

Science & Technology

REVIEW

60 Years of **CANCER RESEARCH**

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About the Cover

Lawrence Livermore has been on the forefront of cancer research for more than 60 years. Early on, interest focused on how radiation affects humans, specifically on Department of Energy workers with long-term exposure. This research quickly morphed into a breadth of cancer research topics, including the development of the first fluorescence detection cytometer by Marvin Van Dilla (pictured on the cover) and the use of advanced computational models to investigate gene mutations. Over the years, Livermore has become regarded as a leader in cancer research from the Human Genome Center to its participation in the National Cancer Institute's (NCI) "Moonshot" project.



About S&TR

At Lawrence Livermore National Laboratory, we focus on science and technology research to ensure our nation's security. We also apply that expertise to solve other important national problems in energy, bioscience, and the environment. *Science & Technology Review* is published eight times a year to communicate, to a broad audience, the Laboratory's scientific and technological accomplishments in fulfilling its primary missions. The publication's goal is to help readers understand these accomplishments and appreciate their value to the individual citizen, the nation, and the world.

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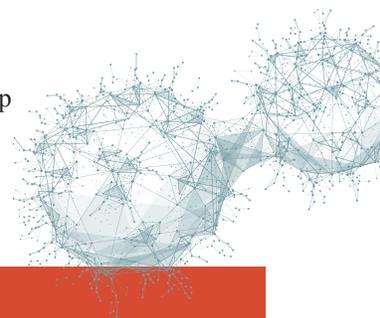
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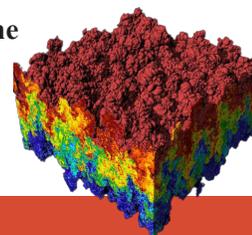
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DOE Awards \$18 Million to LaserNetUS Consortium

LaserNetUS, a network of facilities operating ultra-powerful lasers, including the Jupiter Laser Facility at Lawrence Livermore, has received \$18 million from the Department of Energy (DOE) for user support. Established in 2018 by DOE, LaserNetUS is organized and funded by DOE's Office of Fusion Energy Sciences. The network was created to provide vastly improved access to unique lasers for researchers and to help restore the United States' once-dominant position in high-intensity laser research. This new funding, distributed among 10 partner institutions and including \$1 million for user support, will continue and expand LaserNetUS operations for three years.

LaserNetUS includes the most powerful high-intensity lasers in the United States and Canada, which have a broad range of applications in basic research, advanced manufacturing, and medicine. Some of these lasers have powers approaching or exceeding a petawatt, generating light with nearly 100 times the combined output of all the world's power plants compressed into a tenth of a trillionth of a second.

In its first year of user operations, LaserNetUS awarded beamtime for 49 user experiments to researchers from 25 different institutions. More than 200 user scientists, including more than 100 students and postdoctorates, have participated in experiments so far. The network and future upgrades to LaserNetUS facilities will provide new opportunities for U.S. and international scientists in discovery science and in the development of new technologies.

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Giant Lasers Reveal Rocky Exoplanet Interiors

The increasing number of large rocky exoplanet discoveries, consisting of a variety of sizes, masses, and orbits, intensifies the need to study their material properties, to provide a deeper



understanding of the universe and the potential habitability of exoplanets. In a study, published in the February 11, 2021, issue of *Nature Geoscience*, a Livermore team

led by physicist, Federica Coppari, forced a sample of iron oxide (FeO), a material found in Earth's mantle, to extreme pressures and temperatures, replicating the conditions expected inside large rocky exoplanets.

The team used giant lasers at the University of Rochester's Omega Laser Facility to compress an FeO sample to 7 megabars (1 Mbar equals 1 million times the Earth's atmospheric pressure), pressure equivalent to the deep mantle of an exoplanet five times more massive than Earth. Additional lasers then blasted a metal foil near the FeO to create a brief pulse of x rays bright enough to capture a diffraction snapshot of the compressed sample. When FeO is compressed beyond 3 Mbars, equal to the pressure of Earth's inner-core, the atoms rearrange into a closely packed structure, transforming the sample's properties.

"Extreme conditions found within large rocky super-Earths favor the emergence of new and complex mineralogy where the constituent materials mix/unmix, flow, and deform in completely different ways than in Earth's mantle," says Coppari. "It is mind-boggling to think that our experiments can peer into the interior structure of planets far away with unprecedented resolution and contribute to a deeper understanding of the universe."

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Ruby Does the Math for COVID-19 Research

Lawrence Livermore, along with partners Intel, Supermicro, and Cornelis Networks, have deployed "Ruby," a high-performance computing cluster. Ruby is funded by National Nuclear Security Administration's Advanced Simulation and Computing program, the Laboratory's Multi-programmatic and Institutional Computing program, and the Coronavirus Aid, Relief, and Economic Security (CARES) Act (2020).

Ranked 79th among the 100 most powerful supercomputers in the world in the November 2020 biannual Top500 list, the 6-petaFLOP-peak cluster will be used for unclassified programmatic work in support of NNSA's stockpile stewardship mission, as well as for open science at the Laboratory, and in the fight against SARS-CoV-2, the virus that causes COVID-19.

Early applications for Ruby include large-scale simulating of plasma dynamics and neutron production at Livermore's MegaJoule Neutron Imaging Radiography (MJOLNIR) system, and simulating inertial confinement fusion research conducted at the National Ignition Facility and Sandia National Laboratories' Z machine. In addition, Ruby will support projects selected through Livermore's Computing Grand Challenge and Laboratory Directed Research and Development programs.

Livermore COVID-19 researchers have been using Ruby to compute the molecular docking calculations needed for discovering small molecules capable of binding to protein sites in the structure of SARS-CoV-2 for drug discovery purposes. Ruby is a liquid-cooled cluster consisting of more than 1,500 nodes, each outfitted with Intel Xeon Platinum 8276L processors with Intel Deep Learning Boost and 192 gigabytes of memory.

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Partnerships and Teamwork Drive Cancer Research

HUMAN health-related research, including cancer research, has been part of Lawrence Livermore's DNA since the 1960s. Given Livermore's weapons mission, early efforts were logically focused on the effects of low-dose radiation exposure, but soon branched into other areas. By the 1980s, for instance, Laboratory biologists were exploring the potential dangers of food mutagens—compounds in food that might cause cancer—particularly those found in grilled or fried meat. The results of their endeavors ultimately informed better cooking practices for meat preparation. As the article beginning on page 4 describes, the Laboratory's work on food mutagens is just one example of Lawrence Livermore's diverse and sustained efforts to better understand cancer development and thereby combat it more effectively. Cancer research today spans a range of disciplines, technologies, and focus areas.

