does is trick the cell into creating a molecular copy machine for the virus.

This machine has one task: make copies of the virus's genome. Each new copy tells the cell to build more copy machines, which then spew out even more viral blueprints.

This cycle quickly overwhelms the cell, ultimately transforming it into a dedicated coronavirus production factory. Soon, newly minted coronaviruses flood out of the cell to infect its neighbors and eventually other people.

But the copy machine has weaknesses.

It is complex and is made of many different proteins. These components are stuck together when first created – similar to how the parts of a toy model are held in a plastic frame when first taken out of the box. To free the parts and assemble the machine, the virus uses a pair of protein scissors, called M^{pro} (or main protease).

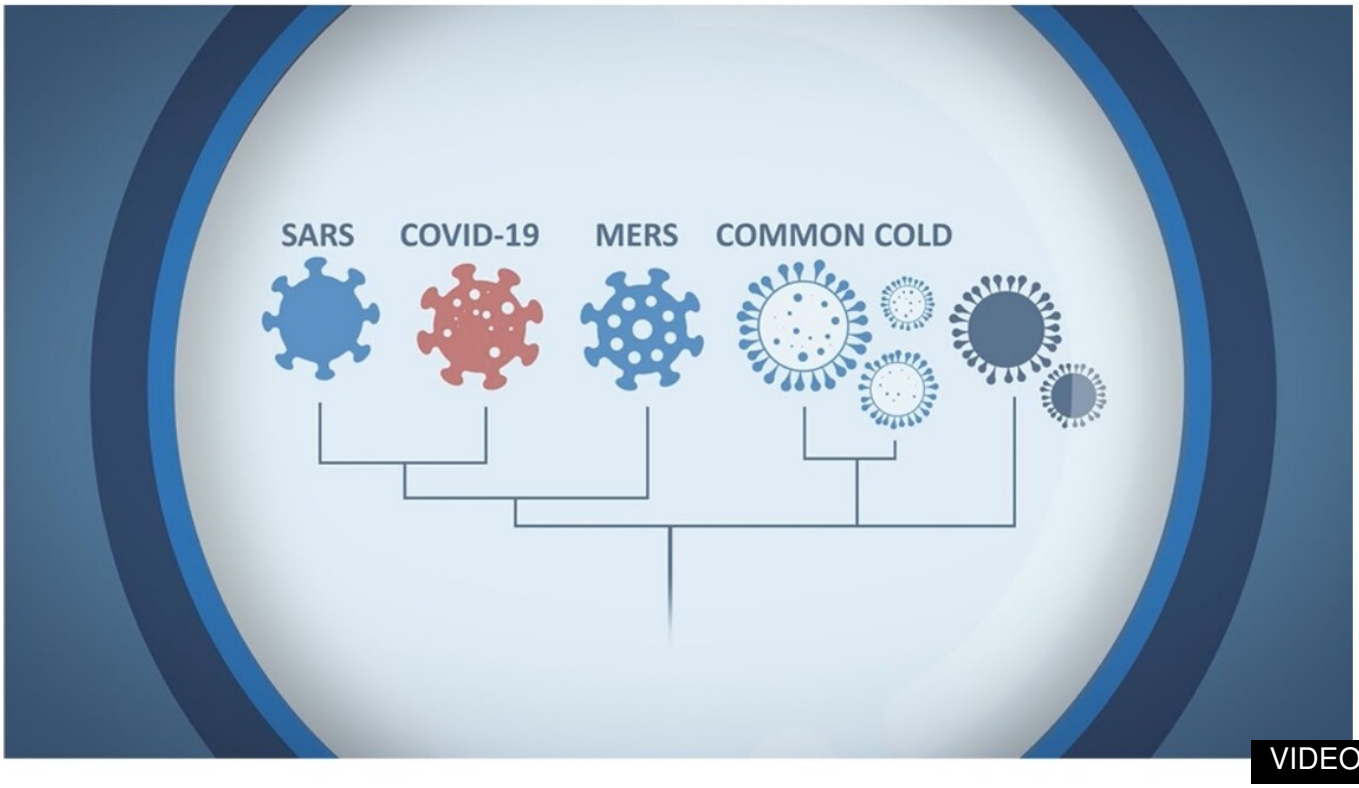
In a collaboration with colleagues at the University of California, Berkeley, in the US, a Novartis team set out to identify molecules that can essentially weld these scissors shut, preventing the copy machine from ever being assembled.

Without the copy machine, the virus can't multiply and cause harm.

Preparing for the next pandemic

The Novartis team has spent the past year studying such molecules, which must be put through their paces in the lab before starting clinical testing. Having narrowed down the possible candidates, it is moving forward, supported by a grant from the Bill & Melinda Gates Foundation. Groups around the world are engaged in similar efforts to neutralize the coronavirus by disabling M^{pro}, copy machine components or other targets.

It will take time to test potential treatments in patients. But medicines that specifically stop M^{pro} could offer intriguing benefits that would extend beyond the COVID-19 pandemic.



VIDEO

All known coronaviruses use very similar M^{pro} scissors to set up their copy machines. A drug that gums up these scissors in one type of coronavirus may also have efficacy against other coronaviruses, including new variants and even ones that have yet to emerge.

This also includes coronaviruses that account for some 20% of common colds – milder cousins of the one that causes COVID-19. As other cold-causing viruses also use similar molecular scissors, efforts to disable M^{pro} may uncover new ways to disable these viruses as well.

“It’s almost certain that future pandemics will be caused by coronaviruses that we haven’t yet identified,” says John Tallarico, who leads chemical biology and therapeutics research efforts at Novartis. “That’s why placing antivirals with pan-coronavirus efficacy into the public health armamentarium is such a major focus of our broad, industrywide response to this crisis. We can’t ever be caught off-guard again like we were with COVID-19.”

Main image of M^{pro} and the coronavirus replication-transcription complex by Mark Mazaitis.

Novartis scientists are searching for new antivirals to combat #COVID19 and future pandemics.

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