Targeting Coronavirus

Physiologists halt their projects to put all their focus on prevention and treatment of COVID-19.

BY MELANIE PADGETT POWERS

Much attention has been focused on the all-important creation and availability of a COVID-19 vaccine. But at the same time, with little to no fanfare, physiologists and other scientists have been working long hours to respond to other aspects of the pandemic. They overhauled their labs, pulled together new teams and halted their previous research, going all in to focus on COVID-19 tests and treatments.

Before the coronavirus pandemic hit the U.S., physiologist and clinical anesthesiologist Michael J. Joyner, MD, had been studying blood loss in combat, the role of hemoglobin in oxygen transport during hypoxia, sex and age differences on blood pressure, and human performance to try to understand how fast humans can go. Joyner is professor of anesthesiology in the Department of Anesthesiology and Perioperative Medicine at the Mayo Clinic in Rochester, Minnesota.

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—Michael J. Joyner, MD

In February 2020, Joyner read a *Wall Street Journal* op-ed written by his researcher friend Arturo Casadevall, MD, PhD, of Johns Hopkins School of Medicine in Baltimore. Casadevall described how during a 1934 measles outbreak a physician used a recovered boy's blood to help his classmates. The physician, believing the boy's blood had protective antibodies, extracted it and injected it into 28 other students. None of them got sick. Casadevall explained that the same concept could be used for SARS-CoV-2, the novel coronavirus that causes COVID-19.

Michael J. Joyner, MD

Joyner was intrigued. "This was probably the first best biologically plausible shot at a therapeutic goal," he explains. He immediately emailed Casadevall, who was starting a prophylactic trial at Hopkins. Joyner proposed a therapeutic protocol at Mayo, and they were off and running.

Joyner is now the principal investigator of the U.S. Food and Drug Administration (FDA) Expanded Access Program for COVID-19 convalescent plasma. The first COVID-19 patients were enrolled in early April, and by the end of July, nearly 46,000 patients across the U.S. had been given convalescent plasma.

"This is by far the biggest thing I've ever been involved with," Joyner says. "My name is on the thousands of consent forms all over the country and also the INDs (investigational new drug applications) at the FDA."

The plasma collection from recovered COVID-19 patients is handled by the blood banking industry, under FDA regulations. More than 2,600 hospital sites in the U.S. have signed up. So far, about 1,800 sites have used convalescent plasma.

The latest safety update of 20,000 patients shows the treatment is safe. (It was not designed to study the efficacy of the convalescent plasma.) Patients who received the treatment between April 3 and June 11 had a seven-day mortality rate of 8.6%. Serious adverse events related to transfusion of the plasma were less than 1%. The diversity of the population studied has continued to improve, with almost 40% women, 20% Black, nearly 35% Hispanic and 5% Asian. (For more, visit **www.uscovidplasma.org**.)

FROM ZIKA TO COVID-19

At Meharry Medical College in Nashville, Tennessee, Donald Alcendor, PhD, has been focusing on developing an antiviral drug to treat COVID-19 patients. Alcendor, associate professor of microbiology and immunology, used his expertise from developing a Zika antiviral in 2016. His COVID-19 reagent aims to stop the coronavirus from replicating in cells. Ideally, it would be given intravenously to patients in early-stage disease, before they have severe symptoms.

"The idea is that the antiviral is used to circumvent replication and prevent the outcome of the replication—tissue damage, pathology and the inflammation that ensues after virus replication," he explains. "If you could stop the virus in its tracks, you'd be able to stop all the pathology that follows infection, and the main pathology would be tissue damage and inflammation.

"And if you're able to do those two things, you'd be well on your way to helping a patient to get better on their own, giving their immune system a chance to maybe clear the virus and allow them to recover."