While the Laboratory's programmatic missions drive its core research commitments of stockpile stewardship, nuclear nonproliferation, and national security, we have always found ways to support the fundamentally human mission of global health. Unsurprisingly, as one of the leading causes of death across the globe, cancer is a key part of that mission. The National Cancer Institute estimates that nearly 40 percent of men and women will be diagnosed with cancer at some point in their lifetime. From a humanitarian standpoint, we need to point our best resources toward this problem.

To understand cancer development and progression, many different areas of expertise must come together, including biology, computing, engineering, and data science. Lawrence Livermore is an institution that excels in multidisciplinary research, approaching complex problems from new directions and taking advantage of our unique facilities and technologies. In fact, our collaborative approach is one of the hallmarks of our success, regardless of the project. The article starting on page 20 about the Livermore-led VisIt visualization and analysis tool exemplifies the Laboratory's tradition of technological advancement through collaboration, in this case, to support scalable, high-quality evaluation of simulations. Similarly, in the article beginning on page 12, an interdisciplinary team of physics, chemistry, surface science, and

nanoscale materials experts developed a new fabrication method to produce "gold foam" aerogels: a major advancement in nanoscale materials engineering. We constantly strive to use our wealth of resources, expertise, and extensive research to advance science.

Nothing illustrates this more than the Laboratory's history of cancer research. These efforts have produced remarkable innovations, from the refinement of tools and processes like fluorescent in-situ hybridization, or FISH, to the advancement of high-performance computing and multiscale modeling—all made possible by our culture of innovation and collaboration.

By working with partners in industry and academia, such as the University of California at Davis Comprehensive Cancer Center, we have gained access to critical clinical data, expertise, and resources. Partnerships like these allow us to bring our unique technologies to the clinicians and spark the creation of teams of scientists, engineers, students, and medical practitioners. These teams give students the opportunity to experience our culture, supporting a hiring pipeline so they can further their research careers at the Laboratory. Similarly, partnerships such as the Joint Design of Advanced Computing Solutions for Cancer (JDACS4C) program, allow us to leverage our strengths in support of a common goal—in this case using Lawrence Livermore's expertise in computing and predictive modeling to better understand the Ras protein. Partnerships are a fundamental thread in the Laboratory's cultural fabric and, as the article beginning on page 16 describes, can even lead to commercialization efforts that help us turn new technologies and tools into products that benefit the public.

Cancer research has played an important part in the Laboratory's biology program for the past 60 years, and it will likely continue to do so until a cure is discovered. It is a vibrant area of research that benefits from Livermore's team science approach, robust tools, and capabilities. It is part of our biology story, and we will continue to find creative ways to approach this innately human problem, so the chapter on cancer research might one day close.

■ Glenn A. Fox is associate director for Physical and Life Sciences.



60 Years of CANCER RESEARCH

From the earliest days of Livermore's history, the Laboratory has leveraged its unique resources and considerable talent against one of the biggest challenges in medicine.

In the early 1800s, the Livermore Valley was rich in rangeland and livestock, finding profit in cattle sales to early gold miners. Over a century later, cattle in Livermore found a very different purpose—helping scientists better understand radiation effects on humans, and in particular workers in the Department of Energy (DOE), from exposure to ionizing radiation and radioactive materials. While humans will always battle new infections and diseases, including the current coronavirus, one constant in our vast range of human health challenges is the fight to cure cancer. The Laboratory's expertise is not explicitly for the benefit of cancer research, but for the past 60 years, the technologies and capabilities built at the Laboratory have advanced our understanding of cancer and carcinogens, from radiation isotope effects in humans to cancer metastasis. As Lawrence Livermore prepares to enter a new decade of cancer research, it builds on a legacy of discovery and innovation marked by its hallmark strengths—specialized facilities, high-precision measurement capabilities, team science, cutting-edge engineering, and computational excellence.

The Nuclear Unknown

The Laboratory's relationship with cancer research began as soon as it was founded in 1952. Following World War II, Lawrence Livermore was created as a second nuclear laboratory to complement existing efforts by Los Alamos National Laboratory. With oversight from the Atomic Energy Commission (AEC), the Laboratory's mission was relatively straightforward: to advance nuclear weapons science and technology. Nuclear weapons research at the time presented a monumental challenge for scientists trying to understand its effects, particularly on human health. Physical reactions like radiation poisoning manifested within days, however, longer-term effects, such as increased rates of neurodegeneration and cancer, would not appear for years. While it was clear that radiation exposure had long-term repercussions in humans, it was not well understood how or why.

