

DISCOVERY REPORT



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Antivirals for the future

What's needed to address the next pandemic plus long-standing threats like HIV and hepatitis

Published by
c&en

\$39.99

Developing antiviral drugs for the future

One of the lessons from the COVID-19 pandemic is that the world must up its game on antivirals. The next time a pandemic threat emerges, we need better tools readily available to deploy—compounds that can address a broad spectrum of viruses and have already been through safety studies.

Meanwhile, there is still work to do to address long-known acute illnesses, such as those caused by Ebola or respiratory syncytial virus—one of the most common causes of respiratory infections in children. And people with chronic infections from viruses such as HIV or hepatitis B would benefit from less onerous treatment regimens, if not cures.

In this Discovery Report, you'll learn about the scientific and business challenges involved in developing antiviral medicines. You'll meet the scientists developing libraries of compounds to meet the next pandemic threat. You'll read about efforts to streamline clinical trials. You'll see how antiviral development is driven by the news of outbreaks. And you'll hear about what it will take to ensure people across the globe have access to the antivirals they need.


Contributing editor Brian Owens, an independent journalist who covers health and the environment, edited this report with Jyllian Kemsley, C&EN's executive editor for policy and content partnerships. The report includes a reading list of papers curated by our sources, as well as by researchers at the CAS division of the American Chemical Society.

As an ACS member, you get exclusive access to the Discovery Report, a quarterly publication bringing you cutting-edge research defining the chemical sciences and our industry. Look for the next one in the fourth quarter of 2021.



Amanda Yarnell

Editorial director, C&EN

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Published by

c&en

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5 questions and answers about antivirals

Q.

What do we need to do to better prepare for new viruses?

- » **The world must move away from the “one bug, one drug” approach** to antiviral drug development.
- » **Targeting parts of viruses that are highly conserved** among strains and across families will help identify drugs that are effective against multiple related viruses.
- » **Drugs that interfere with the host’s cellular machinery** that viruses co-opt for replication could offer protection against a broader variety of viruses.

Q.

Which viruses should we be most worried about?

- » **The World Health Organization says** these viral diseases should be prioritized for R&D because of their risk to public health, whether due to their epidemic potential or lack of countermeasures:
 - ▶ COVID-19, SARS, and MERS
 - ▶ Crimean-Congo hemorrhagic fever
 - ▶ Ebola virus and Marburg virus diseases
 - ▶ Lassa fever
 - ▶ Nipah and henipavirus diseases
 - ▶ Rift Valley fever
 - ▶ Zika fever
- » **The WHO also flags the unknown**, or what it calls “Disease X”—a hypothetical illness caused by a pathogen not currently known to cause human disease.

Q.

What else do we need to address acute viral infections?

- » **Fast and accurate diagnostics** are critical for identifying and treating an infection in time to help, particularly when the window to effectively treat an acute infection is narrow.

Q.

How do we get to a cure for chronic infections, such as for HIV?

- » **Therapies that can be given infrequently**—monthly, every 2 months, or even just once or twice a year—are the first step.
- » **Viruses that go dormant** in the body, like HIV and hepatitis B, will require reactivation before they can be destroyed.

Q.

What’s needed for worldwide access to antivirals?

- » **Building drug manufacturing capacity** in regions such as Africa or South America will help improve supplies of drugs and vaccines.
- » **Fostering scientific research capability** in those regions will support development of therapies to address the diseases that affect them the most.



8 experts weigh in on the future for antivirals



Gaurav Chandra

» Chief operating officer, Enzolytics

Developing antiviral drugs is often a race against time—in many cases, the virus can mutate to escape them almost as fast as the drugs can be created. But there are limits to how much a virus can change.

“When a virus mutates, it needs to maintain some essential functions, so there are certain conserved, immutable sites in its structure,” Gaurav Chandra says. Enzolytics is working with Intel to use artificial intelligence to identify such sites on viruses including HIV and SARS-CoV-2, with the idea that they could make useful targets for monoclonal antibody drugs that would work against an array of viral variants.

The AI platform identified 19 conserved sites for SARS-CoV-2 and 8 for HIV. Enzolytics had previously found one of the HIV sites and developed an antibody to target it; that antibody is now in clinical trials. Using AI, “we were able to do in a few weeks something that took 30 years before,” Chandra says.

Even better, all 19 of the SARS-CoV-2 sites are conserved across 2 million different isolates of the virus, including all the current [variants of concern](#). The company is planning to start clinical trials on the most promising candidates early next year.

Chandra says the platform could be used in the future to quickly create monoclonal antibodies for novel viruses almost as soon as they are discovered, drastically reducing the time it takes to develop effective drugs for new and emerging diseases.



Rosemary Dorrington

» Professor of microbiology, Rhodes University

From the beginning of the COVID-19 pandemic, it was clear to Rosemary Dorrington and her colleagues that inequities in the distribution of vaccines and antiviral drugs were going to be a big problem for the developing world. Most of the world’s capacity for discovering and developing drugs is based in rich countries, because drug development is expensive, and the pharmaceutical industry relies on marketing and sales in those nations to recover their costs.

Companies “make drugs for the people who can pay for them,” Dorrington says. “Countries that have the capacity to pay are getting first access—that’s just the reality we live in.”

But with a pandemic like COVID-19, no one will be safe until everyone around the world has access to the drugs and vaccines that they need. So Dorrington supports efforts by organizations like the Bill & Melinda Gates Foundation to develop scientific and manufacturing capacity in the places where the drugs are needed. Johnson & Johnson and Pfizer have already signed deals with companies in South Africa to package their vaccines there for distribution in Africa. The next step, Dorrington says, is to extend from packaging to manufacturing.

“It’s really important to develop the capacity to make the drugs where they are needed,” she says. Hopefully, that will in time lead to the ability to research, develop, and manufacture the drugs that Africa needs in Africa—not just for COVID-19 but also for the many local neglected diseases.



It’s really important to develop the capacity to make the drugs where they are needed.”



Matthew Hall

» Chief of Early Translation Branch, US National Center for Advancing Translational Sciences

When COVID-19 emerged, there were no antivirals not only for it but for any coronavirus. “It was a pretty blank canvas,” Matthew Hall says.

While virologists and pharmaceutical companies quickly got to work on new drugs for COVID-19, the same problem will likely arise with a pandemic caused by a different virus family. So the US National Institutes of Health and the Biomedical Advanced Research and Development Authority launched the [Antiviral Program for Pandemics](#) (APP) in June 2021 with \$3.2 billion in funding. The APP aims to accelerate antiviral development through early discovery and preclinical development. “It’s an important program because there isn’t a strong commercial imperative to develop drugs for diseases that don’t exist yet,” Hall says.

The goal is to develop a library of potential oral therapies for which the safety profile and dosing regimens are already known, so they are ready to go when the next threat emerges. The drugs can then be plucked off the shelf and quickly put into more advanced clinical trials. To start, the APP is trying to identify which companies and academic researchers are already working on direct-acting antivirals that the program could help move forward. “APP could help mitigate the risk and cost of those programs,” Hall says.



Saye Khoo

» Professor of pharmacology and therapeutics, University of Liverpool

As early as March 2020, Saye Khoo realized that conventional drug development was not fit for purpose during a pandemic. It was too slow and not sufficiently responsive to create the antiviral drugs needed in a useful time frame. The world needed a quicker and more nimble approach, but designing it would take some creativity. “If you want to compress clinical development from 7–10 years to 18 months, something has to change drastically,” Khoo says.

So he and his colleagues, working with the UK’s Medicines and Healthcare products Regulatory Agency, developed [AGILE](#), a clinical trials

platform that uses rapid cycles of evaluation and advanced statistical techniques to compress early Phase 1 and 2 clinical trials into a faster, more streamlined process. For example, the framework allows researchers to test multiple dosing regimens simultaneously by carrying over data from the analysis of one dose to the next, Khoo says. Three trials are underway using AGILE, including one on Merck’s [molnupiravir](#), with two more in advanced development.

Khoo says the AGILE framework could also be useful for testing drugs for other diseases, particularly fast-moving ones, like Ebola, that can flare up and die out before new therapies can be approved. “It’s clear drug development will never be the same again,” he says.



Nathaniel Moorman

» Professor of microbiology and immunology, University of North Carolina School of Medicine

“There has been a real panic-neglect cycle in funding.”

A year before the arrival of SARS-CoV-2 demonstrated just how unprepared the world is for emerging infectious diseases, Nathaniel Moorman and his colleagues established the [Rapidly Emerging Antiviral Drug Development Initiative](#) (READDI) to try to get a head start on the next major outbreak.

The initiative emerged “out of a sense of frustration that this work doesn’t get done in the absence of an outbreak,” Moorman says. The COVID-19 pandemic provided the impetus for READDI to double down on its efforts.

The goal of the initiative is to bring five broad-spectrum antiviral drugs through Phase 1 safety testing in the next 5 years. READDI is focusing initially on the viral families with the most potential to cause pandemics: coronaviruses, the ones that cause COVID-19, Middle East respiratory syndrome (MERS), and severe acute respiratory syndrome (SARS); alphaviruses, which cause brain inflammation; and flaviviruses, the ones responsible for dengue, West Nile, and Zika infections. The researchers are considering both host and viral targets for their broad-spectrum drugs, looking for nodes that will allow them to fight multiple infections with a single drug.

