

WE LOOK AT MORE REMARKABLE WORK DONE BY UCSB FACULTY AND HEALTH-PROFESSIONAL COLLABORATORS TO FIGHT THE PANDEMIC

A GRADUATE STUDENT'S GREAT LEAP IN OMICRON DETECTION

Last December, the highly transmissible omicron variant threatened to again overwhelm the already beleaguered U.S. healthcare system. That was when UC Santa Barbara doctoral student **Zach Aralis** stepped into the fray, developing a test that could distinguish omicron from delta and serve as a template for defense against future major COVID variants.

The importance of making that delta-omicron distinction through testing was foremost in the mind of medical professionals at the time, because it had implications for life-saving treatment using monoclonal antibodies. "There are currently three monoclonal antibody options for treatment against the SARS-CoV-2 virus," said Cottage Health infectious disease specialist (and UCSB alumna) **Dr. Lynn Fitzgibbons**. But only one of the three, Sotrovimab, proved effective against the omicron variant. Treating an omicron infection with any of the other COVID-specific monoclonal antibodies would be, she said, "like shooting blanks," while unnecessarily exposing patients to possible side effects and allergic reactions.

As cases of new COVID infections grew, however, there was no quick way to determine who had the omicron variant and who had delta or any of the other previous major variants. Genomic sequencing took weeks to return results. Meanwhile, caseloads climbed precipitously.

"The big unknown through that third week of December was how many cases were actually omicron," Fitzgibbons said. Data from the State of California's variant assessment program were weeks behind, and, to compound the problem, Sotrovimab had become scarce, making it even more crucial that the therapy be given only to people it could help.

Further, the virus was so new that no company had yet been able to develop and offer a test. "We came to the conclusion that we'd have to make it ourselves," said **Stuart Feinstein**, a UCSB professor of molecular biology, the UCSB COVID-19 Response Team coordinator, and a member of the Local Variant Task Team — a collaboration between the university, local healthcare providers and the Santa Barbara County Public Health Department (SBCPHD) formed to monitor for new and possibly dangerous versions of the SARS-CoV-2 virus.

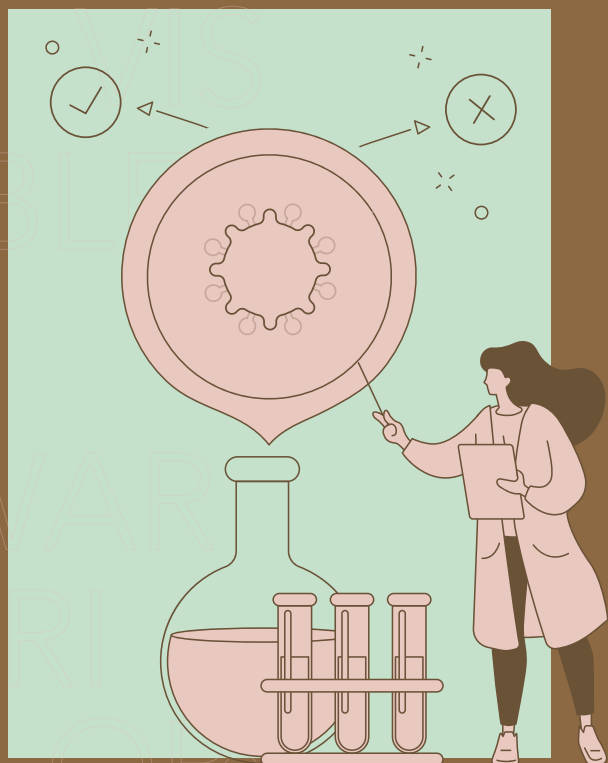
The task fell to Aralis, a graduate student in the molecular biology lab of **Professor Carolina Arias**, who for the past two years had been sequencing samples at the UCSB CLIA-licensed laboratory as part of the campus community's sophisticated variant monitoring program.

Aralis got to work developing a test over the holiday break. Guided by Arias, he designed nucleotide primers at his parents' house, put in orders for reagents amid holiday festivities, and received deliveries at his apartment, because the campus was then closed.

It was no small feat, requiring Aralis to design a test from scratch that could pick up key features that only omicron had, such as the genetic sequences that underlie the variant's significant number of mutations.

"We knew how the genome looked for delta and all the other variants, because of the vast amount of data," he said. Thanks to the collaboration with the local healthcare providers and SBCPHD, he also had access to the new omicron genome.

"The key was to look at these different genomes and compare them to see where there are multiple, significant mutations that would enable the primers to bind to different variants differentially," he said. If these key sections of viral genetic material are present, the commercially synthesized primers would bind to them, initiating a process that exponentially multiplies this genetic material until millions to billions of target DNA



strands are present and detectable by fluorescent probes.