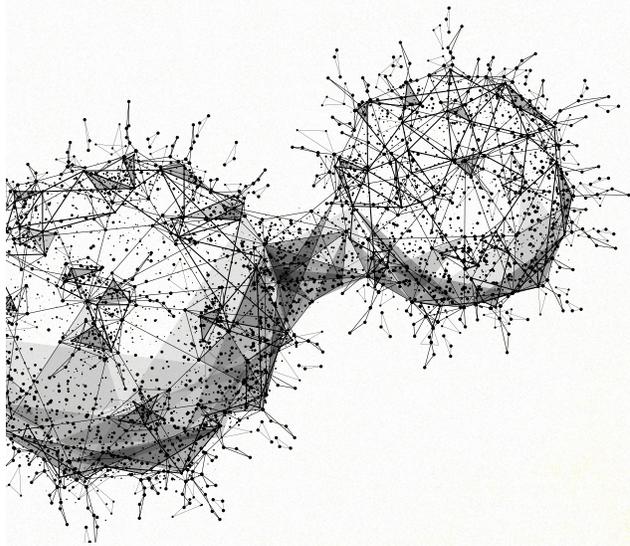
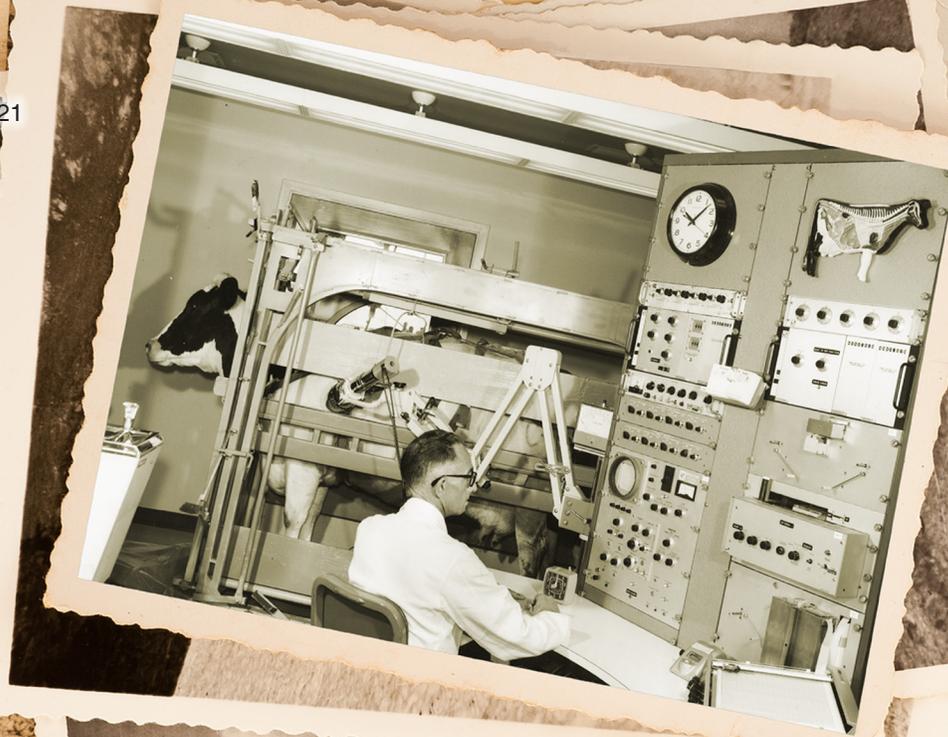
To help answer these questions, Lawrence Livermore established the Biology and Environmental Research (BER) Program in 1963 to study the dose per person of radioactive isotopes in the environment as a result of nuclear weapons fallout. Scientists

at the Laboratory were tasked with understanding how to judge radiation exposure in humans, as well as how to detect radiation damage. "We had a farm onsite to look at radiation effects in milk, livestock, and plants. We also looked at how radiation damages cells and people...we were trying to get a deeper understanding of radiation's effects on the human genome and DNA," says Acting Biosecurity Center Director Ken Turteltaub.

Scientists suspected that genetic material was particularly susceptible to radiation damage, and they began to look at site-specific DNA mutations in various cells. True to Laboratory form, Lawrence Livermore scientists developed early technologies to help investigate DNA mutations and better understand their connection to diseases like cancer. "The Laboratory has a long tradition of taking on important problems that require a long time to solve. We didn't always have the tools we needed, so a lot of our tools were developed to address our scientific queries," says Turteltaub.

New assays were used to look at genetic changes, and technologies like the cytophotometric data conversion system





(CYDAC) helped scientists quantitatively examine DNA in any given chromosome. In fact, CYDAC helped confirm a chromosome abnormality in patients with leukemia—these patients consistently experienced a loss of genetic material in chromosome 22 and an excess of material in chromosome 9—an indicator that DNA translocations were connected to cancer.

While cancer research in the 1960s and 1970s was a relatively small part of the Laboratory's overall mission, it was certainly the most talked-about at the dinner table. "Cancer research was actually a very minor piece of total Lab research, but people liked it because it was something you could talk about at home," says Turteltaub.

In 1974, however, facing natural gas shortages, increasing fuel prices, and the lack of a national energy policy, the United States and the national

laboratories focused on areas of energy research like fossil fuels and nuclear power.

Despite the Laboratory's pivot from radiation biology, scientists were able to deepen Lawrence Livermore's expertise in DNA and genomics. The cytogenetics lab, led by scientist Tony Carrano, was beginning to use techniques like flow cytometry to measure and sort human chromosomes for the first time. Nearby, Laboratory scientists Joe Gray and Dan Pinkel were developing perhaps one of the biggest biomedical patents to date: fluorescent in-situ hybridization (FISH), used to label and identify genes or chromosomes of interest in a cell. These early accomplishments laid the groundwork for later major research efforts, like the Human Genome Project, which advanced our understanding of cancer even further.

