THE COVID-19 PIVOT

BY JENNIFER NACHBUR

LARNER RESEARCHERS CHANGE DIRECTION TO ADDRESS THE PANDEMIC

IT WAS MID-MARCH, WHAT VERMONTERS RUEFULLY CALL "MUD SEASON."

BUT THE PROMISE OF THE SPRING OF 2020 WAS YIELDING TO WIDESPREAD CONCERN AND HINTS OF PANIC, AS CASES OF INFECTION WITH THE NOVEL CORONAVIRUS, SARS-COV2, ROSE IN THE STATE AND ACROSS THE NATION.

WHILE EDUCATIONAL INSTRUCTION AT LARNER HAD SHIFTED TO REMOTE MODE, AND MOST IN-PERSON RESEARCH WAS SUSPENDED, A SIGNIFICANT NUMBER OF LARNER PHYSICIANS AND SCIENTISTS QUICKLY ADAPTED THEIR INVESTIGATIONS TO THE ESSENTIAL WORK OF FOCUSING ON COVID-19.

Across the globe, an international COVID-19 research movement was fast gaining traction, fueled by the immediacy afforded by the social media platform Twitter, which allowed scientists and clinicians to ask questions; share findings, treatments, and investigational approaches; and create collaborations in real time. Early research findings started popping up on preprint servers, like Cold Spring Harbor Laboratory's bioRxiv.org, a platform that allows researchers to post complete, but unpublished, manuscripts—providing critical timely information to scientists.

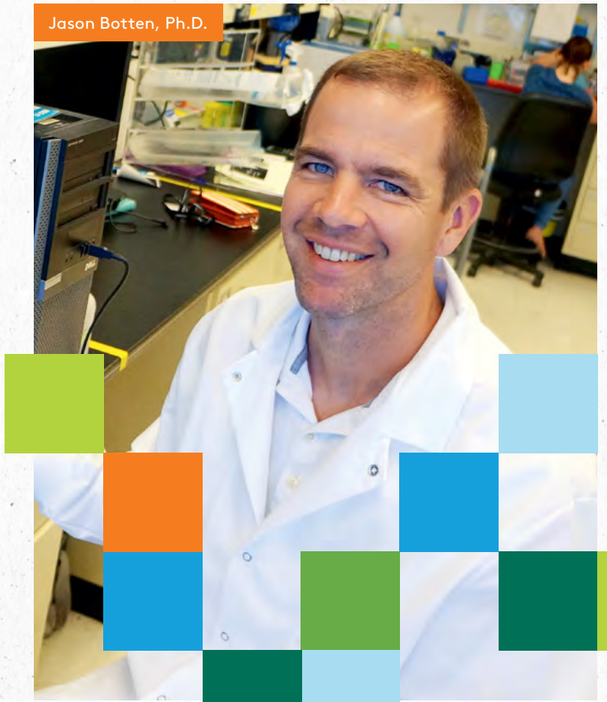
At UVM, administrative offices, departments, and centers quickly dedicated funds to the work, including those that had NIH funding applications under review. With more than a decade of experience conducting both basic science and clinical vaccine development research, many investigators in the UVM Vaccine Testing Center seized the opportunity to switch gears when COVID-19 entered the landscape, with funds available through the University's Translational Global Infectious Disease Research (TGIR) Center at the ready.

One of those faculty members is Sean Diehl, Ph.D., an associate professor of microbiology and molecular genetics, who leveraged his lab's extensive experience to explore the immune response in SARS-CoV2.


Sean Diehl, Ph.D.

SARS-CoV2 and the Immune Response

"We turned on a dime to work exclusively on COVID-19, adapting our expertise in measuring antibodies to such viruses as dengue and Zika to see if we could find out how this novel coronavirus activates the antibody response," explains Diehl.


Jason Botten, Ph.D.

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– JASON BOTTEN, Ph.D.

He's quick to point out that it literally took a village to bring the research to life.

His colleague Florian Krammer, Ph.D., of Mount Sinai's Icahn School of Medicine in New York City, had published a preprint of a serological assay that Diehl deemed appropriate for his team's work. Krammer mailed Diehl the tools needed to build the assay—some DNA spotted onto a piece of filter paper. Diehl's lab got to work quickly: he notes that Nancy Graham, a technician in the lab, with support from technician Ben McElvany and graduate student Kip Strother, "had this assay up and running in less than a month, with our first results on April 14!"

Pathologist Jessica Crothers, M.D., a TGIR research project leader, played a strategic role in several Larner COVID-19 projects, including Diehl's. Crothers secured Institutional Review Board approval to obtain as many blood samples as she could from March through May from the UVM Medical Center's COVID-19 patients. Medical student Dore Grier and clinical research coordinator Ashley Miles compiled patient info so that Diehl and his technicians could design the serology study, which was recently published in *Clinical and Translational Immunology*.

What they learned provides important information about antibody levels in sicker patients and the elderly that could Inform vaccine goals.

"We think that our new insights using this well-characterized cohort of COVID-19 patients gives a good picture of the natural history of how antibodies that likely contain some protective activity are induced by this virus," says Diehl.

Currently, he and his team are recruiting for a study of people who had COVID-19 but did not require hospitalization, in partnership with Professors of Medicine Jason Botten, Ph.D., and Renee Stapleton, M.D., Ph.D. The objective is to follow these participants for a year and obtain blood samples from them to determine if the SARS-CoV-2 immune response lasts at least a year.