While it has historically been difficult to find funding for antiviral drug development outside a serious outbreak, Moorman thinks COVID-19 has changed the calculation. “There has been a real panic-neglect cycle in funding,” he says. “But I think COVID-19 has led to a better understanding of the need for sustained efforts and funding to make these drugs.”



Rosemary Roberts

» Director of Counter-Terrorism and Emergency Coordination Staff, US Food and Drug Administration

and Drug Administration

Sometimes scientists know that a particular virus or family of viruses is likely to pose a serious threat in the future. But the virus is too rare or the illness it causes too dangerous for the normal course of human clinical trials. For these special circumstances, the US Food and Drug Administration created a regulation known as the [Animal Rule](#), which allows the agency to rely solely on data from animal studies to evaluate the effectiveness of new drugs.

The rule is rarely used. “The Animal Rule can be used only when human clinical trials are not ethical or feasible,” Rosemary Roberts says, so the agency is unlikely to use it for routine infections like seasonal influenza. But developing animal models of human diseases caused by potential pathogens from outbreak-prone virus families like coronaviruses or filoviruses could be useful in preparing for the next pandemic.

Roberts notes that earlier this year, the FDA used the Animal Rule to approve brincidofovir, a new treatment for smallpox. As smallpox was eradicated over 40 years ago, it is not possible to conduct clinical trials, but the virus is still considered a threat. Chimerix, which now markets the drug as Tembexa, studied the effectiveness of brincidofovir in two animal models of orthopoxviruses that are closely related to the variola virus. More animals treated with brincidofovir survived than those treated with placebo, allowing the FDA to approve the drug under the Animal Rule.



Erica Ollmann Saphire

» President and CEO, La

Jolla Institute for Immunology

Though research, and especially drug development, is an enterprise built on competition between labs and companies, Erica Ollmann Saphire thinks collaboration is just as important and can lead to important breakthroughs.

It has worked for her before. In 2014, she helped set up the [Viral Hemorrhagic Fever Immunother-](#)



The Animal Rule can be used only when human clinical trials are not ethical or feasible.”

[apeutic Consortium](#) (VIC) to let researchers share their work on Ebola, helping one another identify and test new antibody treatments for the virus. With 43 labs working together, VIC “catapulted the field forward,” Ollmann Saphire says.

“It works well when the problem is too big for any one group to untangle, or when you need broad comparisons of assays and models,” she adds.

Ollmann Saphire has built the same kind of model for COVID-19. [The Coronavirus Immunotherapy Consortium](#) (CoVIC) involves 56 labs around the world and has created a database of around 350 monoclonal antibodies that can be tested, compared, and combined to find the best options for fighting coronaviruses. The antibodies submitted to the database are blinded, meaning other users will see only a code name and some basic biochemical parameters, so contributors retain their intellectual property while gaining access to new assays and potential partners for building an antibody cocktail.

This kind of model should become more common in virology, according to Ollmann Saphire. “We could use this all of the time,” she says. “There’s a time and a place for competition and a time and a place for collaboration, and they need to happen simultaneously.”



Kimberly Smith

» Head of R&D, ViiV Healthcare

Although there have been huge advances in the treatment of HIV over the past few decades, Kimberly Smith points out that a lot of work remains to be done. “HIV is the right place to be focused because of the impact it has on the world,” she says.

While about 38 million people worldwide are affected by the virus, only about half of them are taking antivirals. That’s a far cry from the UN’s ambitious 90-90-90 targets for 2020—90% of all people infected with HIV knowing their status, 90% of those diagnosed receiving treatment, and 90% of those on treatment achieving viral suppression—even in many developed countries.

To improve, and to meet the even more ambitious 95% targets set for 2025, the field needs to evolve and move in the direction of longer-lasting therapies and even permanent cures, Smith says. While the single daily pill treatments now available are highly effective at controlling the infection, even that is too much for many people. “We need to address that burden, reduce the frequency of the dose, and move aggressively towards a cure,” Smith says. ViiV is already heading down that path, with a monthly treatment approved, and hopes to increase the interval even more. ■

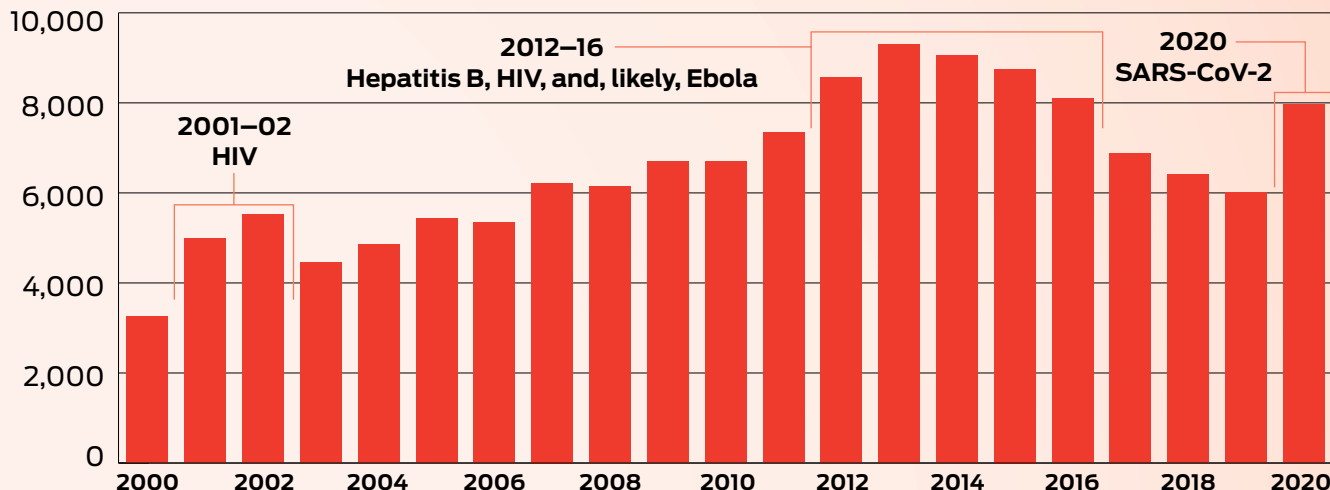


Discover trends in antiviral drug development

Fluctuations

Publishing and patenting activity related to antivirals varies over time, driven at least in part by the virus newsmakers of the day.

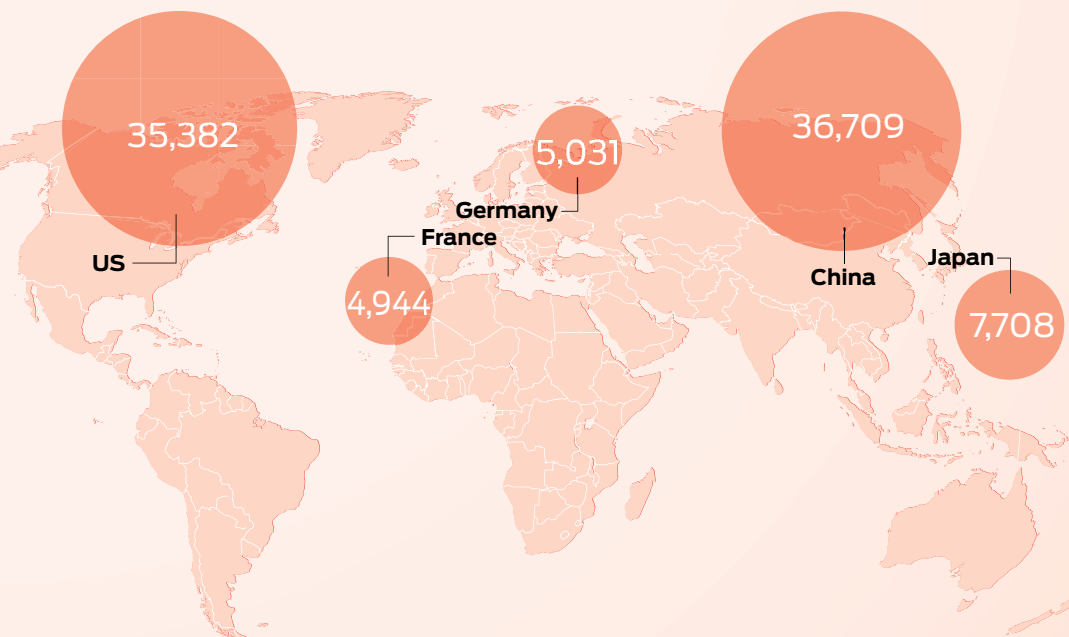
Number of patents and papers



Where in the world

China and the US far outdistanced other countries in publishing and patenting on antivirals from 2000 to 2020.

Number of patents and papers



Who's who

These companies and institutions filed the most patents related to antivirals in 2000–2020.