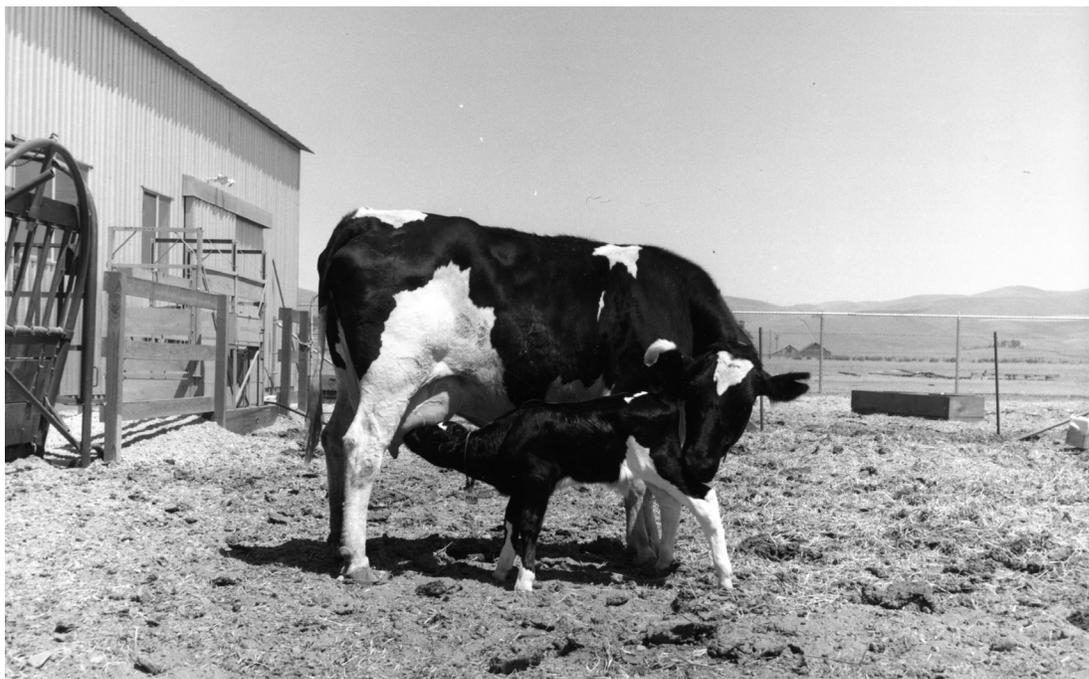
Focus on Food Mutagens

In the 1980s, scientists began to focus on compounds in food that might cause cancer—specifically heterocyclic amines, which form in meat when it's cooked at high temperatures for prolonged periods of time. Bruce Ames from the University of California at Berkeley developed the now famous Ames test—a quick screen for genetic mutation-causing chemicals using a strain of salmonella bacteria—which soon became the standard for determining whether or not a chemical substance was mutagenic. Lawrence Livermore also became involved in this research, focusing on DNA adduct formations, instances where a cancer-causing chemical attaches to a DNA strand and can be used as potential indicators of a human body's exposure to carcinogens. Research in this area was enhanced by the Laboratory's construction and start up of the Center for Accelerator Mass Spectrometry (CAMS) in late 1987—a center designed specifically to study and measure isotope ratios with high precision and sensitivity (see *S&TR*, April/May 2018, pp. 5–11). Turteltaub and John Vogel saw vast potential for the application of CAMS to biosciences, conducting the first biomedical experiments in 1990.

Using ^{32}P -postlabeling and accelerator mass spectrometry (AMS), Turteltaub and his team at Livermore studied DNA damage caused by heterocyclic amine carcinogens found in certain foods. They found early correlations between dose amount and DNA adduction in rodents—and later studies on human subjects confirmed bioavailability of carcinogens with normal levels of dietary exposure.

Lawrence Livermore's use of AMS for biomedical science was a first at the Laboratory and, with support from the National Institutes of Health (NIH), led to CAMS's eventual designation as the official National Research Resource for biomedical applications of AMS. The Laboratory's work on food mutagens contributed significantly to public

The Laboratory maintained an onsite farm for radiation research in the 1960s, complete with cattle, sheep, peccaries, and two rare pygmy goats. The Holstein cattle pictured composed part of the "Bovinatron" cow barn.





health—informing later-developed food standards and more detailed guidance on how to safely cook meats at prescribed temperatures and durations.

The Human Genome Project

In 1983, Carrano's cytogenetics laboratory began its first human DNA library project. The project was led by scientist Marv Van Dilla in partnership with researchers from Los Alamos and represented an early effort to expand the application of flow cytometry to developing fragmented genome libraries based on flow-sorted human chromosomes. The group focused much of their efforts on chromosome 19—a chromosome suspected to have a high gene density—and which also exhibited genes involved in DNA repair. Around the same time, the historic Alta Summit was taking place in the snowy mountains of Utah, where experts nationwide discussed the prospect of using DNA analytical tools to study mutation rates among survivors of the bombings of Hiroshima and Nagasaki nearly 40 years prior. This historical meeting laid the groundwork for the initiation of

The Center for Accelerator Mass Spectrometry (CAMS) has played an important role in Livermore's cancer research efforts since it began operations in late 1987. In biomedical research, CAMS uses an ion beam to determine the ratio of radioactive atoms to normal atoms in organic material. Before CAMS, the Laboratory had never used accelerator mass spectrometry for biomedical science, and its pioneering impact led CAMS to being named the official National Research Resource for such work.

the Human Genome Project by DOE in 1987, which grew into a partnership with the NIH in 1990 with help from 18 genome centers worldwide. The meeting also led to establishing the complementary Human Genome Center at Lawrence Livermore—directed by Carrano.

“People thought it would take 100 years to assemble the entire human genome, but DOE wanted to sequence it and LLNL was bringing tools to bear,” says Turteltaub. The Laboratory already had the technology to cut and manipulate DNA in addition to other expertise it was able to refine and share with the scientific community at large. Many of the tools cultivated in Carrano's laboratory by scientists like Van Dilla, Gray, and Larry Thompson advanced DNA-relevant technologies including flow cytometry,

FISH, and mutant cell development. Flow cytometry, particularly the later-patented MoFlo (modular flow) cytometer, was used to sort chromosomes for the Human Genome Project. The FISH technique, which stained specific parts of chromosomes, allowed for fast detection of aberrations in cells, such as deletions, translocations, or duplications, which are commonly found in cancer cells. Mutant chinese hamster ovary cells cultivated by Thompson provided a cell line that was perfect for building a human chromosome-19 gene library.

While the Laboratory's particular piece of the Human Genome Project was focused on sequencing chromosome 19, perhaps the most significant results of the Laboratory's involvement in the Human Genome Project were the technology and

whole genome libraries it developed in partnership with other laboratories. In the late nineties, Livermore's Human Genome Center joined forces with Berkeley and Los Alamos laboratories to form the Joint Genome Institute (JGI). "JGI helped develop a deeper understanding of the human genome, DNA repair, and how we fix damage," says Turteltaub. "When chemicals or radiation damages your DNA, your body tries to fix it, but sometimes it does this incorrectly and can cause or prevent cancer. Through JGI, we gained a deeper understanding of sequencing and DNA repair which helped us understand how cancer is caused and how to treat it."

The Laboratory's research efforts during this time led to rapid and significant improvements in the supporting technology, particularly in computing devoted to this effort. "Early on, we didn't have a lot of computing and early sequencing wasn't high-throughput. It was experimental. You would compare very specific sequences side-by-side. With the Human Genome Project, it became clear we needed better computing capabilities," says Turteltaub. Computers ultimately helped fill the gaps that human minds could not. "Sequencing is not linear, so computers helped align DNA and see the overlaps. Over time, the pieces became longer and we developed more research queries, like identifying protein structures. Research evolved from DNA alignments and comparing sequences to physics informatics and looking at mutations in proteins," explains Turteltaub.

The first draft of the human genome was published in 2001, and the project was formally completed and published in 2003. In this time period, the Human Genome Center at Livermore developed and maintained an extensive database for chromosome 19 information, as well as a library, which enabled the cloning of specific genes for delivery to other scientists. Laboratory scientist Lisa Stubbs enhanced this effort through a successful program to annotate and assign biological functions to genes harbored



Early groundbreaking work in flow cytometry, a technique for separating specific cells from other cells, has led to numerous medical research applications in genomics research and national security applications, such as biosensors that detect specific agents used in biological weapons.

on chromosome 19. She focused on a particular cluster of transcription factors, determining how they evolved and diverged across species.

