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TOP STORY

A crystallization lab in Buffalo is at center of global war against coronavirus

Scott Scanlon
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Sarah Bowman is among a small group of scientists at work on novel coronavirus drug and preventative treatment efforts at the Hauptman-Woodward Institute in Buffalo. Bowman, associate research scientist and director of the institute's High-Throughput Crystallization Screening Center, demonstrates the use of a pipette computer that transfers samples to run tests to create crystallized models of some of the proteins in the virus, including the spiked protein.

James P. McCoy/Buffalo News

Scott Scanlon

A group of scientists on the Buffalo Niagara Medical Campus has spent the last year using biology and X-ray technology to help fellow researchers foil the novel coronavirus.

The scientists take individual proteins that make up the virus, coax them into 3-dimensional models and send them to researchers across the globe at work on preventative therapies and potential treatments.

They also can forge models that show how some of the 29 proteins that make up the virus interact with human cells, as well as experimental drugs and off-label medications that might thwart Covid-19.

“The virus is like a Lego set and we want to know what the different pieces look like,” said Sarah Bowman, director of the High-Throughput Crystallization Screening Center at the Hauptman-Woodward Medical Research Institute.

The center is among few labs worldwide with the equipment and staff to do high-throughput structural screen that so far has killed more than 2.3 million people worldwide, including 460,000 Americans.

It is a cornerstone **of an institute started in 1956** and later named to honor Herbert A. Hauptman, one of its scientists, who won the 1985 Nobel Prize in Chemistry for groundbreaking work using X-ray crystallography and mathematics to better visualize how proteins and drug therapies interact.

The Crystallization Center opened in 2000. Bowman, a Detroit native, came to Buffalo almost four years ago to run it.

She and her staff work with scientists in hundreds of laboratories. Their efforts also focus on proteins that serve as building blocks of other diseases, including AIDS, arthritis, metabolic disorders, Alzheimer's, Parkinson's and some cancers – as well as how potential medications interact with them.

They said they are honored to help find ways to disable the new coronavirus and build resistance to its infectious power.

"It's been incredible to observe and to be part of that effort," Bowman said. "People are understanding more and more as we go."

Sarah Bowman, director of the Hauptman-Woodward Medical Research Institute and director of its High-Throughput Crystallization Screening Center, works with research samples in part of her lab.

James P. McCoy

The process

Proteins that make up the coronavirus, SARS-CoV-2, are too small to be seen using microscopes common in science kits or chemistry labs. A single virus is about 0.1 micron in diameter. About 600 virus particles could sit side-by-side across a single human hair.

"The institute is, quite literally, making the invisible visible," said Edward Snell, Hauptman-Woodward CEO. "Our efforts allow us to see and know the enemy, one of the keys to victory in any battle."

The Crystallization Center began working with new coronavirus samples a year ago, shortly after the pandem
United States.

Some drug-makers and universities have similar labs, but the center is unique because of its high-throughput options, equipment, and expertise. Many scientists send samples there for cost and efficiency reasons, Bowman said.

Labs from across the world send samples to Hauptman-Woodward that contain individual proteins, sometimes with drugs bound to them that might stop the virus from replicating.

Center scientists use robotics to put the same sample into as many as 1,536 tiny wells under different chemical conditions. Imagers are used to zoom into these wells to see how the crystals are forming. “We need a lot of specialized equipment and magnification for that,” Bowman said.

Researchers hope that at least one of the reagent chemical reactions yields a sample that forms into a 3-dimensional, microscopic-sized crystal.

“The same protein can crystallize in a number of different ways, too,” she said, “and that can be informative.”

The entire process takes up to six weeks. It yields usable samples almost half the time.

When crystals develop as hoped, they are sent to a Hauptman-Woodward team that operates at Argonne National Laboratory in Chicago, where an X-ray beam is shot into the crystals. The scattered X-rays form a pattern that researchers can use to make 3D structures for further study.

A new tool

Researchers from Oak Ridge National Laboratory, the University of Minnesota, and Arizona State, Columbia and Stanford universities are among those that have worked closely with the Crystallization Center on coronavirus samples.

“Once we have a sense of what the pieces and parts of the virus are made out of, we can generate large samples in the lab using standard molecular biology equipment and techniques,” Bowman said. “And they're not infectious, so that's really good.”

The center also works with the proteins to make crystals with potential drug therapies to see how the combinations interact.

Experimental therapies are used, Bowman said, “but there's also a tremendous effort to take these protein samples and screen them against drugs that are already in use for other diseases, because if we can use something that's already gone through approval, that will speed treatment.”

The 73,000-square-foot institute also will soon start to use a cutting-edge structural technique called cryo-electron microscopy at its Buffalo headquarters.

Cryo-EM yielded the first images last February of individual proteins that make up the new coronavirus.

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KC Kratt, provided by Hauptman-Woodward Institute.