Bode Gene Development, Shanghai

1,819 – Number of patents

Shanghai Biowindow Gene Development

627

Bristol Myers Squibb

527

Fudan University

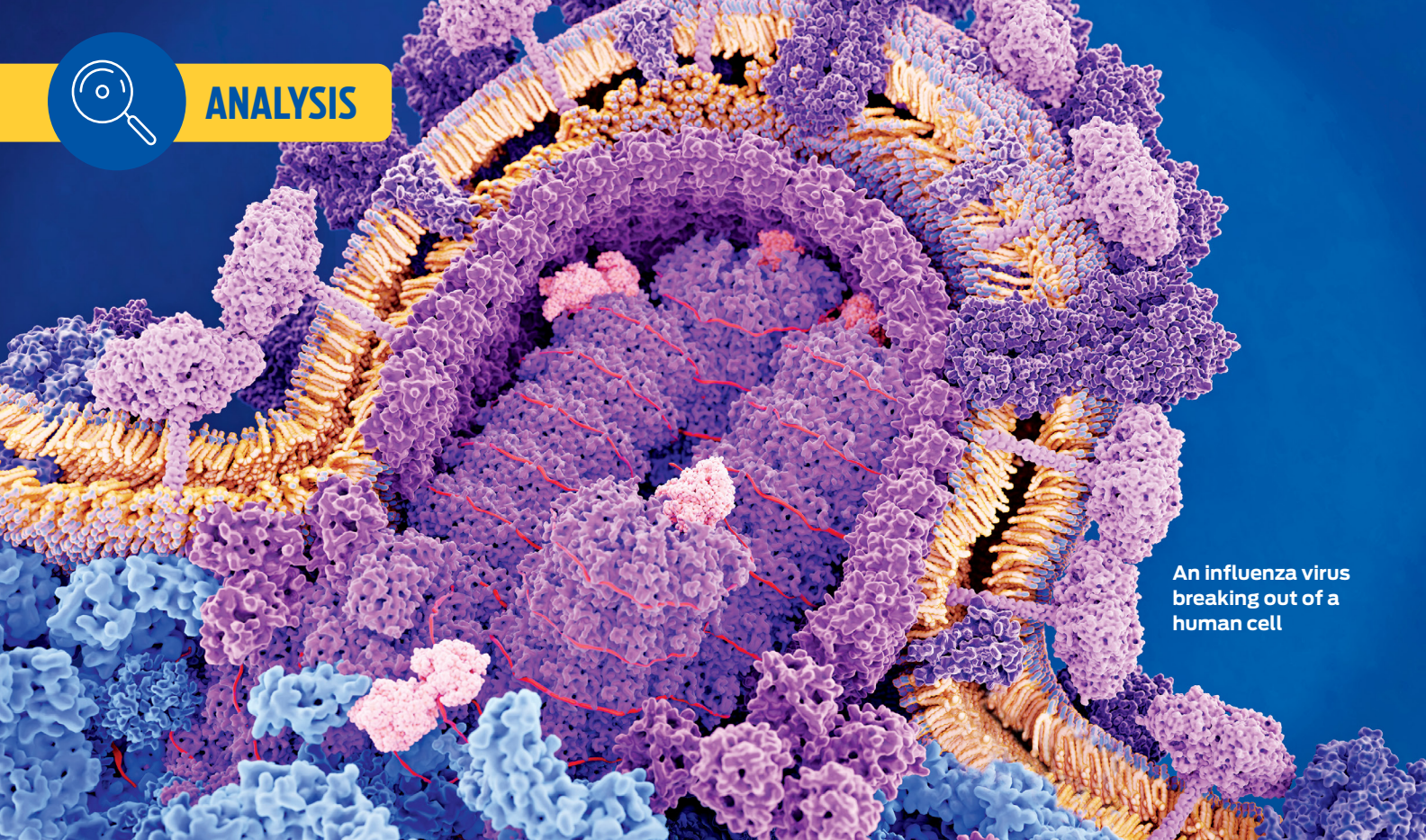
310

Gilead Sciences

269

Source: CAS, a division of the American Chemical Society.

Notes: Figures for Germany may include patents that were filed in the former East Germany and published after a long delay.



An influenza virus breaking out of a human cell

Why are antivirals so hard to develop?

LAURA HOWES, C&EN STAFF

Viruses are tricky. They're small, mutate quickly, and make thousands and thousands of copies of themselves every day. Or rather, infected cells produce those new copies of the virus. Viruses can't reproduce on their own—they sit inert until they can infect a cell.

And when it comes to finding drugs that can kill a virus, that's part of the problem: viruses don't have a lot of their own proteins and enzymes to target.

The handful of proteins and enzymes they do

have might perform the same basic functions—allowing the virus to enter cells, replicate, and escape to do it all over again—but their sequences and structures differ even among viruses in the same class, let alone among families of viruses.

So even if you develop a drug against one virus, it is unlikely that you can use it to treat another. Add a lack of reliable animal models and a lack of investment, and it becomes clear that antiviral drug development is a complex problem.

From bug to drug

For decades, scientists didn't know whether viruses had any of their own enzymes. Researchers assumed that hijacked cells just built new copies of a virus using the cells' own enzymes and proteins. Then, in 1967, scientists discovered the first

viral enzyme, a poxvirus DNA-dependent RNA polymerase (*Proc. Natl. Acad. Sci. U.S.A.*, DOI: [10.1073/pnas.58.1.134](https://doi.org/10.1073/pnas.58.1.134)). That enzyme takes the virus's DNA-encoded genome and transcribes it into RNA to start the production of new viral proteins. Once researchers identified those first viral enzymes, they realized they could start designing drugs to target viruses themselves. But progress was slow.

"Antiviral development has always lagged behind antibiotic drug development," says Saye Khoo, an expert in antiviral pharmacology at the University of Liverpool. "And other than the topical treatments for warts and things like that, it's really been pretty poor until acyclovir came along."

Acyclovir is used to treat herpes simplex infections, chicken pox, and shingles. Patented in 1974 and first approved for use in the 1980s, the drug is converted inside cells to a form that looks like a component of DNA. This tricks the virus's DNA polymerase into incorporating a version of the drug into growing DNA chains, stopping replication.

And unlike earlier antivirals, acyclovir completely inhibits the viral DNA polymerase without stopping the cell's own enzyme, meaning it causes very few major side effects. Researchers have been trying to take a similar approach ever since by targeting viral proteins that have no human equivalents. Marti Head, director of the Joint Institute for Biological Sciences at Oak Ridge National Laboratory (ORNL), likens understanding how viruses keep going to diagnosing engine trouble in your car. "If I'm running low on oil, I know from experience I can keep driving. And yet if my timing belt goes out, I'm dead in the water," she says. Antiviral drug designers must determine which piece of the virus is most equivalent to the timing belt and whether it varies across viruses.

Every stage of infection and viral replication offers a chance to stick a wrench in the works. But because viruses code for only a few proteins of their own, there might be only one or two proteins that a drug can target. And those viral enzymes may have functions that host cells also perform. That overlap creates the potential for an antiviral to inadvertently harm healthy human cells.

Still, over the years, drug developers have found ways to safely target several key viral proteins—ones they turn to first when a new threat emerges. Much time has been devoted to enzymes responsible for RNA or DNA being copied—like the target of acyclovir. That's because those enzymes often look similar in several viruses, meaning an inhibitor could be useful in multiple infections. Reverse transcriptases, which some viruses use to transform RNA into DNA, have been a major target in HIV. And proteases, which cut up viral proteins in the cell, have been a target in both chronic infections, like HIV infection and hepatitis C, and acute ones, such as SARS-CoV-2. "There aren't a lot of antivirals that have a broad-spec-

trum effect," says Ashley Brown, an expert in antivirals at the University of Florida. "You have to make your drug target a specific protein in a specific virus." In other words, one drug for every bug. But the good news is that targeting a specific viral enzyme decreases the risk of also affecting a host enzyme, making a drug safer. "So when you do manage to get an inhibitor, the chance of it moving forward right the way through to the clinic and beyond is quite high," says Eddy Littler, chief operating officer of the UK biotech ReViral, which is developing a drug for respiratory syncytial virus, or RSV.

Some drug developers are targeting host cells, a strategy that in theory could generate drugs that will work against whole viral families, says John Bamforth, the interim executive director of the Rapidly Emerging Antiviral Drug Development Initiative (READDI).

READDI's targets are families of viruses that have pandemic potential, and the initiative aims to get five broad-spectrum antivirals through early safety studies in humans within 5 years. One way to do that, Bamforth says, is to target host biology. "If we can affect the host cell, then, to a degree, it doesn't matter what the virus does," he says. That approach makes drugs more flexible and viruses less likely to develop resistance. But focusing on the host cell comes with a trade-off: a higher risk of significant side effects. The challenges for antiviral drug discovery aren't limited to designing a good inhibitor. The next step is to show that the drug works—first in cells, then in animals, and finally in humans. But the cell and animal models can present new obstacles for researchers working on viruses.

For example, researchers struggled for years to get hepatitis C to replicate in cells in a lab. Scientists solved that problem after some clever synthetic biology created self-replicating viral RNA from the hepatitis C virus, which allowed them to study how disrupting individual proteins affected the viral life cycle.

And once the drug stops the virus in cells in a petri dish, scientists need to test it in reliable animal models that can give physiologically relevant results. Drugs can be designed to interrupt a virus's life cycle at many points between its entry into and exit from a cell.

Every virus uses cellular proteins and affects cellular processes downstream, complexity that can't always be mimicked in an animal with a different biology than humans'. Gilead Sciences' remdesivir, for example, worked well against the Ebola virus in small animal models and in nonhuman primates (*Nature* 2016, DOI: [10.1038/nature17180](https://doi.org/10.1038/nature17180)). It didn't work so well in humans.