As part of the JGI, Livermore contributed to the full sequencing of chromosomes 5, 11, 16, and 19. While the JGI still operates today, Livermore is much less involved. Its contributions to sequencing, genome assembly, gene annotation, and other technologies, however, left it well-positioned for cancer research efforts nearly two decades later.

Cancer Moonshot

Due to funding shifts and sponsor directives, the Laboratory's cancer research was scaled back in the early 2000s, and the biology focus shifted to biosecurity. In 2016, however, that changed with the initiation of the Cancer Moonshot program. A year prior, President Barack Obama issued an executive order to establish the National Strategic Computing Initiative (NSCI)—a multiagency effort to find new ways to apply high-performance computing to scientific discovery. One of these

approaches emerged through conversations between DOE and the National Cancer Institute (NCI). NCI expressed a need to advance oncology with computational and data analytics with three levels of research: cellular, molecular, and demographic. While serving as vice president in 2016, Joe Biden announced the National Cancer Moonshot—a concerted effort to discover a cure for cancer, which took the life of his son Beau in 2015.

The Moonshot involves multiple initiatives, including the Joint Design of Advanced Computing Solutions for Cancer (JDACS4C), which is a pilot pursued by NCI and DOE (see *S&TR*, November 2016, pp. 4–11). As part of JDACS4C, Lawrence Livermore works with NCI and its Frederick National Laboratory for Cancer Research (FNLCR), and with Los Alamos, Oak Ridge, and Argonne national laboratories to tackle three pilot programs.

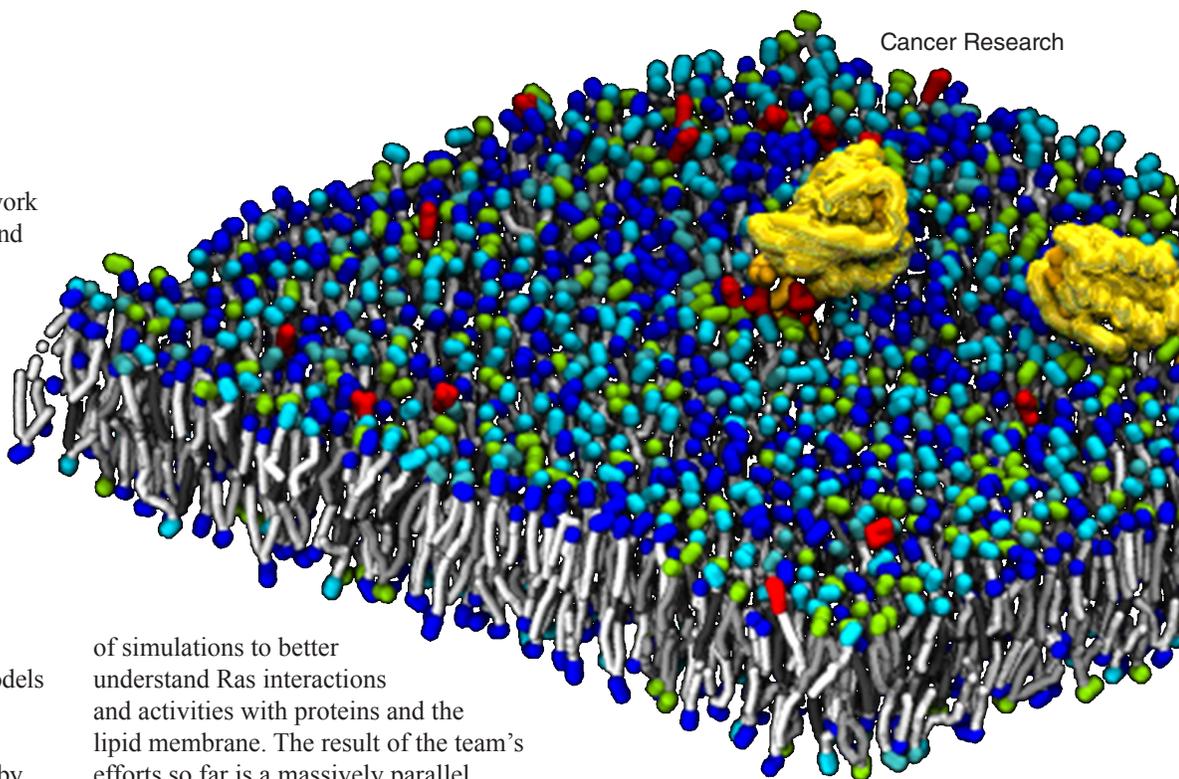
Amy Gryshuk, who at the time served as the program development liaison and now leads the Laboratory's Physical and Life Sciences Directorate Strategic Science Engagements Office, and Eric Stahlberg,

representative for FNLCR, coordinate work between the DOE labs and NCI. “Eric and I facilitate collaborative conversations and identify new growth opportunities,” explains Gryshuk. “With so many moving parts, it’s important to understand the dynamics of each partner and how we can leverage each national laboratory’s strengths for the pilots’ successes.” This close-knit partnership has been critical to the pilot programs’ accomplishments so far.

The first pilot, led by Argonne, NCI, and FNLCR, focuses on identifying new treatments using computations and developing and validating predictive models which can “grow” a patient’s tumor and guide therapeutics based on modeling predictions. The second Ras pilot is led by Fred Streitz of Lawrence Livermore and Dwight Nissley of FNLCR. It endeavors to gain a deeper understanding of cancer biology, starting with the Ras protein which plays a critical role in cell growth and is often at the source of cancer development. Finally, the third pilot, led by Oak Ridge and NCI, is focused on cancer surveillance and applying computation to find patterns in cancer-based data, including diagnostics, treatments, and individual patient factors. Los Alamos’s role touches all three pilots—providing uncertainty quantification for machine learning to better understand predictive models and simulation reliability.

For the Ras pilot, the Laboratory has made significant contributions in computing and predictive models to better understand cancer development. The research involves a close synergy between experiments and computation, allowing scientists to get a better picture of the Ras protein and how it interacts with a cell’s lipid membrane. “Ras is the undruggable protein. We want to target it specifically because oncogenic mutations of Ras are implicated in some of the most aggressive cancers we know, such as pancreatic and colon,” says Gryshuk.