Donald Alcendor, PhD

Evangeline Motley-Johnson, PhD

Alcendor's antiviral was ready for preclinical testing in mice in July to determine safe dosage levels. After that, his team will move to an infection model to test treatment efficacy. Then, Alcendor will file for an FDA compassionate use proposal for an early phase I study to test on seriously ill COVID-19 patients. If all goes well, he expects his antiviral to be ready for patients by spring 2021.

Alcendor's work is not only important scientifically; it goes hand in hand with the mission of Meharry, which is a historically Black institution.

"At Meharry, our mission is to serve the underserved, and the underserved population is at the greatest risk for disease in this epidemic," Alcendor says. "We want to do our part in this. We want to protect those underserved populations by developing an intervention that could be effective and safe against this virus."

Black Americans have the highest overall death rates from COVID-19. As of June, the death rate for Black Americans was about 2.3 times as high as for whites and Asians, about twice as high as the Latino and Pacific Islander rate, and 1.5 times as high as the Indigenous rate, according to APM Research Lab.

Alcendor's open access review article on COVID-19 disparities, "Racial Disparities-Associated COVID-19 Mortality among Minority Populations in the US," was published in the *Journal of Clinical Medicine* on July 30.

Early on in the pandemic, Meharry, working closely with the City of Nashville, offered free drive-through and walk-up testing in its predominantly Black neighborhood. Under the leadership of Meharry President and CEO James E.K. Hildreth, PhD, MD, the school eventually took over the city's other testing sites too. Hildreth, who is an infectious disease expert, has continued to educate Nashville residents about COVID-19 and preventive strategies.

Hildreth has also proposed to Congress forming a consortium to address the Black health disparities among COVID-19 patients in partnership with the three other historically Black medical schools: Howard University in Washington, D.C.; Morehouse School of Medicine in Atlanta; and Charles R. Drew University in Los Angeles. No funding has been provided specifically for the consortium, but in June, Morehouse was awarded a $40 million grant to address the same issue.

Evangeline Motley-Johnson, PhD, says Hildreth has been an "important voice" for the city and the country. Motley-Johnson, professor of physiology and interim dean of Meharry's School of Graduate Studies and Research, was involved early on in the discussions about creating drive-through and walk-up testing sites. She now volunteers at the sites three days a week.

In the future, Motley-Johnson wants to be able to look back and say, "Meharry stepped up and was there to give a service to the community."

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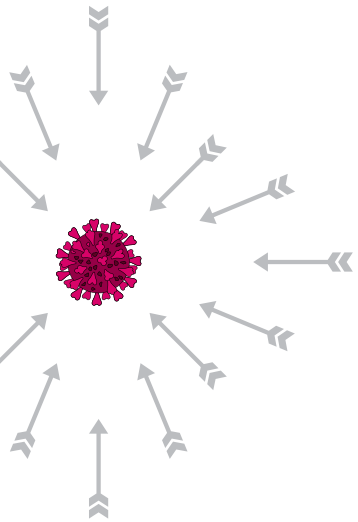

EMBRACING SCIENTIFIC CURIOSITY

The coronavirus has scientists in all fields brainstorming and hypothesizing what might help stop the disease. Lipids researcher Valerie O'Donnell, PhD, was lead author on a review in the APS journal *Function* about the potential of dental mouthwashes to destroy the lipid envelope of coronaviruses, thus reducing the spread of COVID-19. The paper calls for immediate clinical trials to test the effectiveness of the approach.

Valerie O'Donnell, PhD

O'Donnell, director of the Division of Infection and Immunity and co-director of Systems Immunity Research Institute at Cardiff University in Wales, became interested in the idea after she heard, early in the pandemic, the recommendation to use hand sanitizer with 60–70% alcohol to kill the coronavirus. That percentage seemed "harsh" and unnecessary to use against an enveloped lipid like SARS-CoV-2, she says.