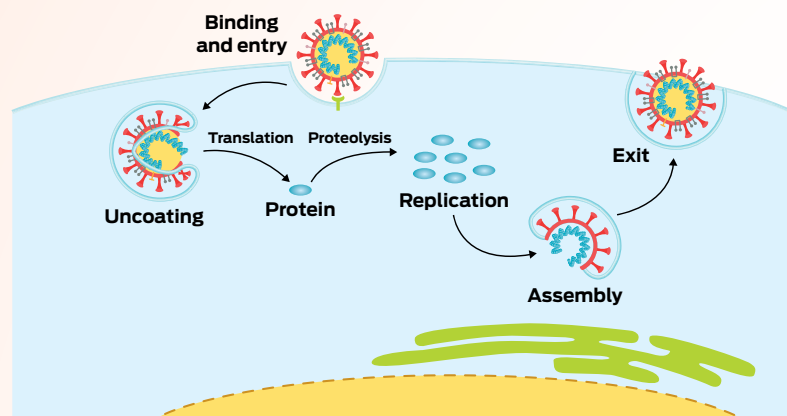
Several experts also cite the lack of good models as a stumbling block in antiviral development. For example, Littler says, mouse and rat models of RSV are not very predictive. ReViral tested its compound in a human challenge model, in which healthy people are purposely infected with RSV. It's an artificial situation, Littler says, but it pro-



If we can affect the host cell, then, to a degree, it doesn't matter what the virus does.”

The viral life cycle

Drugs can be designed to interrupt a virus's life cycle at many points between its entry into and exit from a cell.



Source: Adapted from *Nat. Rev. Microbiol.* 2020, DOI: [10.1038/s41579-020-00468-6](https://doi.org/10.1038/s41579-020-00468-6).

vides a good idea of how the drug will work in the clinic.

Brown, who uses in vitro and mathematical models to optimize therapeutic regimens for antiviral compounds, says that at every stage, drug designers need to think about what models can and can't tell them. "These models are all necessary to move to the next stage, but you always have to be careful in your considerations on what's going to translate" to the real world.

From biology to business

Ultimately, biological problems make antiviral drug development tricky, but research over the past 50 years has shown that the right incentives can drive innovation.

Decades of investment in understanding and developing drugs for HIV and AIDS have been a major boost to the field of antivirals. Similarly, years of work transformed the prospects for people with hepatitis C, treatment for which used to entail nearly a year of drugs with harsh side effects. Now, a relatively short course of pills can cure it. "It's a success story," says ORNL's Head. But "boy," he adds, "was it a hard one to get to that success story."

Both AIDS and hepatitis C are chronic and affect a large number of people globally. Those factors created a large market to target for the pharmaceutical firms that could develop new and better treatments.

For acute viral infections, the time to take an antiviral is as soon as you're infected. That small therapeutic window can shrink the market for a drug, as can the fact that a virus might affect areas of the world that might not have pockets deep enough to pay for expensive drugs.

While public funding can help fill the gaps, many investors also have a short attention span. "The funding goes with the interest in public health, you know, so you'd see it move around



There aren't a lot of antivirals that have a broad-spectrum effect."

from Ebola to Zika, and then back to Ebola," Brown says. "There's no perfect solution."

The current pandemic has the world considering how to approach antiviral drug development differently.

In 2020, Littler's biotech start-up, ReViral, secured C-stage funding. He says that venture capital firms and investors are becoming more interested in investing in areas related to infectious disease. "There's a lot of money around to invest in good programs, whether or not that's private investment or public investment," he says. Littler also says he's noticed that pharma companies with virology expertise are putting more resources [into antiviral development](#).

That awakening to the need for new antivirals is, unsurprisingly, due to the lack of treatment options for COVID-19. Only a handful of antivirals have shown promise against SARS-CoV-2 in clinical trials. Since March 2020, Khoo has been part of the UK's [AGILE Coronavirus Drug Testing Initiative](#), which was created to accelerate the testing of drugs. When C&EN spoke to him in April 2021, AGILE had just injected the first patient with VIR-7832, a monoclonal antibody developed by Vir Biotechnology and GlaxoSmithKline for treating COVID-19. It's one of a handful of antibody drugs discovered amid the pandemic. But Khoo says he has been surprised at just how few small-molecule treatments against COVID-19 have appeared.

"You would have thought, a year into the pandemic, a lot of small molecules would be creeping into the market," Khoo says. "Some of them are, but it's largely not as much as we'd hoped for."

Experts say the world should be considering what research can be done to prepare us for future pandemics and developing funding models to support that work.

Bamforth says that by the time READDI launched in April 2020, as the pandemic was spreading, interest in what it was doing had grown. READDI board members stressed that the initiative needed to double its efforts. Bamforth expects that if READDI gets the funding and support it's hoping for, some of the therapeutics the team develops will target existing infections, while other assets will be held ready and waiting for viruses that we have yet to encounter. Those prospective treatments can be put through safety studies in humans and then stockpiled for when a virus appears.

That's an approach other people agree could work, but it needs an investment model to support it. "Once we get back to some sort of semblance of normality, we think there'll be about a window of 6 months where people are still interested," Bamforth says. The question is whether enough work can be done before that window closes.

This article is reprinted with permission from C&EN. A version of this article was published on cen.acs.org on May 20, 2021, and in C&EN's print magazine on May 24, 2021, on page 32.



We chose 20 promising companies developing antiviral therapies



- » **Adagio Therapeutics**
- » adagiotx.com
- » **Based:** Waltham, Massachusetts
- » **Launched:** 2020
- » **Money raised in start-up funding rounds:** \$466 million
- » **Publicly traded:** Yes; IPO 2021
- » **Key partnerships:** None
- » **Strategy:** Adagio focuses on developing broadly neutralizing antibodies that target proteins conserved across multiple members of the coronavirus family, not only to deal with the current COVID-19 pandemic but also to address future coronavirus outbreaks.
- » **Why watch:** The company's lead product candidate, ADG20, is in Phase 2/3 trials for both the treatment and prevention of COVID-19. Additional products, aimed at other coronaviruses and influenza, are in the early stages of development.



- » **Aligos Therapeutics**
- » aligos.com
- » **Based:** San Francisco
- » **Launched:** 2018
- » **Money raised in start-up funding rounds:** \$308.6 million
- » **Publicly traded:** Yes; IPO 2020
- » **Key Partnerships:** Merck
- » **Strategy:** Aligos is working on targeted antiviral therapies for chronic hepatitis B and coronaviruses. It is also using its expertise in liver diseases to develop, in partnership with Merck, targeted therapeutics for nonalcoholic steatohepatitis (NASH).
- » **Why watch:** The company has two drug candidates, one oligonucleotide and one small molecule, in Phase 1 clinical trials for hepatitis B. Phase 1 trials for three other candidates, for

hepatitis B and NASH, are expected to start in late 2021 and early 2022.



- » **AlloVir**
- » allovir.com
- » **Based:** Houston
- » **Launched:** 2013
- » **Money raised in start-up funding rounds:** \$159 million
- » **Publicly traded:** Yes; IPO 2020
- » **Key partnerships:** ElevateBio
- » **Strategy:** AlloVir develops virus-specific T cell (VST) therapies to treat or prevent viral diseases in people with T-cell deficiencies who have limited or no treatment options, including transplant recipients, immunocompromised cancer patients, older adults, and children.
- » **Why watch:** Diana Brainard, former head of virology at Gilead Sciences who oversaw the [repurposing of remdesivir](#) as a COVID-19 therapeutic, joined AlloVir as CEO in March 2021. The company has one candidate, posoleucel, in clinical trials to treat five different viral infections and several other candidates in preclinical development.



- » **Antios Therapeutics**
- » antiostherapeutics.com
- » **Based:** Atlanta
- » **Launched:** 2018
- » **Money raised in start-up funding rounds:** \$125.4 million
- » **Publicly traded:** No
- » **Key partnerships:** Arbutus Biopharma
- » **Strategy:** Antios aims to develop therapies to treat and cure chronic

hepatitis B infections, as well as hepatitis D coinfections.

- » **Why watch:** The company's lead candidate, ATI-2173, a first-in-class nucleotide that inhibits the hepatitis B virus's polymerase, is in Phase 2a clinical trials. Antios believes that when combined with an existing nucleoside analogue, it will form the backbone of an oral, once-daily, and potentially curative treatment for hepatitis B.



- » **Arbutus Biopharma**
- » arbutusbio.com
- » **Based:** Vancouver, British Columbia
- » **Launched:** 2007
- » **Money raised in start-up funding rounds:** \$127 million
- » **Publicly traded:** Yes; IPO 2010
- » **Key partnerships:** Antios Therapeutics, Assembly Biosciences
- » **Strategy:** Arbutus is focused on developing a cure for people with chronic hepatitis B virus infection. The company is working on multiple candidates with distinct mechanisms of action that in combination could provide a cure for hepatitis B.
- » **Why watch:** The company's lead candidate, an RNA interference drug called AB-729, is in Phase 2 clinical trials. In June 2021, Arbutus joined with Antios Biopharma to test AB-729 in combination with Antios's ATI-2173.



- » **Assembly Biosciences**
- » assemblybio.com

- » **Based:** Carmel, Indiana
- » **Launched:** 2005
- » **Money raised in start-up funding rounds:** Not available
- » **Publicly traded:** Yes; IPO 2010
- » **Key partnerships:** Arbutus Biopharma, Door Pharmaceuticals
- » **Strategy:** Assembly is dedicated to curing chronic hepatitis B infections using a novel class of small molecules to inhibit the virus core protein that is key to forming the virus's capsid.
- » **Why watch:** VBR, the company's most advanced drug candidate, is currently in Phase 2 clinical trials. More effective next-generation candidates are also in Phase 1 and 2 trials and may be as much as 50 times as potent as VBR, the company says.