Using high-performance computers, like Lawrence Livermore’s Sierra machine, scientists have run tens of thousands



of simulations to better understand Ras interactions and activities with proteins and the lipid membrane. The result of the team’s efforts so far is a massively parallel Multiscale Machine-Learned Modeling Infrastructure (MuMMI) that has helped scientists find relevant seed data for further modeling and analysis of Ras protein interactions.

As JDACS4C enters its fifth year, Gryshuk reflects on the importance of interagency collaborations—one of the pillars of team science. “I don’t think there’s been an interagency collaboration at this level before. This collaboration has allowed us to share resources, integrate experimental and computational efforts in an iterative form, and gain valuable access to clinical data, which national laboratories don’t normally have access to. We’re using computing to identify potential treatments, better understand cancer biology, and analyze cancer-based data. We’re continuing to grow in partnership,” says Gryshuk.

Past Meets Present

The Laboratory’s current cancer research efforts span a range of departments, disciplines, and focus areas—a unique fact considering cancer research is not, and never was, one of the Laboratory’s core mission areas. “Cancer research isn’t spelled out in our core mission. It can be broadly categorized under health security,” explains

Lawrence Livermore researchers led a multi-institutional collaboration to develop a machine learning-based simulation capable of modeling the protein interactions and mutations that play a role in many forms of cancer. This micro-model simulation shows the aggregation of Ras proteins (yellow) on top of a cell membrane model. (Rendering by Timothy S. Carpenter.)

Biosciences and Biotechnology division leader Kris Kulp. “The role we play is that we take advantage of the strengths of the Laboratory. We offer computing and new experimental techniques to help investigate cancer research questions,” says Kulp.

The laboratory of Lawrence Livermore scientist Gaby Loots is one place where experimentation, technology, and diverse expertise intersect on a regular basis in support of cancer research. Loots came to the Laboratory 18 years ago with a degree in genetics and genomics, seeking to better understand the function of DNA regions that are evolutionarily conserved and control transcription of genes. She now leads a successful program in bone and cartilage research, examining the risk factors that contribute to degenerative disorders like osteoporosis and osteoarthritis. Cancer

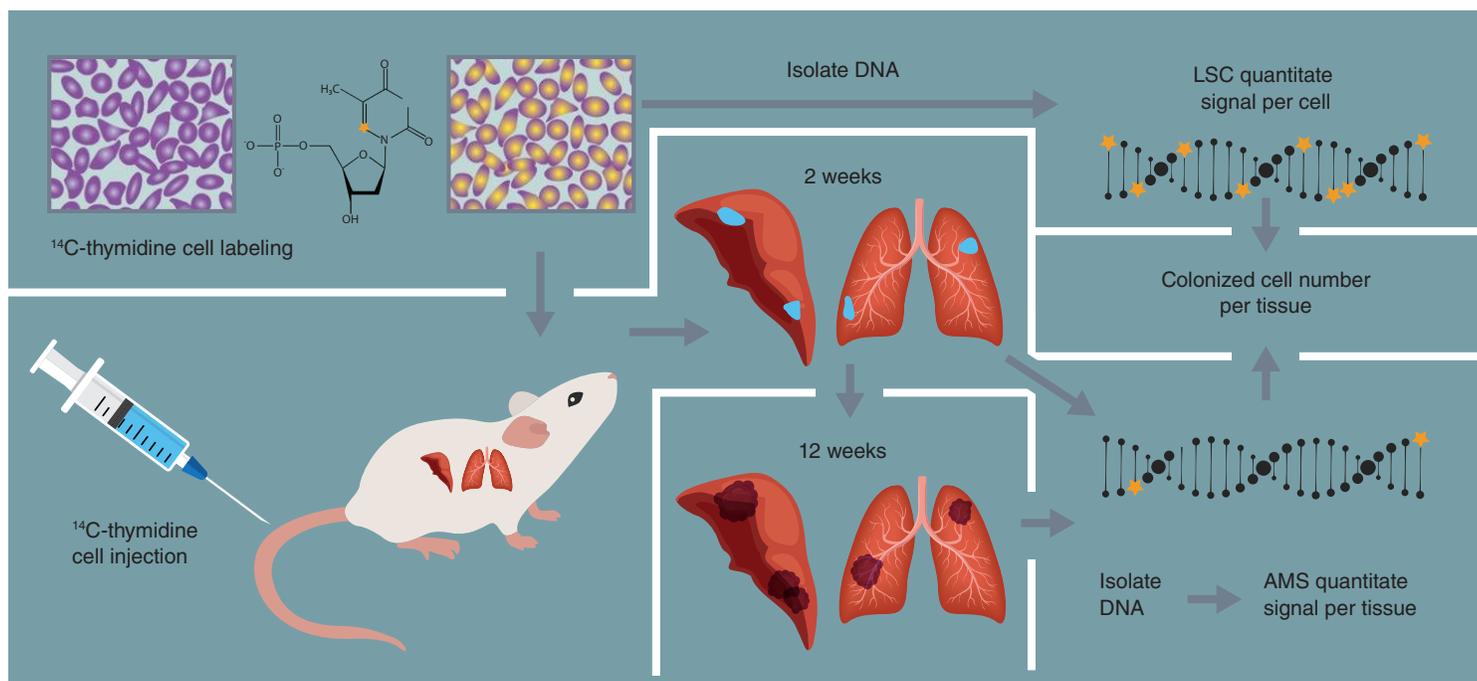
research became a natural secondary research area in her lab because cancer metastasis—when cancer spreads to other parts of the body from its origin site—spreads to bone in most aggressive forms of the disease. “We started cancer research 10 years ago, and we noticed a lot of the signaling pathways active in bone are also up-regulated in some cancers, so we studied the process of cancer metastasis to bone. We wondered, ‘What is it about the bone environment that allows cancer to thrive?’” says Loots. Once cancer has metastasized to bone, it becomes much more challenging to treat and rapidly increases mortality. “Cancer adapts quickly and can block the immune system. When the balance shifts in favor of cancer, there’s little chance of going back.”

