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Transferring Laboratory Technology to Fight the COVID-19 Pandemic

Livermore technology transfer and relationships with private sector partners played an important role in fighting the COVID-19 pandemic.

WITHIN months of its emergence in late 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) rapidly proved itself to be a lethal threat to humans, mobilizing the world's science and technology community as never before. Lawrence Livermore National Laboratory's researchers immediately began working on COVID-19 (the disease caused by SARS-CoV-2) solutions in early 2020 (before any of the U.S. shelter-in-place orders). Computing and life scientists applied high-performance computers to accurately predict the spike protein structure of SARS-CoV-2 in one week's time, screen for potential antibodies that could bind to and neutralize SARS-CoV-2, and identify the molecules that might be used in pharmaceuticals to aid those infected with COVID-19.

That new vaccines and therapeutics would be essential weapons to use against COVID-19 was a given, but other tools and technological solutions, such as rapid testing for SARS-CoV-2 and critical, life-saving medical equipment were also needed on the frontlines of this pandemic as quickly as possible. Laboratory experts in advanced materials and manufacturing sought alternative approaches to address a shortage of medical supplies such as nasal swabs and ventilators (see *S&TR*, June 2021 pp. 4–11), and extant

Livermore technologies previously developed to detect pathogens in clinical and biowarfare settings were swiftly adapted to spot SARS-CoV-2. During the pandemic, Livermore's Innovation and Partnerships Office (IPO) launched efforts to contribute to the fight against COVID-19 by accelerating the process of transferring Livermore technologies with COVID-fighting potential to its private sector partners. "Oftentimes, a technology with a great payback has a long, tortured story behind it," says Senior Science Advisor Dave Rakestraw, who coordinated Livermore's COVID-19 research response. "It can take decades for a technology to become the foundation of a successful company." To expedite the tech-transfer process during COVID, IPO deployed three key strategies: communicating and coordinating with existing commercial partners and the biomedical community, accelerating its licensing processes, and providing temporary royalty-free licenses for existing technologies with anti-COVID potential.

Strong Diagnostics

Past Laboratory success stories of licensed diagnostic technologies became contemporary success stories against COVID-19 early in the pandemic. Two companies, Bio-Rad Laboratories, Inc.and Cepheid, Inc. developed diagnostic tests for the SARS-CoV-2 virus using technologies that they had licensed from Livermore years ago. Both technologies provided the foundation for products used for years to identify other pathogens. "The Laboratory has a strong competency in diagnostics, so it's no surprise that we had technologies in our portfolio to apply against COVID-19 right away," says IPO Director Rich Rankin.

Polymerase chain reaction (PCR) is a well-established technology that biologists use to amplify small amounts of DNA into millions and billions of copies. Invented in 1983, PCR tests provided an innovative tool in medical diagnosis and biological research. Then, in the early 2000s, Livermore bioscientists refined the PCR technique to produce an even more sensitive test originally designed to detect tiny amounts of biowarfare pathogens in the battlefield. The successful droplet digital PCR test (ddPCR) simultaneously partitioned a sample into thousands of nanoliter volume droplets along with targeted PCR reagents. The ddPCR detects a variety of pathogen-expressed genes ranging from viruses such as human immunodeficiency virus, to bacteria including Salmonella and Listeria, and parasitic infections that cause diseases such as Malaria, as well as the presence of somatic or germline mutations. Its comprehensive detection capabilities elevated ddPCR to an essential, dynamic tool for diagnosing diseases in patients generally, as well as for genetic research.

Early in the pandemic, an ad hoc Livermore team assembled this mechanical ventilator (left) in five weeks using available parts from outside of the ventilator supply chains to meet demand for COVID-19 patients.

Two companies, including one founded by a Livermore team led by Bill Colston in 2008, QuantaLife, Inc., commercialized the technology. QuantaLife was acquired in 2011 by Bio-Rad, which went on to develop ddPCR™ systems for a range of medical and research applications including cancer detection, pre-natal testing, stem cell treatment, food science, and microbial drug resistance. The technology won an R&D 100 Award in 2012. More than 5,100 research projects utilized ddPCR during the pandemic, including a study of COVID-19 residue on surfaces, which determined that hand-contact was the main transmission pathway to contamination in a laboratory setting.