- » **Atea Pharmaceuticals**
- » ateapharma.com
- » **Based:** Boston
- » **Launched:** 2014
- » **Money raised in start-up funding rounds:** \$283.4 million
- » **Publicly traded:** Yes; IPO 2020
- » **Key partnerships:** Roche
- » **Strategy:** Atea uses its purine nucleotide prodrug platform to develop oral, direct-acting antiviral drugs that interfere with viral replication.
- » **Why watch:** Atea's most advanced drug candidate, AT-527, has been well tolerated and has shown antiviral activity in patients with hepatitis C. It is now in Phase 3 clinical trials for the treatment of mild and moderate COVID-19 in an outpatient setting.



- » **BioCryst**
- » biocryst.com
- » **Based:** Durham, North Carolina
- » **Launched:** 1986
- » **Money raised in start-up funding rounds:** \$581.9 million
- » **Publicly traded:** Yes; IPO 1994
- » **Key partnerships:** None
- » **Strategy:** BioCryst uses structure-based drug design to develop molecules that will bind to the active site of

a specific enzyme to halt disease progression. The company's primary focus is on developing drugs for rare diseases in which patient needs are still largely unmet.

- » **Why watch:** BioCryst's first successful drug, peramivir (Rapivab), was approved by the US Food and Drug Administration in 2014 to treat influenza. Another antiviral, galidesivir, has completed Phase 1 trials. It is a broad-spectrum antiviral for the treatment of a range of viruses, including Ebola, Marburg, SARS-CoV-2, yellow fever, and Zika.



- » **Brii Biosciences**
- » briibio.com
- » **Based:** San Francisco
- » **Launched:** 2018
- » **Money raised in start-up funding rounds:** \$415 million
- » **Publicly traded:** No
- » **Key partnerships:** Vir Biotechnology
- » **Strategy:** Brii is focused on developing medicines to prevent, treat, and cure a wide range of infectious diseases. It focuses in particular on diseases of importance in China, such as hepatitis B, HIV, and SARS-CoV-2.
- » **Why watch:** Brii has two human monoclonal antibody drug candidates for SARS-CoV-2 in Phase 3 clinical trials, as well as several for hepatitis B and HIV at earlier stages of clinical research.



- » **Cocrystal Pharma**
- » cocrystalpharma.com
- » **Based:** Bothell, Washington
- » **Launched:** 2004
- » **Money raised to date:** \$48 million
- » **Publicly traded:** Yes; IPO 2017
- » **Key partnerships:** Merck
- » **Strategy:** Cocrystal employs its structure-based drug design platform to develop small-molecule antiviral therapeutics that target the replication process of viruses that cause serious chronic illness.
- » **Why watch:** The company's research is led by Roger Kornberg, who won the [2006 Nobel Prize in Chemistry](#) for his work on RNA polymerase. Cocrystal has completed a Phase 2a clinical trial of a hepatitis C drug.



- » **Enanta Pharmaceuticals**
- » enanta.com
- » **Based:** Watertown, Massachusetts
- » **Launched:** 1998
- » **Money raised in start-up funding rounds:** \$84.6 million
- » **Publicly traded:** Yes; IPO 2013
- » **Key partnerships:** Abbott Laboratories, Shionogi
- » **Strategy:** Enanta develops small-molecule drugs for hepatitis B, human metapneumovirus, respiratory syncytial virus (RSV), and SARS-CoV-2.
- » **Why watch:** The company has successfully developed two drugs for hepatitis C, glecaprevir and paritaprevir, which are sold by AbbVie. It has several other drugs in its pipeline for hepatitis B, RSV, and SARS-CoV-2 at various stages of clinical development.



- » **Ennaid Therapeutics**
- » ennaidthera.com
- » **Based:** Alpharetta, Georgia
- » **Launched:** 2012
- » **Money raised in start-up funding rounds:** Not available
- » **Publicly traded:** No
- » **Key partnerships:** Strides Pharma Science
- » **Strategy:** Ennaid seeks out and acquires early-stage science that is not being exploited by large pharma companies to develop cures for the mosquito-borne Zika and dengue viruses.
- » **Why watch:** In addition to its promising treatments for Zika and dengue, Ennaid has partnered with Strides to manufacture a potential treatment for COVID-19 based on an already-approved compound identified by a computer model.



- » **Excision BioTherapeutics**
- » excision.bio
- » **Based:** Philadelphia
- » **Launched:** 2015
- » **Publicly traded:** No
- » **Money raised in start-up funding rounds:** \$70.8 million

- » **Key partnerships:** None
- » **Strategy:** Excision is developing CRISPR-based gene-editing therapies for viral infectious diseases.
- » **Why watch:** The company has drug candidates in preclinical development for a number of viral infections, including hepatitis B, herpes, HIV, and SARS-CoV-2.



- » **ExeVir Bio**
- » exevir.com
- » **Based:** Ghent, Belgium
- » **Launched:** 2020
- » **Money raised in start-up funding rounds:** \$49 million
- » **Publicly traded:** No
- » **Key partnerships:** None
- » **Strategy:** ExeVir is working on therapies for SARS-CoV-2, including variants, based on antibody fragments from llamas.
- » **Why watch:** Llama-derived nanobodies attracted attention early on in the COVID-19 pandemic for their ability to attach to parts of a virus that are difficult for the human immune system to access. XVR011, ExeVir's lead candidate, is in Phase 1b trials for SARS-CoV-2.



- » **Pardes Biosciences**
- » pardesbio.com
- » **Based:** Carlsbad, California
- » **Launched:** 2020
- » **Money raised in start-up funding rounds:** \$51.6 million
- » **Publicly traded:** No
- » **Key partnerships:** None
- » **Strategy:** Pardes uses structure-based drug design and a reversible covalent chemistry platform to develop antivirals for SARS-CoV-2.
- » **Why watch:** Founded by former executives from Assembly Bio, Gilead, and other pharmaceutical companies, the company is developing PBI-0451 as an oral antiviral drug designed to inhibit the SARS-CoV-2 main protease, which is highly conserved across all coronaviruses.

Note: Companies were included because of the novelty and potential of their methods, amount of capital raised, number of partnerships, and number and identity of investors.



- » **Replicor**
- » replicor.com
- » **Based:** Montreal
- » **Launched:** 1998
- » **Money raised in start-up funding rounds:** Not available
- » **Publicly traded:** No
- » **Key partnerships:** None
- » **Strategy:** Replicor develops nucleic acid polymers, a type of oligonucleotide, to treat liver diseases such as hepatitis B and hepatitis D.
- » **Why watch:** The company's lead candidate, REP 2139, has shown good results in Phase 2 trials for hepatitis B as well as hepatitis D—the deadliest form of hepatitis, for which there is currently no FDA-approved treatment.



- » **ReViral**
- » reviral.co.uk
- » **Based:** Stevenage, England
- » **Launched:** 2011
- » **Money raised in start-up funding rounds:** \$121 million
- » **Publicly traded:** No
- » **Key partnerships:** LianBio
- » **Strategy:** ReViral is focused on developing therapies for respiratory syncytial virus (RSV), one of the most common causes of respiratory infections in children, older adults, and immunocompromised people.
- » **Why watch:** Despite the prevalence of RSV, there are few FDA-approved therapies for it, and none for adults. ReViral's lead candidate, sisunatovir, has shown promising results in Phase 1 and 2 trials.



- » **Ridgeback Biotherapeutics**
- » ridgebackbio.com
- » **Based:** Miami
- » **Launched:** 2016
- » **Money raised in start-up funding rounds:** Not available

Sources: Crunchbase (accessed August 2021), company websites, news reports.

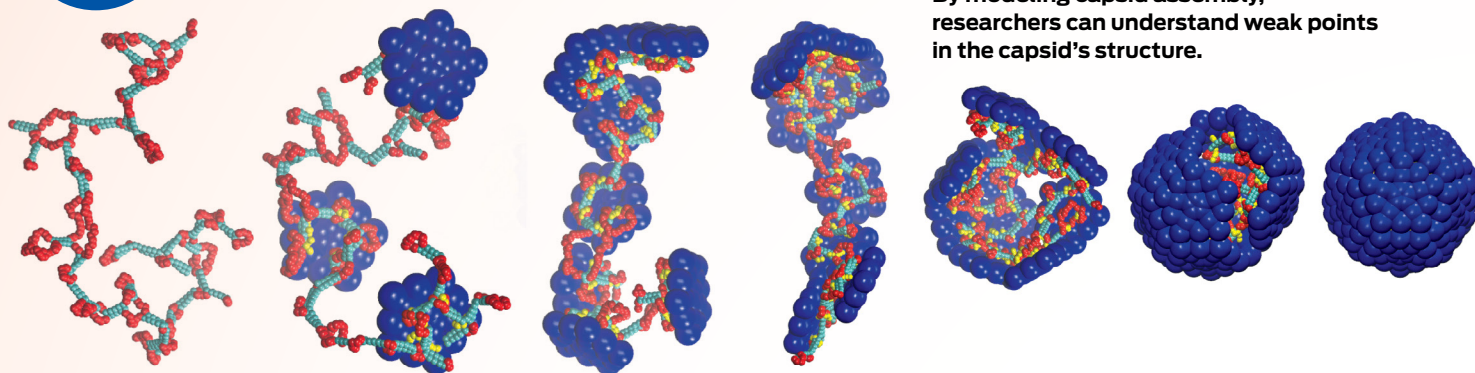
- » **Publicly traded:** No
- » **Key partnerships:** Merck
- » **Strategy:** Ridgeback focuses on developing therapies for emerging infectious diseases with limited treatment options, such as Ebola and COVID-19.
- » **Why watch:** Ridgeback's drug ansuvimab (Ebanga) was approved by the FDA to treat Ebola in December 2020, while its COVID-19 drug molnupiravir is in Phase 3 trials in collaboration with Merck.