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—Valerie O'Donnell, PhD

O'Donnell discovered that that percentage was not created specifically for this coronavirus but based on more general information. Historically, it was discovered that microbicide agents would need at least 60% alcohol to kill a broad spectrum of viruses and bacteria. The alcohol levels needed to kill SARS-CoV-2 could be much lower, which led O'Donnell to start thinking about oral mouthwashes, which contain about 14–27% ethanol.

"When you look at the literature on enveloped viruses and how to inactivate them, there's a lot of literature in vitro on how to inactivate them in test tubes," O'Donnell says. "And it's very clear that common agents in mouthwashes or low concentrations of ethanol can work quite effectively. The question then is if you go from a test tube to somebody's mouth and somebody's throat, could it work there?"

As the virus replicates, cells continue to shed out through the throat, which leads to the question of how long a response from an oral mouth rinse would last. That's where clinical trials are needed, O'Donnell says. The findings could help lead to another way to prevent spread of the disease, as well as providing potential protection for dentists. In response to the pandemic, the American Dental Association issued some "common sense recommendations" that include having patients rinse with 1.5% hydrogen peroxide or commercially available rinses that contain 1.5% hydrogen peroxide before treatment.

Evidence shows high viral loads are found in sputum, and yet, O'Donnell says, preventing oral transmission is a neglected area. "Simple antiviral approaches to target the oral cavity is an area that just feels like it's not being addressed."

TESTING OHIO

After the pandemic reached the U.S., cardiovascular physiologist Loren E. Wold, PhD, became instrumental in the creation and distribution of COVID-19 test kits across his state of Ohio. Wold is professor of nursing and medicine, assistant dean for biological health research and director of the Biomedical Laboratory at The Ohio State University College of Nursing in Columbus.

After non-essential research was shut down on campus, Wold was restless working from home when the vice dean for research called him and asked if he would oversee the process of making test kits. "Initially, that was an opportunity for me to get to go into the office as an essential COVID-related researcher, so I jumped at the chance," he says. "Very quickly, my lab basically took over the entire process."

It was early April and the university was making about 1,000 test kits a day. That number needed to ramp up significantly, so Wold and his research team of about 15 people transformed his two lab spaces and took over six more in the building.

Loren E. Wold, PhD

Faculty and staff from across the university offered to help, from other physiologists to faculty from the colleges of medicine, nursing and engineering. Even a few coaches volunteered. In a few weeks, the team was making over 10,000 test kits a day. Eventually, they made nearly 300,000 kits. Demand slowed down after a couple of months, and by June 15, production was scaled back to 2,000 to 4,000 kits a day with newly hired staff. Researchers were given back their labs.

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—Loren E. Wold, PhD

At the beginning, everything was on backorder: test media, sterile conical tubes and long nasal swabs. So, a colleague of Wold's created the university's own medium, which they dubbed Buckeye Media, after the university's mascot. They began making it in-house and were soon making 250 liters of media a week.

For tubes, the team gathered up a supply from the university labs' own stock until their order of 1 million tubes arrived. The next challenge was finding swabs. "We had set up the capabilities to do our own 3D printing of swabs, but … to be able to produce what we needed, it was going to take a ton of time with the manufacturing capabilities we had," Wold says. Luckily, he says, more manufacturers began making swabs and they were able to order what they needed.

Figuring out the production process was the biggest learning curve, he says. "Now it's wonderful because I've met people from all over campus I probably would have never met before. … I had never worked with anything related to supply chain, having to order on these levels. I had to get to know the people at such a huge university who were the ones that could make this happen—those in supply chain, those in leadership and those in the business operations who had to sign off on all these things."

THE WORK CONTINUES

As fall arrives, physiologists and other scientists across the U.S. continue to brainstorm on ways they can contribute to the study, prevention and treatment of COVID-19. At Mayo, Joyner says being a physiologist helped him pivot from his research to leading the convalescent plasma program.

"Sometimes it's better to be a generalist than a specialist because we did not know all the limitations to what we were doing," he says. "We didn't really know why we couldn't do this, and we didn't know how things had been done in the past."