In May 2020, Bio-Rad released a SARS-CoV-2 ddPCR test kit granted emergency use authorization (EUA) by the U.S. Food and Drug Administration (FDA). The SARS-CoV-2 ddPCR test runs on Bio-Rad's QX200 and QXDx ddPCR systems. "The test's high degree of sensitivity and ability to analyze difficult samples such as blood and saliva makes it more effective than other PCR tests for identifying the early stages of infection and detecting minimal residual disease in people recovering from COVID-19," says Yash Vaishnav, a Livermore business development executive (BDE). "It has been shown that ddPCR has a threshold for detecting SARS-CoV-2 lower than that of traditional PCR and an ability to detect the virus in saliva better than any other test. When the patient's sample might have a low viral load, ddPCR still has a better chance of correctly identifying a positive patient." The ddPCR COVID-19 test won the Federal Laboratory Consortium's (FLC's) 2021 awards in the "Impact" and "COVID-19 Response" categories and was one of two national FLC awards won by the Laboratory for its contributions to combatting the COVID-19 pandemic.

Bio-Rad Laboratory Inc.'s Droplet Digital™ PCR (ddPCR™) System (left) incorporates technology originally licensed from Livermore. Bio-Rad developed an FDA-approved SARS-CoV-2 test early in 2020 enabling its ddPCR™ system to detect COVID-19 in clinical and environmental samples.

In the 1990s, Livermore scientist Allen Northrup and his team developed a microfluidic chip designed to accelerate PCR tests. Traditional PCR machines take hours to perform a thermal cycle—the heating of the sample—to reach a result. The Livermore microelectromechanical systems (MEMS) chip is much smaller than the conventional PCR apparatus and integrates the steps required to perform a test onto one chip. Heating the sample to the right temperature increases the genetic material's rate of replication. In the MEMS chip, tiny heaters and reaction chambers create a rapid heat–cool cycle that reduces the time to produce a result compared to conventional PCR tests.

Licensed in the early 1990s, "the Livermore technology used in this system is the foundation for some of the most popular methods for detecting COVID today," says Rakestraw. "It was originally developed at Livermore to detect biowarfare agents before using molecular diagnostics became common. When it was first created, this invention had no commercial market, but Livermore had developed a groundbreaking technology to address an important national security problem. It took more than 15 years for that technology to become clinically successful, but in today's world, this technology has made a difference by speeding up the time it takes to let someone know if they have tested positive for COVID-19."