- » **Selva Therapeutics**
- » selvarx.com
- » **Based:** San Diego
- » **Launched:** 2017
- » **Money raised in start-up funding rounds:** \$3 million
- » **Publicly traded:** No
- » **Key partnerships:** None
- » **Strategy:** Selva is developing a small-molecule cathepsin inhibitor as an indirect antiviral therapy that acts against several types of viruses.
- » **Why watch:** The company's leading drug candidate, SLV213, has completed Phase 1 trials for SARS-CoV-2. It has also shown activity against Ebola, Marburg, and Nipah viruses as well as Chagas disease, which is caused by a parasite.



- » **Vir Biotechnology**
- » vir.bio
- » **Based:** San Francisco
- » **Launched:** 2016
- » **Money raised in start-up funding rounds:** \$793.6 million
- » **Publicly traded:** Yes; IPO 2019
- » **Key partnerships:** GSK, Alnylam
- » **Strategy:** Vir takes inspiration from the immune system, using antibodies, T cells, small interfering RNA, and other components to develop treatments for infectious diseases.
- » **Why watch:** The company's monoclonal antibody drug sotrovimab has received emergency use authorization for the treatment of COVID-19 and has shown efficacy against several SARS-CoV-2 variants including Delta. Its pipeline includes several other immunology drugs for hepatitis B, HIV, and influenza.



By modeling capsid assembly, researchers can understand weak points in the capsid's structure.

Lessons learned from watching viruses assemble

LAURA HOWES, C&EN STAFF

Inside a cell, a single protein emerges from the cell's protein-making machinery, then another, and another. They move about—bouncing into one another, wriggling around, and drifting away again. Soon, two proteins link up. Sticky patches on the proteins come together, protecting each other from the cell's watery contents. Positively charged proteins attract negatively charged nucleic acids. Hydrogen bonds form and break. An assembly process has begun.

But these proteins aren't building a piece of cellular machinery. This cell has been hijacked, and now it is making more hijackers. It has been infected by a virus, which has transformed the cell into a factory for making more of its kind.

Scientists have spent their careers trying to understand how viruses, the ultimate nanomachines, build themselves from smaller components. Combining biochemical data, microscopy, and complex calculations, they are modeling the conditions and chemical properties that allow so many individual pieces to form a complex shape. The details of that self-assembly process could help researchers defeat the virus with antivirals or build protective shells for drug delivery.

Viruses are "incredibly simple yet incredibly complicated," says Helena Maier, an expert in coronavirus replication at the Pirbright Institute. Their genomes might code for only a tiny fraction of the proteins made by plants or animals, but

"they can take over entire biological systems to do what they need to do," Maier says.

Be they SARS-CoV-2, HIV, or phages that infect bacteria, all viruses comprise at least two components: their genetic material—DNA or RNA—and a protective shell called a capsid. Depending on the virus, that shell could be made from 100 to 10,000 individual protein subunits. The size, shape, and particular elements of the capsid are unique to each virus, but they are all built from smaller components, says Brandeis University's Michael Hagan, who models how the protective protein cages of viruses form.

When it comes to the assembly of that cage, he says, "there are a lot of common threads." As a capsid shuffles into its optimal shape, each interaction between subunits is relatively weak. Hagan says that might be the point: the process is self-correcting, and once the capsid is fully formed, it's optimized for its job. The interactions that are crucial to viral replication, including assembly, would be a "perfect target for an antiviral," Maier says.

A capsid can have one of two general shapes. Icosahedral capsids completely encase the viral genome in a round box, while helical capsids complex the genome, creating a spring shape. According to Juan Perilla at the University of Delaware, whichever shape a virus's capsid takes, the delicate balance of interactions that holds the capsid together can tell him how the virus enters the cell and what it does when it gets there. Perilla describes a virus as a little machine with intimate knowledge of its host cell and the expertise to negotiate that cell's defenses.

Take, for example, the Ebola virus. Like coronaviruses, filoviruses like those that cause Ebola have a genome made of RNA and feature a helical nucleocapsid. Ebola uses a complex entry mech-



We study [viruses], and they're fascinating. They make these beautiful structures, and one can learn so much from them. But you can also see the havoc that they wreak."

anism to get into the cell, Perilla explains, but once inside, its nucleocapsid complex quickly falls apart to release the viral RNA. Individual capsid proteins interact with the infected cell's RNA to disrupt healthy function.

By contrast, HIV has a different capsid structure—one that plays a different role, Perilla says. Inside the membrane of an HIV particle, an icosahedral shell of protein subunits arranged in hexagons and pentagons forms a conical box that protects a genome made of RNA. Once the virus infects the cell, this box-like arrangement of proteins regulates many cellular processes while remaining undetected. It interacts with cellular proteins that help import the viral DNA into the nucleus, the very heart of the cell. Only when the virus is in the right place will the capsid crack open to deliver its cargo.

Understanding the minute details of these infection processes—the physical and mechanical properties that enable a capsid to disassemble and form again—could reveal ways to take down a virus. Researchers can design vaccines to stop viruses from getting into cells or develop antivirals to prevent different steps in a virus's replication. For example, researchers can interfere with the production of the virus in cells or with the viral capsid's properties.

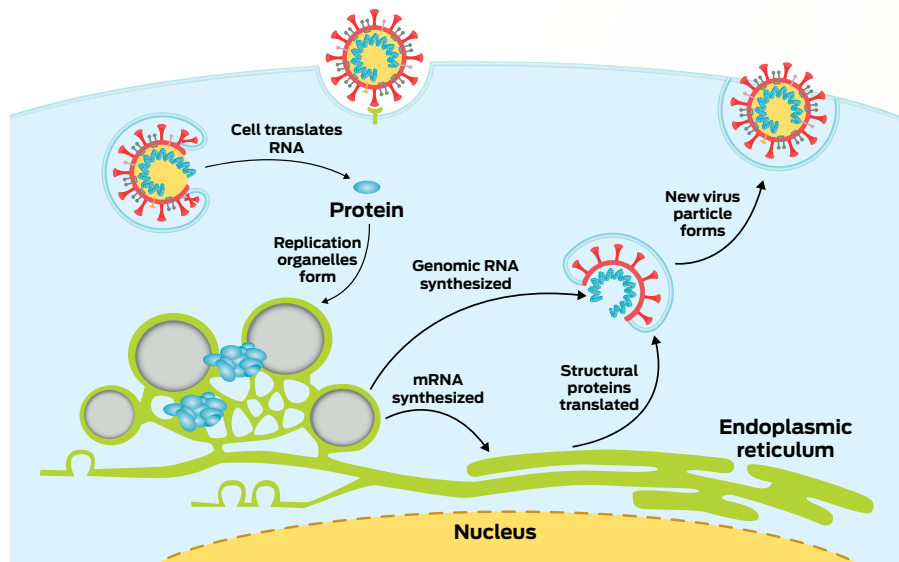
Perilla runs vast calculations to understand capsid stability at an atomic level and says that even a small disruption in the delicate balance of interactions can have catastrophic effects for a virus. He and his team use their calculations to find regions in the capsid that are important for structural stability. Perturbing those areas with a small molecule might mean the capsid opens at the wrong time or place, allowing the cell to digest the viral components. Conversely, those perturbations might instead lock the capsid shut so it never releases its nucleic acid cargo.

Using a drug to disrupt capsid assembly or stability isn't just theoretical. In 2006, Gilead Sciences began a project to look for small molecules that would disrupt the formation of the HIV capsid. The team mixed small molecules with purified capsid proteins in biochemical screens to find compounds that either sped up or slowed down the spontaneous assembly of protein complexes. Then in 2009 and 2011, academic researchers published the crystal structures of the heptamers and pentamers that stitch together to form the capsid (*Cell* 2009, DOI: [10.1016/j.cell.2009.04.063](https://doi.org/10.1016/j.cell.2009.04.063); *Nature* 2011, DOI: [10.1038/nature09640](https://doi.org/10.1038/nature09640)). That information, and another 6 years of structure-guided design, resulted in a drug candidate, lenacapavir, that is still undergoing clinical trials.

How SARS-CoV-2 builds itself

When the coronavirus that causes COVID-19 infects a cell, it unfurls the genetic blueprint for a few key components, which the cell begins to construct. The first proteins produced perform multiple jobs. One key job is to build replication organelles, virus-producing factories that are filled with viral proteins and bits of host-cell machinery. They churn out more and more copies of the viral genome until the infected cell turns all its attention to making viral RNA and proteins.

Structural proteins, the building blocks of new virus particles, collect in a part of the cell called the endoplasmic reticulum, where small micelles containing the spike, membrane, and envelope proteins are created. The nucleocapsid proteins complex with the newly produced genomic RNA to form the nucleocapsid. The nucleocapsid pushes into a small bend that forms in the membrane until—pop—a new virus particle emerges. And off it goes to infect another cell.