One way Loots and her laboratory team study cancer metastasis is by developing innovative ways to track cells and small secreted vesicles, called “exosomes.” In an effort led by scientist Nicholas Hum, the team recently found a new way to quantify the number of cells that initiate metastatic tumors using the Laboratory’s BioAMS signature facility. “We label cancer cells *ex vivo* with ^{14}C -thymidine, and the chemical incorporates into the cell’s DNA and creates a signature that can be tracked in the body. With this approach, we can estimate the number of cancer cells that migrate to a distant organ and quantify how many cancer cells initiate a metastatic tumor,” explains Loots. The AMS is able to accurately measure the initial number of ^{14}C -labeled cells that formed a tumor in a

tissue after defined periods of time because of the long half-life of ^{14}C . The method also helps scientists determine if tumor cells have been completely removed in response to treatment. “Remission is a huge issue—after treatment, sometimes cancer cells remain dormant and undetectable for months or years, but when they reignite, they form drug-resistant tumors that readily metastasize. Our method allows us, with very high precision, to see if any cancer persists or has been eradicated,” says Loots.

The team relies heavily on AMS to both track cancer cells and label chemotherapeutics to observe their success in treating cancer. One way their team is approaching chemotherapeutics research is via microdosing—an effort started by Turteltaub. “Microdosing allows you to give a small amount of therapeutics and determine the amount of drug present in cells or bound to DNA, which usually correlates with chemo resistance or sensitivity. We use AMS to determine how many molecules of the drug actually make it to a tumor,” says Loots. Microdosing is important because it

By injecting mice with a ^{14}C -thymidine radioisotope, CAMS researchers examined radiation’s effect on cell development. Tissue was harvested at 2 and 12 weeks to show different stages of growth, and the mouse DNA was isolated and quantified using AMS. In parallel, cultured DNA was quantified with liquid scintillation counting (LSC), a method that mixes organic material with a fluorescing solvent and measures the resultant photon output. The AMS and LSC results were then combined for a calculation of how many cells in each organ had been colonized with cancer cells.





Scientists in Livermore's gene library project prepare to ship out one of the first gene libraries in 1984. From left, (first row, seated) is Lil Mitchell, Nancy Allen, and a summer intern. Second row: Lynn Minker, Tony Silva, Linda Ashworth, Janine Perlman, Lo Chung Yu, and Jim Fuscoe. Third row: Anthony Carrano, Karla Henning, Marvin Van Dilla, Leilani Corell, Mortimer Mendelsohn, Joe Gray, Dan Pinkel, and Don Peters.

facilitates a Goldilocks approach to chemotherapy treatment—too much or too little can actually hurt a patient. “In a petri dish, any drug can seem effective, but you have to balance the toxicity of the treatment with its efficacy. It may look like it’s killing 100% of the cancer but it may also be killing healthy cells, making the patient sick,” says Loots.

Determining pharmacokinetics is a key application of AMS. “You can label any drug with ^{14}C and determine its uptake, distribution, and clearance, including how long drugs stay in the system. We can also look at factors such as whether or not the drug is crossing the blood–brain barrier. AMS helps you quantify trace amounts of a drug in different tissues,” says Loots. The Laboratory’s extensive use of the AMS is part of what makes its cancer research unique. Kulp explains, “We have a long history of using the AMS for cancer questions. Our team includes world experts in AMS, and the facility is a really compelling reason for us to do cancer research.” Another key element of the AMS is collaboration—it’s currently set up as a user facility with support from the NIH, so other laboratories and organizations can also take advantage of its unique capabilities.

Also critical to the Laboratory’s cancer research is its partnership with local universities. The Loots lab specifically

leverages its partnership with the UC Davis Comprehensive Cancer Center (UCDCCC) to bring in graduate students and postdocs, as well as share resources. “We are a consortium with UCDCCC—I’m essentially a matchmaker between UC Davis and Livermore. They can use the Laboratory’s technology, and we can have access to human samples and reagents, which we wouldn’t have access to otherwise,” says Loots.

Research for the Cure

Other exciting, current cancer research areas include scientist Monica Moya’s research into cancer metastasis using three-dimensional bio-printing. Her project involves engineering human tissues to mimic actual biological functions, which would potentially allow scientists to model how cancer moves through blood vessels without having to test therapeutics on humans or animals. Scientist Claire Robertson is using a similar method to look at cell communication during the progression of breast cancer. Another effort, led by scientist Sean Gilmore and funded by the Laboratory Directed Research and Development program, is focused on nanometer-scale, particle-based immunotherapy for cancer treatment. Gilmore’s project is investigating use of a combination of chemotherapy and immunotherapy to treat cancer that takes advantage of the natural pharmacokinetic properties of nanometer-scale particles, like nanolipoproteins.

From researching the effect of radioactive isotopes in humans, to food

mutagens, to understanding the human genome and cancer metastasis, the Laboratory’s relationship with cancer research has continued to evolve with new technology and information. Livermore’s efforts benefit both the Laboratory’s national security mission and the mission closer to home: human health. Says Loots, “Any animal models we generate are directly applicable to national security, to developing countermeasures to malicious chemical and biological agents, and to improving resilience in our military personnel. We can use the same approaches to determine harmful effects of pathogens as we do to study mechanisms of cancer development. Our methodologies and infrastructure always have the mission at heart.” As the Laboratory enters a new decade of cancer research, it will continue to apply its range of unique resources and expertise until one day cancer is cured.

—Lauren Casonhua

Key Words: accelerator mass spectrometry (AMS), bio-printing, cancer metastasis, cancer moonshot, cancer research, chromosomes, cytophotometric data conversion system (CYDAC), DNA adducts, flow cytometry, fluorescent in-situ hybridization (FISH), food mutagens, gene library, genomics, heterocyclic amines, high-performance computing, Human Genome Project, Joint Design of Advanced Computing Solutions for Cancer (JDACS4C), Joint Genome Institute (JGI), MoFlo, Multiscale Machine-Learned Modeling Infrastructure (MuMMI), National Cancer Institute (NCI), National Institutes of Health (NIH), predictive models, radioactive isotopes, Ras protein, Sierra supercomputer.

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GOLD MONOLITHS LIGHTER THAN AIR



GOLD, that dense but soft metal, is more than a raw material for making jewelry. One of the least chemically reactive and most malleable of the noble metals, gold's high electrical conductivity makes it ideal for applications in electronics, medicine, and scientific research.

Over the last decade, Livermore materials engineers working at the nanoscale have uncovered techniques for generating metal aerogels: a unique, emergent class of lightweight, low-density,

super-porous but durable materials that present huge potential advances for scientific research and industrial applications. Now, a team of Livermore researchers has given gold a new incarnation as an aerogel "foam" that is literally lighter than air.