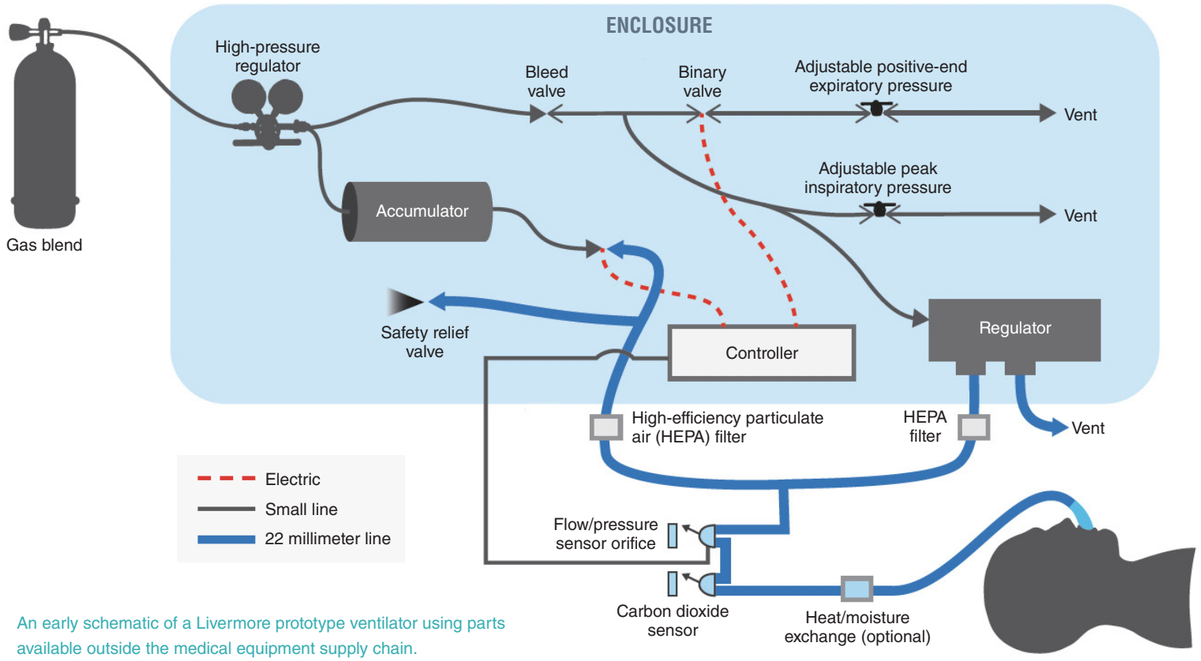
Cepheid is a molecular diagnostics company (acquired by Danahan Corporation) that develops molecular diagnostic testing systems for organisms and genetic-based diseases. In March 2020, it received an EUA from the U.S. FDA for its Xpert® Xpress SARS-CoV-2, a rapid molecular diagnostic test for qualitatively screening SARS-CoV-2. The test was designed to operate on any of Cepheid's automated GeneXpert® Systems, with a detection time of approximately 36 minutes. More than 23,000 of these systems are in use worldwide.

The Laboratory is now working on expanding the success of ddPCR and the MEMS chip with its Lawrence Livermore Microbial Detection Array (LLMDA) technology, which can detect more than 12,000 microbes and is used in clinical settings to assess co-infection with other diseases to help plan patient treatment. "Using its royalties, the Laboratory has funded adding a COVID test to our virus diagnostic system, which will provide medical professionals and emergency responders with a point-of-care tool for rapid detection," says Rankin. The LLMDA royalties from licensed Livermore inventions are also funding a study for detecting SARS-CoV-2 in wastewater samples to provide early warning of local outbreaks.

New Know-How Transfer

Working from home during the initial lockdown in March 2020, Jack Kotovsky, the leader of the Micro- and

Cepheid's GeneXpert® System uses Livermore-licensed technology that tests for pathogens using microelectromechanical (MEMS) chips to heat and amplify samples containing a pathogen. The company quickly developed and added an FDA-approved test for SARS-CoV-2 in early 2020 as the pandemic expanded. Shown above are the cartridge used by this test and the GeneXpert®II.



An early schematic of a Livermore prototype ventilator using parts available outside the medical equipment supply chain.

Nano Technology Section of the Materials Engineering Division, wondered how he and his colleagues could contribute to finding solutions for the COVID-19 pandemic. Estimates in the early days of the crisis anticipated that hospitals could be short hundreds of thousands of ventilators for critically ill patients. Kotovsky and his colleagues recruited an interdisciplinary team, sometimes meeting virtually and sometimes in person while masked in a laboratory, to design a ventilator that could be assembled from off-the-shelf parts outside the standard medical supply chain to resolve a potential shortage of life-saving ventilators. "We wanted to design something that we could send to clinicians within five weeks," says Kotovsky. "This process was new territory for us. Instead of inventing an entirely new technology, we were creating a piece of medical equipment that already exists, but from parts on-hand that could be assembled rapidly."