SOURCE: ADAPTED FROM *NAT. REV. MICROBIOL.* 2020, DOI: [10.1038/S41579-020-00468-6](https://doi.org/10.1038/S41579-020-00468-6).

In email correspondence with C&EN, Stephen Yant, director of HIV discovery virology at Gilead, explains that lenacapavir uses electrostatic interactions and hydrogen bonding to change how the HIV capsid assembles and interacts with the cell. For example, the drug promotes binding between the individual protein components during assembly and then binds to and stabilizes the multimers that join to form the capsid. Collectively, Yant says, these interactions accelerate capsid formation, “resulting in malformed capsids” that cannot be replicated.

During the development of lenacapavir, researchers also learned more about the role of the capsid protein, Yant says. They found that the drug not only disrupts capsid assembly but also interferes with other capsid protein-dependent functions throughout the viral replication cycle. One of those disrupted functions, Yant says, is the process by which the HIV capsid helps import viral DNA into an infected cell's nucleus and then integrate it into the cell's DNA.

And if HIV succeeds in infecting a cell, lenacapavir can slow disassembly and interrupt other capsid protein-dependent functions to stop new copies of the virus from being made. Studies on HIV capsid biology “continue to uncover fascinating new roles for the capsid at nearly every stage of the viral replication cycle,” Yant says.

Capsid inhibitors could also address other viruses. For example, firms such as Arbutus Biopharma and Assembly Biosciences are betting that by inhibiting assembly of the hepatitis B virus (HBV) capsid, they can block replication and treat the disease more effectively. They aim to improve on the current HBV treatment, which requires a regimen of drugs that suppresses but does not eliminate the virus. Both Arbutus and Assembly have HBV capsid inhibitors in clinical trials.

The modeling and calculations that scientists like Perilla and Hagan perform can guide the design of capsid inhibitors by suggesting areas of the shell that are important for its stability or assembly. Perilla recently identified the key interactions for the Ebola nucleocapsid, and he and his team started investigating the SARS-CoV-2 nucleocapsid early in 2020. Those SARSCoV-2 models, Perilla says, are still evolving as more experimental and biochemical data become available.

While some researchers try to disrupt the in-

But designing these systems isn't trivial. Viruses have had millions of years to work out how to do it, Wilson says, and they are experts at building their protective structures from simple starting materials. She says chemists do have one design advantage: they can use materials and polymers that are different from the proteins, RNA, and DNA that viruses rely on.

University of Minnesota Twin Cities chemist Theresa Reineke agrees. "As a synthetic chemist, we have essentially infinite chemical space and infinite architectural space to work from," she says. For example, Reineke's lab develops delivery systems made from synthetic polymers; these systems are designed to deliver their therapeutic contents into cells similarly to the way viruses deliver their genetic cargo.

Reineke's team has built and characterized two architectures made of glycopolymers that, like a viral capsid, assemble using noncovalent interactions and entropy. In one architecture, a shell of polymers noncovalently associates around the

“There are still “fundamental things to be learned about self-assembly from viruses because they do it so well.”

tricate processes of infection, replication, and assembly, others rely on viruses to inspire self-assembling systems that can package drugs and even deliver them to where they need to go.

To design a self-assembling system that mimics a virus, researchers need to remember that viruses consist of molecules with certain affinities and specific interactions, says Daniela Wilson, head of systems chemistry at Radboud University. While descriptions of viruses can often ascribe agency to the little machines, she says, they are just a collection of interacting compounds. Their self-assembly relies on noncovalent interactions that are familiar to chemists, including hydrogen bonding, the hydrophobic effect, and electrostatic attraction.

Although viral assembly can involve host-cell proteins and other active processes, it is mostly random, Hagan says. Proteins just bump up against one another and then stick together as the capsid travels down a free-energy path. And it might seem counterintuitive, but entropy, the measure of disorder in a system, can also help the shell form. Instead of being able to freely rotate and move through space, each protein subunit becomes more fixed in space as it joins the assembling structure. But at the same time, counterions and water molecules are released as each new subunit joins the growing capsid, increasing the entropy overall. "It's actually entropy driven at the end in some cases," Hagan says.

Those same noncovalent interactions and entropic factors can be used to build artificial assemblies. For example, systems chemists like Wilson are trying to build small, bottom-up self-assembling structures that can deliver drugs. These structures form spontaneously, package up cargo, and then release the drug where it needs to go, functioning like a virus, but with a helpful rather than harmful payload.

payload. In the second, self-assembled polymer micelles attach to or wrap around a protein or nucleic acid payload but don't fully contain it in a shell.

The second approach, Reineke says, might be more promising. The polymer seems to bind the payload tightly enough to get it into the cells but loosely enough that it can then be released (*J. Am. Chem. Soc.* 2019, DOI: [10.1021/jacs.9b06218](https://doi.org/10.1021/jacs.9b06218)). Just as with viral capsids, the binding needs to be balanced to find that sweet spot for release.

Many researchers, like Reineke, are using synthetic polymers to develop self-assembling containers. Others have built synthetic nucleocapsids out of nonviral, laboratory-designed proteins (*Proc. Natl. Acad. Sci. U.S.A.* 2018, DOI: [10.1073/pnas.1800527115](https://doi.org/10.1073/pnas.1800527115)) or created DNA-origami nanostructures that can deliver drugs and then release them when inside the right cells.

Hagan says that as the field of capsid biology and smart materials evolves, there are still "fundamental things to be learned about self-assembly from viruses because they do it so well." Researchers expect that the growing understanding of how viruses assemble will inform the design and understanding of other self-assembling systems—and help researchers put together lots of small interactions to create something more significant than the constituent parts.

Viruses can cause all sorts of chaos, Hagan says. "We study them, and they're fascinating. They make these beautiful structures, and one can learn so much from them," he says. "But you can also see the havoc that they wreak."

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To conquer COVID-19, create the perfect pill

BETHANY HALFORD, C&EN STAFF

As the COVID-19 crisis unfurled, scientists [accomplished feats](#) once considered impossible. Cheap, reliable [COVID-19 tests](#) are now readily available in many parts of the world. And the fact that hundreds of millions of people have taken safe and effective [vaccines](#) for a virus first identified less than 2 years ago is a marvel of modern medicine.

But those advances may not be enough to end the pandemic.

COVID-19 isn't going away, says Sarah Read, the deputy director of the Division of AIDS at the US National Institute of Allergy and Infectious Diseases (NIAID). Many countries don't have access to enough doses of vaccine to come close to immunizing the masses. Low- and lower-middle-income countries, which account for almost half the world's population, have received only 17% of COVID-19 vaccines, according to the [World Health Organization](#). Even places where vaccination rates are high—Israel, the UK, and the US—continue to see infections, albeit less deadly ones. What's more, some proportion of the population, which Read says could be as high as 20% in the US, either can't or will choose not to be vaccinated.

COVID-19 could linger for years as many remain unvaccinated and as the virus continues to mutate, potentially making [variants that render vaccines less effective](#). Doctors and public health experts say



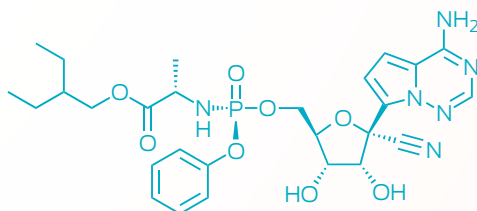
they're still missing one key tool—an oral antiviral.

“There's always going to be a need for another mechanism of protection,” says Read, who for the past year has focused on evaluating clinical therapeutics for COVID-19. “What we need to really make a dent in the pandemic is to be able to treat people very early in the course of their illness, right when they're diagnosed: give them a safe, oral antiviral they can start immediately and prevent them winding up in the hospital, prevent them from dying, and prevent those strains on the health-care system.”

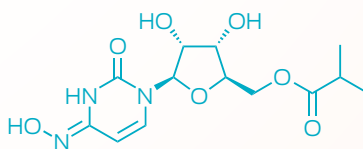
Making antivirals specifically for infections of SARS-CoV-2—the virus that causes COVID-19—or for acute viral infections in general has been tough. Antivirals are effective for only a short period between infection and full-blown disease. What's more, it usually takes years to develop an antiviral and bring it to market. Often, public health measures eradicate a virus before a new antiviral can become available.

Approved antivirals that predate the current pandemic either haven't been effective at stopping SARS-CoV-2 infections or have had only limited success. Nevertheless, drugmakers continue to pursue the elusive goal of a pill that kills SARS-CoV-2. Gilead Sciences is hoping to tweak its antiviral drug [remdesivir](#) (marketed as Veklury) so that it can be given orally. Merck & Co. is pouring resources into [molnupiravir](#), a compound that was in early development at the Emory Institute for Drug Development for other diseases before the COVID-19 pandemic. And Pfizer started developing its oral SARS-CoV-2 inhibitor [PF-07321332](#) from scratch.

Being able to give a pill to people experiencing the first symptoms of a SARS-CoV-2 infection or to people who know they've been exposed to the virus could give doctors a way to intervene early in the course of the disease, says Mangala Nara-



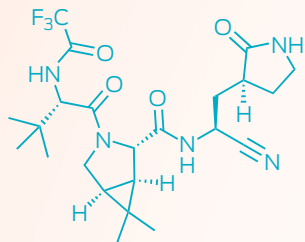
Remdesivir



Molnupiravir

simhan, a physician and director of critical care services at Northwell Health in New York.