A Less-Than-Perfect COVID-19 Test Shows Promise

Like Diehl, Botten has had his hands in multiple COVID-19 projects since early in the pandemic. An expert on pathogenic RNA viruses, Botten's first—and most immediately impactful—project was his work with Emily Bruce, Ph.D., faculty scientist in medicine, Crothers and others in developing and studying an alternative COVID-19 diagnostic test. The method for the test, published first in a BioRxiv preprint and more recently in the journal *PLOS Biology*, omits the step in the widely used reverse transcription polymerase chain reaction (RT-PCR) test, considered the gold standard of COVID-19 diagnostics, where the scarce reagents are needed. Shared widely on Twitter, the preprint was downloaded 18,000 times and the abstract was viewed 40,000 times.

A critical connection between Crothers and Keith Jerome, M.D., Ph.D., director of the University of Washington's Molecular Virology Lab, provided the perfect partnership for examining the test's accuracy on a broader scale. The site of the first confirmed U.S. COVID-19 case, Washington had far more cases than Vermont—more than 1500 people had already tested positive by March 20—and Jerome's lab had plenty of samples with a wide range of viral load to study.

The UVM test correctly identified 92 percent of the positive samples


Renee Stapleton, M.D., Ph.D.

funded clinical trial examining the use of cycle ergometry and amino acid supplementation in ventilator-dependent patients with acute respiratory failure. She and her collaborators at Johns Hopkins and Queens University realized an opportunity to target their focus on COVID-19 patients who had been on ventilators. She applied for a supplement to the R01 grant for a cohort study investigating these patients' inflammation and immune response outcomes over the course of a year and, using existing resources, she and her colleagues began enrolling participants.

Ultimately, the supplement did not secure funding, but with the blood samples her team had already obtained, she teamed up with Professor of Medicine and Chief of Cardiology David Schneider, M.D., to develop a study on biomarkers for thrombosis in COVID-19 patients. "Recent reports have noted that thrombosis complicates 16 percent of hospitalizations and thrombosis is a key contributor to respiratory failure," says Stapleton.

While the grant won't be reviewed until April 2021, Stapleton continues to be involved in SARS-CoV2 research. In collaboration with Botten, she's enrolling COVID-19 positive patients for his lab's work developing human monoclonal antibodies as a therapeutic for COVID-19.

and 100 percent of the negatives, only failing to catch the positive samples with exceptionally low levels of the virus. Public health experts increasingly believe that ultra-sensitive tests that identify individuals with even the smallest viral loads are not needed to slow spread of the disease.

"You can go for the perfect test, or you can use the one that's going to pick up the great majority of people and stop transmission," says Botten. "If the game now is focused on trying to find people who are infectious, there's no reason why this test shouldn't be front and center, especially in developing countries where there are often limited testing programs because of reagent and other supply shortages."

Botten, Bruce and colleagues' test is now being run in labs worldwide through a program called PROPAGATE, run by the Health and Environmental Sciences Institute (HESI), a non-profit that marshals scientific expertise and methods to address a range of global health challenges. HESI Director Syril Pettit, Dr.PH., saw the preprint and reached out to Botten in April and the relationship has yielded great momentum for the research.

Pivot Once, Pivot Twice

In some cases, great concepts for adapting existing research were halted, due to lack of funding. Stapleton, a pulmonary and critical care specialist, was already three years into a National Institutes of Health-

A Virus that Robs Cells' Ability to Sound Alarm and Defend

In addition to their many other projects, Botten and Bruce also collaborated with Dev Majumdar, Ph.D., assistant professor of surgery, and Mitchell Guttman, Ph.D., a professor of biology at the California Institute of Technology. Working in the shared UVM - Vermont Department of Health BSL-3 facility, they examine each of the roughly 30 viral proteins in SARS-CoV-2 and helped map out how they interact with host human cells within a cell-culture dish. The results, published in October in the journal *Cell*, found that SARS-CoV-2 proteins attack three critical cellular processes that serve as the cell's alarm system to call for help or warn nearby cells of infection. This new information provides insights into how to fight the virus.

"We understand so little about this virus compared to HIV or Influenza," says Majumdar. "I'm looking forward to more basic science work so we can get a first draft of how this virus replicates and takes over the cell. Armed with that kind of information, we can think meaningfully about targeted therapeutics, monoclonals, and vaccines."

A Vermont Model for Rural COVID-19 Communications

Launched in 2017, the Northern New England-Clinical and Translational Research (CTR) Network supports a wide range of clinical and translational studies that emphasize health problems endemic in the rural populations of Vermont, New Hampshire and Maine, where many of the residents are over 65 years of age and barriers can compromise rural health care delivery.

Associate Dean for Public Health and Health Policy Jan K. Carney, M.D., M.P.H., who co-leads the Rural Health Research and Community Engagement Core for the network, saw an opportunity to supplement this work in the face of the COVID-19 pandemic. She proposed and has been leading development of a unique, virtual two-way Rural Health

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Communications Network (RHCN), engaging all 11 U.S. CTR programs and working in collaboration with state departments of health to provide rapid, evidence-based health communication to vulnerable rural populations for COVID-19 and all future epidemics. Vermont's RHCN project features an inventory of communications channels in Vermont towns; a tracking system for evidence-based health information delivery and receipt; tele-health and online technologies for education; outreach to vulnerable rural populations; and will host a Virtual Rural Health Communication Forum.

"CTR programs are serving as a regional and national resource to promote rural health communication," says Carney. "Our goal is to develop a sustainable communications infrastructure with innovative technology and a 'how to' model for our predominantly rural populations that can be used today and long into the future."

As Mud Season had, eventually given way to spring and summer, and spectacular early-Autumn foliage season faded into "Stick Season." Vermonters, like people across the globe, looked warily toward the year ahead. On UVM's campus, more than 50 COVID-19-related projects continued, in the hope that, with diligent research and successful vaccine trials, future Mud Seasons would once again be a time when the greatest worry for most people would be a rutted driveway. VM