The team of 20 scientists and engineers from the Laboratory's Computing, Engineering, and Physical and Life Sciences directorates consulted medical doctors and ventilator manufacturers around the country to determine what features a rugged, easy-to-manufacture ventilator would need. The team also tried (and rejected) other approaches such as repurposing CPAP (continuous positive airway pressure) machines used to treat sleep apnea by circulating air into a sleeper's breathing passages. Instead, they looked for a source of low-pressure air regulators separate from any existing medical supply chains, to avoid stressing that manufacturing sector. The compressed schedule meant that any technology they developed had to make its way to frontline use faster than the usual technology transfer process. "It was clear that we needed to make the commercialization process happen in parallel with technology development, and that our anticipated partnership had to have manufacturability in mind," says Kotovsky. Just two weeks into the process, the design team and IPO began talking to potential manufacturing partners.

Genaro Mempin, the BDE who oversaw the ventilator's technology transfer process, says that the Laboratory released a federal business opportunity (FBO) notice to canvas the private sector for companies willing to work with the Laboratory on the ventilator and found Equilibar, a company that manufactures the type of regulator the team needed for the ventilator. BioMedInnovations, LLC (BMI), the partner company of Equilibar, which also manufactures precision air and fluid flow devices for medical applications, indicated their willingness to take on the entire process of prototyping the ventilator from the Laboratory's design, obtaining FDA EUA approval, and manufacturing the product. "Normally, we transfer intellectual property (IP) through licensing patents," he says. "In this case, the IP came in the form of the researchers' know-how, which is difficult to transfer without a patent."

IPO set up a cooperative research and development agreement (CRADA) with BMI to transfer the engineering know-how and allow the Laboratory and BMI to continue to collaboratively develop and test a prototype. CRADAs normally require months to negotiate and approve, but with the cooperation of the Laboratory's Office of General Counsel and the National Nuclear Security Administration's Livermore Field Office, this particular CRADA was approved in record time: less than two weeks.

BMI called on a partner company, Industrial Hard Carbon, LLC, which manufactures parts for NASCAR racing teams, and two of their partner companies, Roush Yates Manufacturing Solutions and Joe Gibbs Racing, to build ventilator components—with racing temporarily halted, they had available space on their production lines. BMI's ventilator product, marketed under the name SuppleVent™, received an FDA EUA in early June 2020. In April 2021, the FLC gave Lawrence Livermore and BMI a national Excellence in Technology Transfer award for designing and delivering the ventilator in just three months.

Kotovsky and his colleagues continue to explore alternative methods to ventilate patient lungs, including a simpler version of the extra-corporeal membrane oxygenation (ECMO) machine, which is used to pump and oxygenate a patient's blood outside the body during surgery. They are also examining the use of perfluorocarbon to diffuse oxygen into the bodies of patients with low blood oxygen. "In the next national emergency, I want to make sure those agencies think of Livermore first. We're a brain bank, we're used to teaming across disciplines, we're well-equipped, and we're motivated to respond. This is how we fulfill our mission," says Kotovsky.

Friendly Tech License

"When COVID-19 came along, we evaluated every technology we had that had any possible use against it," says Deputy Director of IPO Elsie Quaite-Randall, who oversaw the royalty-free license offering. "We developed a special nonexclusive, royalty-free, time-limited license that would allow anyone outside the Laboratory to use Livermore technologies to combat the COVID pandemic. It's designed to be as flexible as possible." The license is valid for a 12-month period as long as licensees use it to develop technologies against COVID-19. Two types of licenses are available, one for patents and one for software.

The license applies to about 30 Laboratory technologies, which are listed on the IPO website (ipo.llnl.gov) and cover data analysis and visualization, diagnostics, epidemiology, machine learning, protective equipment, and vaccines. For example, Cardioid, an optimized code that merges electrophysiology, fiber-generation, cardiac mechanics, torso-electrocardiograms, and cardiac meshing, simulates the electrical current running through cardiac tissue that triggers cells to contract like cascading dominoes, stimulating the heart to beat. Cardiotoxicity is a major concern in drug development. Cardioid software could be used as part of a machine learning–based simulation engine to predict and evaluate the effects of potential anti-COVID drugs on the heart.