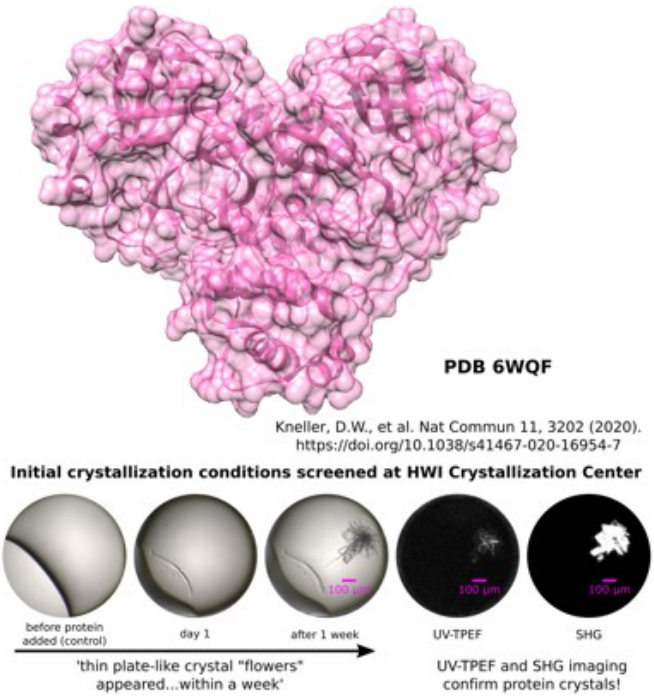
The new $8.1 million Hauptman-Woodward Cryo-EM Center, directed by molecular biologist Qiu-Xing Jiang, also will include new high-powered computers to better calculate what these proteins look like. It will open later this month.

Cryo-EM allows a great look at molecular structures at really extremely cold temperatures. Crystallography allows a look more physiologically, at or near body temperature.

"Crystallography is great for smaller proteins, like many in the coronavirus, and for looking at how drugs bind to those proteins," Bowman said. "At this point, virtually all of the structures that have been solved for SAR-CoV-2 proteins with drugs bound have been done using crystallography – and the full structures of the bigger proteins like the spike have been solved using CryoEM.

"Having both methods available here in Buffalo is an incredibly powerful combination because we should be able to look at almost everything in the virus."

This will help the institute further speed drug research and development worldwide, including with collaborators at the University at Buffalo and other institutions and companies in the region focused on biotechnology.



The new coronavirus active site cavity revealed by room temperature X-ray crystallography.

Oakridge National Laboratory image

Key parts

SARS-Co-V2 has become particularly adept as wreaking havoc in cells common to the lungs, heart and kidneys. Those cells travel throughout the body and, when infected, harbor an ability to infect other cells and overwhelm human defenses.

Most people envision the virus as a gray ball topped by a collection of studded red spikes. Under high-powered microscopes, it is a lumpier structure filled with RNA that looks like swirled ribbon and old telephone line. Four proteins form the exterior of the virus and surround the RNA coiled inside.

The Crystallization Center is among labs focused on the cell-binding properties of the virus surface – particularly the spiked protein that cuts a docking station into a human cell and another protein that drills into the host cell.

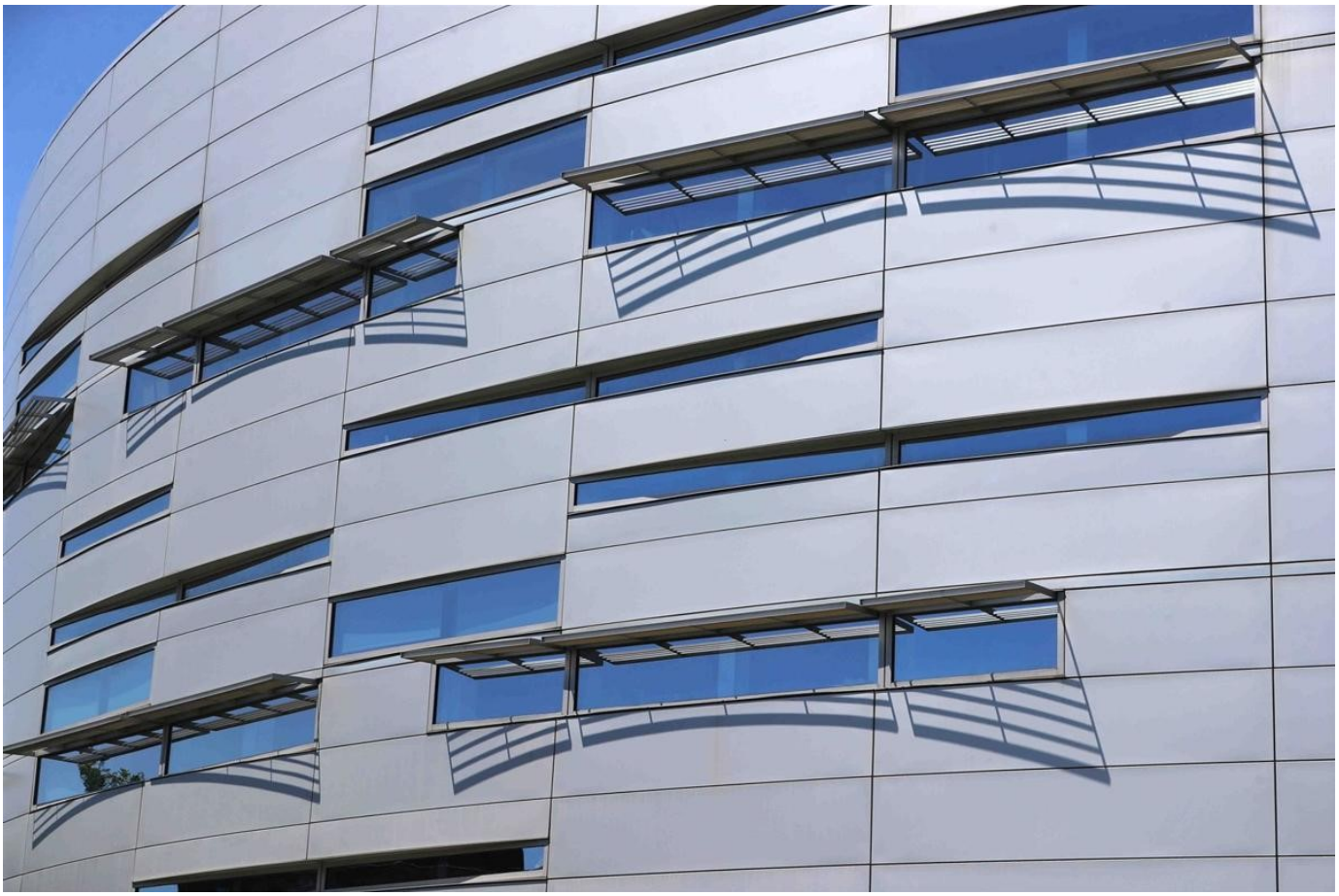
Bowman and her staff also have zeroed in on the main protease protein inside the virus that aids in infection and is a major target for treatment development.