“We find antivirals for the flu, like Tamiflu, to be very helpful,” Narasimhan says. When people start taking influenza antivirals early, she says, “it does change the course of illness and how sick they get.” Having an effective pill for SARS-CoV-2 would really help, she says.



PF-07321332

Tamiflu has a downside: to be effective, it must be taken shortly after symptoms emerge. COVID-19 doesn't progress as quickly as influenza, Narasimhan says. People with COVID-19 develop mild symptoms 3–5 days after they've been exposed to the virus, but their symptoms often aren't severe enough to require hospitalization for another week. “If you had an oral drug that could be given to them at home and we could educate people to call when their symptoms start,” she says, it could make the disease milder. But right now, she says, “we don't have anything really that works well.”

Remdesivir is the only antiviral approved by the US Food and Drug Administration to treat COVID-19. The drug was originally developed for hepatitis C and was tested during the 2018 Ebola virus disease outbreak in the Democratic Republic of the Congo. Gilead tested remdesivir's activity against COVID-19 early in the pandemic and saw promising results. But remdesivir can be given only intravenously in a hospital. By the time an infection is serious enough to send someone to the hospital, the disease is usually too advanced for an antiviral to help.

Narasimhan says remdesivir has been a disappointment. “We haven't really seen big, miraculous benefits for patients. Remdesivir really sort of hasn't made a difference. We've almost shied away from using it,” she says.

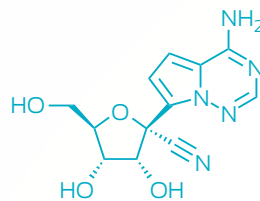
“At some point with every antiviral drug, there's a point of no return,” says Tomas Cihlar, Gilead Sciences' vice president of virology. He explains that remdesivir suppresses the virus's ability to copy itself by interfering with a key enzyme, the RNA-dependent RNA polymerase. But when a person's COVID-19 infection is past a certain stage, the disease is driven by an inflammatory process, and stopping replication doesn't have much of an effect on symptoms.

“The sooner the antiviral is administered, the better. So ideally, we would like to shift most of our impact with antivirals to outpatient settings, where the antivirals could make the most difference, primarily in preventing the hospitalizations,” Cihlar says.

To that end, Gilead has been working on an inhaled formulation of remdesivir, which is in Phase

1 clinical trials. But Cihlar acknowledges that what Gilead would really like is a version of the drug that could be taken as a pill. Remdesivir won't work as an oral drug, though—not enough of it gets into the system to be effective when it's swallowed.

“You have to redesign the molecule to some extent,” Cihlar says. “That's what we've been doing over the last year.” Gilead scientists have been re-decorating the core molecule, known as GS-441524, in an attempt to boost its oral bioavailability. They haven't released any other details.



GS-441524

Other companies have also studied antivirals developed for other diseases as COVID-19 treatments. BioCryst Pharmaceuticals' investigational antiviral galidesivir, originally developed for hepatitis C, went through Phase 1 clinical trials for COVID-19 in Brazil, but the company decided not to pursue it further.

Fujifilm's favipiravir, which is marketed as the emergency flu treatment Avigan in Japan, has been studied in both small inpatient and outpatient trials for the past year with mixed results, says Robert Finberg, a professor of medicine at the University of Massachusetts Medical School who was involved with the trials. The drug offered little benefit to

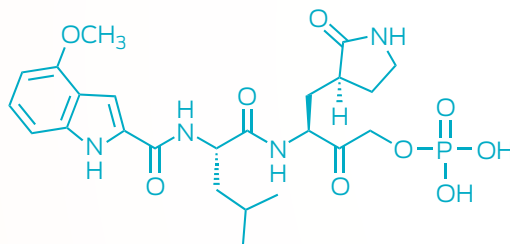
people hospitalized with COVID-19, and the results from outpatient trials, which look more promising, haven't been published yet, Finberg says. To be effective, he says, “it probably needs to be given very early.”

One investigational compound generating a lot of interest in the past year is molnupiravir, an oral antiviral which is being developed by Merck & Co. and Ridgeback Biotherapeutics. In April, the companies announced they were beginning a Phase 3 clinical trial of molnupiravir for people who have COVID-19

but aren't in the hospital. The companies scrapped plans to use the antiviral candidate in hospitalized COVID-19 patients after deciding that population is probably too sick to see any benefit from the antiviral. Merck also plans to start a trial in the second half of this year to study whether molnupiravir can prevent infections in people who have been exposed to SARS-CoV-2.

“We know from animal studies that, like influenza antivirals, antivirals against coronavirus work best when they're used very early in infection,” says Daria Hazuda, vice president of infectious diseases and vaccine discovery at Merck. “And they work phenomenally when given to prevent transmission.”

Researchers at the Emory Institute for Drug Development started exploring molnupiravir, which they called [EIDD-2801](#), several years ago as a treatment for viral infections including influenza and Venezuelan equine encephalitis virus. Molnupiravir interferes with a virus's RNA-dependent RNA



PF-07304814

“What we need to really make a dent in the pandemic is to be able to treat people very early in the course of their illness, right when they’re diagnosed: give them a safe, oral antiviral they can start immediately and prevent them winding up in the hospital, prevent them from dying, and prevent those strains on the health-care system.”

—Sarah Read, deputy director of the Division of AIDS, US National Institute of Allergy and Infectious Diseases

polymerase, leading to copies of the virus that can’t function.

The mechanism works against a broad spectrum of viruses. “Vaccines are great, but vaccines are incredibly specific,” Hazuda says. Because molnupiravir is active against many types of viruses in addition to SARS-CoV-2, it has the potential to be deployed for future outbreaks of unknown coronaviruses and for novel strains of the flu, she says. “To have an antiviral that has that sort of a broad spectrum that can be used across these kinds of pathogens is really very exciting.”

Other drugmakers are similarly focused on creating antivirals that can target multiple coronaviruses. “We want to be ready and equipped for future pandemics,” says Charlotte Allerton, Pfizer’s head of medicine design. Also, she adds, while COVID-19 vaccines appear to offer broad protection, that might not always be the case. Vaccine-resistant variants of SARS-CoV-2 could develop.

To create a broad-acting antiviral for coronaviruses, scientists at Pfizer have been working on compounds that target SARS-CoV-2’s main protease, also known as the 3CL protease. Blocking this enzyme stops the virus from breaking up long protein chains into the components it needs for reproduction. And this protease’s structure is essentially the same in all coronaviruses. That means that a small molecule that blocks 3CL in SARS-CoV-2 could also block a novel coronavirus’s 3CL, giving doctors a tool to stamp out a virus before it spreads.

Last year Pfizer announced it had an intravenous SARS-CoV-2 drug candidate—PF-07304814—in clinical trials. The compound originated in a 2003 project aimed at developing an antiviral for severe acute respiratory syndrome (SARS). The company shut down the project when that SARS outbreak was under control.

It was clear that PF-07304814 couldn’t be made into a compound that could be delivered orally, so in 2020, Pfizer scientists began a new effort to find a compound that could be. Allerton says that although the new team benefited from information gleaned in the 2003 project—the 3CL in the viruses that cause SARS and COVID-19 are essentially identical, so the researchers understood the geography of their target’s active site—the scientists were building their molecule from scratch.

Pfizer unveiled the results of that effort in April at the American Chemical Society Spring 2021 meeting. The oral clinical candidate PF-07321332 was identified in July 2020 and began Phase 1 clinical trials in February. In July, the company began

a Phase 2/3 trial of PF-07321332 combined with ritonavir, and on Sept. 1 it announced it had begun a Phase 2/3 trial of PF-07321332 alone.

Scientists at Novartis also have their sights set on an antiviral that could kill multiple coronaviruses. John Tallarico, head of chemical biology and therapeutics at Novartis Institutes for BioMedical Research, says Novartis has been working on an oral coronavirus 3CL inhibitor, although the company doesn’t expect to disclose any of its lead compounds before 2022.

Tallarico says that when Novartis started working on the project more than a year ago, it wasn’t clear that the world would still be grappling with SARS-CoV-2 now, which is why scientists there are looking for a pancoronavirus inhibitor. From March to September 2020, he says, their mantra was “this is about the next pandemic.” When it became clear that SARS-CoV-2 is going to be a global problem for years to come, their focus shifted to the current pandemic. A pill for preventing or treating the virus could help curb outbreaks, particularly in countries where supply chain hurdles, such as cold storage and distribution, make vaccinations more challenging.

Given the limited success of our current collection of approved antivirals, researchers hope this next batch will provide better protection for future outbreaks. But will this handful of drug candidates be enough?

“We really didn’t have much to start with during this pandemic,” NIAID’s Read says. “In terms of preventing future pandemics or responding more quickly to future pandemics, I think it would be good to have a better starting point.” Whatever scientists learn about antivirals now will give them a better foundation for addressing emerging threats.

Merck’s Hazuda says devoting more resources to developing antivirals for acute infections will help with future outbreaks. “The antiviral world, for many years, maybe decades, was focused primarily on chronic viral infections,” such as HIV infection and hepatitis C, she says. There hasn’t been much attention paid to acute infections, like SARS. “Hopefully we have learned that antivirals play a very important public health role in addition to vaccines when there are outbreaks, whether they’re seasonal outbreaks or they’re pandemic outbreaks,” Hazuda says.

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Our picks of the journal literature on antivirals

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