A Diamond in the Rough

Facilitating the transfer of technologies developed at the Laboratory to the private sector requires specialists who develop partnerships aimed at commercialization. Business development executives (BDEs) in the Laboratory's Innovation and Partnerships Office (IPO) evaluate the features of newly reported Livermore inventions for commercial potential and determine whether the Laboratory should file patents, or copyrights in the case of software. "Livermore technology is considered 'early stage,'" Elsie Quaite-Randall, deputy director of IPO, explains. "Often, the researchers themselves don't know how their discoveries might be applied commercially. That's the job of a technology transfer office like Livermore's IPO. We're looking at a diamond in the rough." With patent or copyright protection in place, BDEs network with their industry contacts to zero in on each technology's commercial potential. In many cases, BDEs help secure additional funding for testing and improvements to cross the gap from early-stage invention to marketable technology. (See *S&TR,* May 2021, pp. 16–19.)

Once the technology is refined, BDEs offer licensing and partnership opportunities to industry partners with the expertise and resources to further develop and deliver Livermore's inventions to the marketplace. Licensees have the right to sell products or software based on a Livermore technology for uses defined in their licensing agreements in exchange for Laboratory licensing fees and/or royalties paid. Other partnerships, such as cooperative research and development agreements (CRADA) support specific capabilities of an invention. Livermore "tech transfer" ensures that Livermore inventions and software find their way into the world and meet the Department of Energy's goal of transitioning national laboratory innovations to society, and the pool of royalty funds then supports further Laboratory research and development.

The Biological Aerosol Mass Spectrometry (BAMS) system analyzes individual aerosol particles in real time to identify the potential presence and concentration of harmful biological particles in air samples. BAMS was designed for use in office buildings or at ports of entry such as airports or train stations to monitor for potential epidemic diseases or the release of biowarfare agents and could be adapted to rapidly detect aerosolized droplets of COVID-19.

Livermore scientists and other members of the ATOM (Accelerating Therapeutics for Opportunities in Medicine) Consortium created the ATOM Modeling Pipeline (AMPL), an open-source, modular, software pipeline for building and sharing models. AMPL generates machine-learning models that can predict safety and pharmacokinetic parameters and could speed safer, more effective anti-COVID drug development.

Other patents available under the license program include diagnostic technologies used in portable systems to rapidly detect pathogens. Another example is a new breathable smart material to guard against chemical and biological agents that could be used to protect health workers from exposure to SARS-CoV-2 and other viruses that spread before detection (see article on p. 16).

IPO publicizes these licenses through its website, and the Lab Partnering Service (LPS), which is managed by the Department of Energy's (DOE's) Office of Technology Transitions. The LPS website (covid19.labpartnering.org) offers COVID-relevant technologies available from all of DOE's national laboratories including Livermore, as well as relevant national laboratory facilities available to research partners. DOE's COVID-19 Technical Assistance Program helps small companies and businesses quickly connect with national laboratory expertise and provides U.S.-based entities performing COVID-19 research and development (R&D) with short-term help to overcome technical hurdles.

Starting with the Livermore ventilator design, BioMedInnovations, Inc. developed its mechanical ventilator and released it as a commercial product under the name SuppleVent™. The prototype was finished, licensed, and FDA-approved three months after the Laboratory began the design project. (Photo by Garry McLeod.)

Before 1980, any technology development funded by the federal government was owned by it. That year, the Bayh-Dole Act passed shifting ownership of federally funded inventions, with the condition that the government develop a technology transfer process for those with commercial potential. "This act gave federal laboratories a technology transfer mission," says Quaite-Randall. "We have to figure out how to get these technologies to U.S. companies—it's really an economic development mission." Thanks to decades of R&D funding, DOE national laboratories are treasure troves offering technology to the private sector to apply against COVID-19, to spur economic growth, and to implement effective solutions during national emergencies.