A common way medications and other therapies defeat viruses, bacteria and fungi is to target individual proteins and

inhibit the way they help microscopic invaders work.

"We've got a structure of what that interaction looks like," Bowman said. "That has come from crystallography, by taking a portion of the spike protein and a portion of the human protein and saying, 'OK, what do these look like when they're allowed to interact with each other?'

"That is part of what then helps us to consider, 'so if we want to disrupt this interaction, how could we do that?' That stops things from happening at the earliest stage of infection. The reality is that it usually takes a long time to design those drugs and those interactions, then test them and see if they work."



The Hauptman-Woodward Medical Research Institute gleams on the Buffalo Niagara Medical Campus. The institute started in 1956 as the Medical Foundation of Buffalo at another address. The name changed in 1994 to honor Herbert A. Hauptman, a foundation scientist who won the 1985 Nobel Prize in Chemistry for groundbreaking work using X-ray crystallography and mathematics to better visualize how proteins and drug therapies interact. The name also honors the first foundation benefactor, Helen Woodward Rivas, an heir to the Genesee Food Co. and its Jell-O fortune.

John Hickey/Buffalo News file photo

Discoveries

Once crystallography or Cryo-EM create images, researchers can apply math and science to enlarge the microscopic data and try to find ways to prevent the coronavirus dockage or throw some other sort of wrench into the replication process.

The Covid-19 vaccine will soon arrive in Buffalo Niagara. Here's what you need to know

Most vaccines are made from parts of the infecting virus or bacterium, called antigens, that are weakened or killed before they are injected. The new Johnson & Johnson vaccine is one example.

The first two coronavirus vaccines approved in the U.S. – Pfiizer-BioNTech and Moderna – use a new genetically engineered platform: component parts of the novel coronavirus designed to create an immune response and teach human T-cells, which seek and destroy infectious invaders, to do so if they see SARS-CoV-2 in the future.

Bowman and other researchers also hope work including theirs will one day hit on a treatment as effective against Covid-19 as Tamiflu is for those who contract influenza viruses.

What about variants?

Addressing mutated SARS-CoV-2 strains will have to come first. More contagious variants that started in Great Britain, Brazil and South Africa have surfaced in small numbers in the U.S., including one confirmed case in Niagara County.

Infectious disease experts fear that without strict adherence to well-known prevention steps – including mask-wearing, physical distancing and frequent hand-washing – these variants could make several weeks in the spring the most deadly of the pandemic.

Because many of the same proteins in the new coronavirus – including the spiked protein – are in other coronaviruses, Bowman and others believe that vaccines and other treatments designed to interfere with those proteins should prove largely effective against mutated versions.

Still, this isn't always true.

"That's why we need to kind of focus on as many different things as we possibly can," she said. "The more disruption you can cause in individual proteins that make up a virus, the better."

That greater understanding of this basic biology also will create a body of research that can help in future pandemics.

"History and science tell us that there will always be new viruses, and new public health wars to fight," said S[illegible] Hauptman-Woodward CEO. "With a state-of-the-art Crystallization Center and bringing Cryo-EM technology to Buffalo, we are positioning our facility and our region to take on an even more meaningful role in those future wars."

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I have covered a variety beats and editor positions in South Florida, Syracuse and, since 2004, my home Buffalo Niagara region. Since 2013, I've been editor of WNY Refresh, which focuses on health, fitness, nutrition and family life.