Just after the new year, Aralis had an assay to put to work, a test that could deliver an answer in a few hours, as opposed to the weeks required for genetic-sequencing results.

Even as the assay underwent refinement, it proved immediately useful, first by successfully identifying seven of nine test samples as positive for omicron, and later confirming 25 positive omicron cases out of 28 samples provided by County Public Health and Pacific Diagnostic Laboratories. Though the state's data had not shown it at the time, the results indicated that omicron had already gained a foothold in the community.

"We clinicians have been making our best guesses based on indirect evidence and theory, and doing the best we can," Fitzgibbons said. "But Zach gave us an anchor and the knowledge we needed." Thanks to the new assay, she added, local physicians who had been wondering if they should use the other two more readily available monoclonal antibody treatments, REGEN-COV and BAM-ETE, had increasing confidence to forgo them.

Looking at the future beyond omicron, Feinstein said, "This could be used as a starting point in combatting the next problematic variant that comes along."

Meanwhile, in the wake of this success, Aralis remains poised and ready to jump into the next phase of the arms race between virus and human, saying, "We've got a kind of pipeline for doing this now if a new, aggressive variant appears."

DIALING UP A RAPID COVID TEST

COVID testing — having enough tests, while making them fast, affordable, and accurate — has been a huge hurdle throughout the pandemic, and especially during periods of rapidly increasing cases, when testing is most needed. Recently, in a potential game changer for COVID-19 pandemic control efforts, a new cell phone app and lab kit were developed that can transform a smartphone into a COVID-19 (and flu) detection system.

The system's test is among the most rapid, sensitive, affordable, and scalable known, and it can be readily adapted for other pathogens having pandemic potential. It also provides a platform for inexpensive home-based testing. Developed by a research team of UC Santa Barbara scientists and Santa Barbara Cottage Hospital scientists and physicians, the app was described in an article titled "Assessment of a Smartphone-based Loop-mediated Isothermal Amplification Assay for Detection of SARS-CoV-2 and Influenza Viruses," and published in the January 2022 issue of the journal *JAMA Network Open*.

The app uses a smartphone's camera to measure a chemical reaction containing a chemical dye that fluoresces when the virus is amplified — the more glow, the more virus is present — and determines a diagnosis in 25 minutes, at a fraction of the cost of current diagnostic methods and with accuracy matching that of PCR tests, with the result ready in a fraction of the time. Free and available to all, both the app and the methodology were developed by UCSB professors **Michael Mahan, David Low, and Charles Samuel**, along with Santa Barbara Cottage Hospital physicians Jeffrey Fried, M.D.,

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(UCSB alumna) **Lynn Fitzgibbons, M.D.**, and additional collaborators at both UCSB and Santa Barbara Cottage Hospital.

"As new COVID variants emerge globally, testing and detection remain essential to pandemic control efforts," said Mahan, lead author on the paper. "Nearly half the world's population has a smartphone, and we believe that this holds exciting potential to provide equal access to precision diagnostic medicine."

The collaboration was launched to develop rapid, low-cost diagnostics that can be used by healthcare providers anywhere in the world to diagnose COVID-19. The kit can be produced for less than \$100 and requires little more than a smartphone, a hot plate, and LED lights. The screening tests can be run for less than \$7 each versus \$10 to \$20 per rapid antigen test and \$100 to \$150 per PCR test. The so-called LAMP tests match the sensitivity and accuracy of the gold-standard PCR test at a fraction of the time and cost. Further, LAMP occurs at constant temperature, which is suitable for point-of-care and home-based testing.

The process, termed smaRT-LAMP, is simple and straightforward. To use the kit, a small amount of a person's saliva is collected in a cup, put onto a hot plate, and then analyzed by the smartphone app using the phone's camera and the diagnostic kit. Twenty-five minutes later, the app shows a green button for a negative result and a red button for a positive one. No additional special materials are required.

"The key finding was solving the problem of false positives resulting from the high sensitivity of the LAMP systems, something scientists have struggled with for more than twenty years," UCSB collaborating scientist **Douglas Heithoff** explained. "It took more than five hundred attempts to solve it for COVID-19, after which flu viruses were detected on the very first try."

The simple lab test can detect and differentiate COVID-19 and the flu, which show very similar respiratory disease symptoms, making misdiagnosis common.

"Rapid and affordable point-of-care testing is critically important for underserved communities around the world, many of which are struggling with inadequate diagnostic testing access and limited laboratory infrastructure," explained Fitzgibbons, who is an infectious-disease physician.

"We hope technologies like this offer new ways of bringing state-of-the-art diagnostics to underserved and vulnerable populations," Low explained.

"Such early detection and quarantine can also reduce the risk of future global outbreaks," added Fried, a critical-care physician.

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