Tomorrow's Tech Today

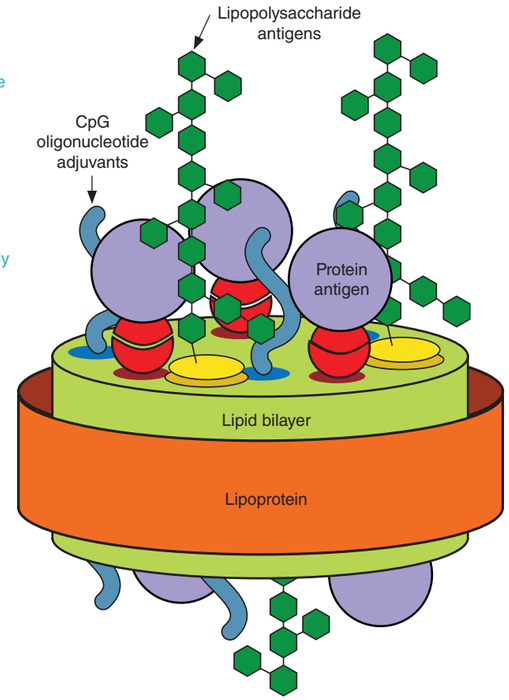
Lawrence Livermore's tech transfer efforts made important contributions in the fight against COVID-19 over the last year and a half, but realizing that evolving microorganisms pose an ongoing threat, the Laboratory expects to expand its work in this area to meet current needs and prepare for future threats. In 2006, funded by the Laboratory Directed Research and Development Program, researchers developed nanolipoprotein particles (NLPs) that were originally intended to isolate proteins that thwarted conventional isolation means. NLPs also turned out to be useful for other applications including vaccinations. A Laboratory team led by Nick Fischer, Amy Rasley, and Matt Colemen is currently working with ConserV Bioscience Limited to use NLPs to develop a broad-spectrum (universal) coronavirus vaccine.

In partnership with the ATOM Consortium, the Laboratory is also using high-performance computing (HPC) to design new therapeutics against emerging diseases. The effort was begun in 2013 under a Lawrence Livermore Director's Research Initiative to apply HPC simulation and modeling to new drug discovery before this approach was widely accepted by the pharmaceutical industry. Today, the biomedical community recognizes that computing will play a significant role in fine-tuning pharmaceutical development. "We are on the cutting edge, and in 15 years, projects like these will make valuable impacts similar to the diagnostic technologies the Laboratory developed decades ago," says Rakestraw.

"The pandemic has demonstrated that we can move quickly during a national emergency," says Rankin. "Many discussions are taking place as the nation prepares for future pandemics—a tremendous amount of momentum is built into these areas."

—Allan Chen

The structure of a nanolipoprotein particle with representative cargos (protein antigens, lipopolysaccharide antigens, and Cytosine-phosphorothioate-guanine (CpG) oligonucleotide adjuvants). Nanolipoproteins, developed with funding from the Laboratory Directed Research and Development Program, were originally intended to help isolate proteins that were difficult to purify by other means, but have shown to be excellent delivery mechanisms for vaccines. The Laboratory has teamed with ConserV Bioscience to develop a broad-spectrum vaccine against coronaviruses.



Key Words: ATOM (Accelerating Therapeutics for Opportunities in Medicine) Consortium, BioMedInnovations, LLC, Bio-Rad Laboratories Inc.,Cardioid, ConserV Bioscience Limited, cooperative research and development agreement (CRADA),COVID-19, COVID-19 Technical Assistance Program (CTAP), Department of Energy Office of Technology Transitions, emergency use authorization (EUA), Equilibar, federal business opportunity (FBO), Federal Laboratory Consortium (FLC), Food and Drug Administration, intellectual property (IP), Lab Partnering Service (LPS), Lawrence Livermore Microbial Detection Array (LLMDA), nanolipoprotein particles (NLPs), microelectromechanical systems (MEMS) chip, National Nuclear Security Administration, polymerase chain reaction (PCR), QuantaLife, Inc., SARS-CoV-2, technology transfer.

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