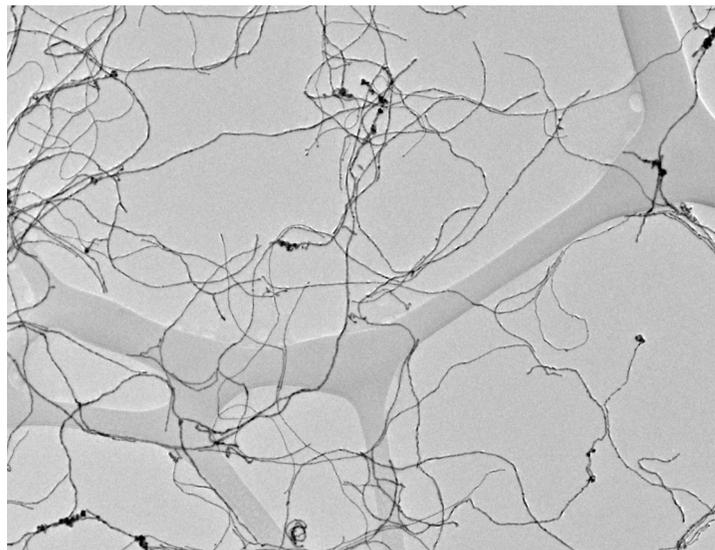
Nanoengineered Chemical Reactors

Researchers have developed experimental metal aerogels of nickel, cobalt, copper, and silver in order to initiate, facilitate,



A mosquito standing on cotton fibers carries a sample of the Livermore team's ultra-low-density gold aerogel, which is literally lighter than air. (Photo by Joshua DeOtte.)

and speed up chemical reactions, as well as assist in filtration. With their high mechanical rigidity, they can also serve as microscopic support structures for enzymes and other proteins embedded within their micrometer-scale pores as they react to other biomolecules. As scientists have realized the significant advances these aerogel metals present, researchers at Lawrence Livermore and around the world have been competing to uncover an efficient and inexpensive method to produce large



Lawrence Livermore scientists have fabricated gold aerogels with incredibly low density, with strong, spaghetti-like threads called nanowires forming a lattice throughout the material. Each nanowire is approximately a thousand times thinner than a human hair.

quantities of these aerogels—while still predictably controlling their nanoscale architecture, surface area, and pore size.

To create the first aerogels, researchers used “sol-gel” chemistry: a process that synthesizes solids from a colloidal suspension by converting molecular precursors into nanometer-sized particles that link up, forming a spaghetti-like three-dimensional liquid-filled network. Freeze-drying removes the liquid, leaving behind a porous low-density aerogel that looks like a stale marshmallow, but is referred to as a “monolith.” The sol-gel method, however, did not produce the robust, high-quality ultralight monoliths the researchers needed. A radically new approach was required.

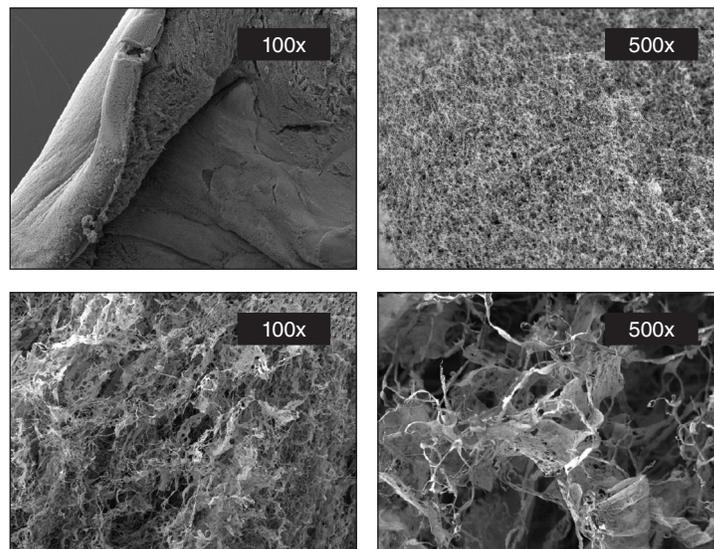
Livermore's Road to Success

In 2016, a Laboratory team led by materials scientist Fang Qian reported a simple method for growing and purifying copper nanowires. “The research problem was how to purify these materials at a large-enough scale to manufacture nanofoams,” says Qian. As the building blocks of metal aerogel, nanowires need to be produced in large enough batches to serve as raw material for producing monoliths of aerogel. Nanowires are typically on the order of 20 to 30 micrometers (μm , millionths of a meter) long and just 20 to 30 nanometers (nm) in diameter—about a thousand times thinner than a strand of human hair. Once the purity and quantity riddle was solved, another Lawrence Livermore team developed a method of forming

low-density copper nanofoams that same year. And in 2018, a Laboratory team announced the development of a method for fabricating ultra-low-density (less than 10 mg/cm^3) monolithic silver aerogels.

Gold, however, was the most difficult of noble metals to fabricate into an ultralight aerogel. By bringing together an interdisciplinary team from Lawrence Livermore that included experts in freezing physics, organic and inorganic chemistry, surface science, and nanoscale materials characterization, ultralight gold aerogel finally materialized. The team's pioneering fabrication method combined chemical techniques with industrial freeze-drying and freeze-casting. "Gold foam has been made before, but nowhere near the low density, high purity, and controlled pore geometries of ours," says Livermore materials scientist and principal investigator Michael Bagge-Hansen. "Our recipe is totally unique."

The method begins with immersing negatively charged gold nanoparticles (AuNPs), and positively charged silicon wafers in a solution. The silicon wafers' positive charges attract the AuNPs, which uniformly coat the surface of the wafers, creating seed sites. AuNP atoms then deposit only at the seed sites, growing roughly perpendicular to the wafer into nanowires with the same length and diameter. The researchers then detach the gold nanowires from the wafers using ultrasonication or soundwaves. The result is a black liquid filled with gold nanowires.



Then, researchers use liquid nitrogen to freeze the gold nanowire suspension. "The ice crystals form and enlarge as the freezing starts," says Qian. "As they do, they push the nanowires into networks of pores, creating a highly uniform pore structure." As the solution vaporizes or sublimates away during the freeze-drying phase, it leaves behind a self-supporting network of gold nanowires that form the aerogel.

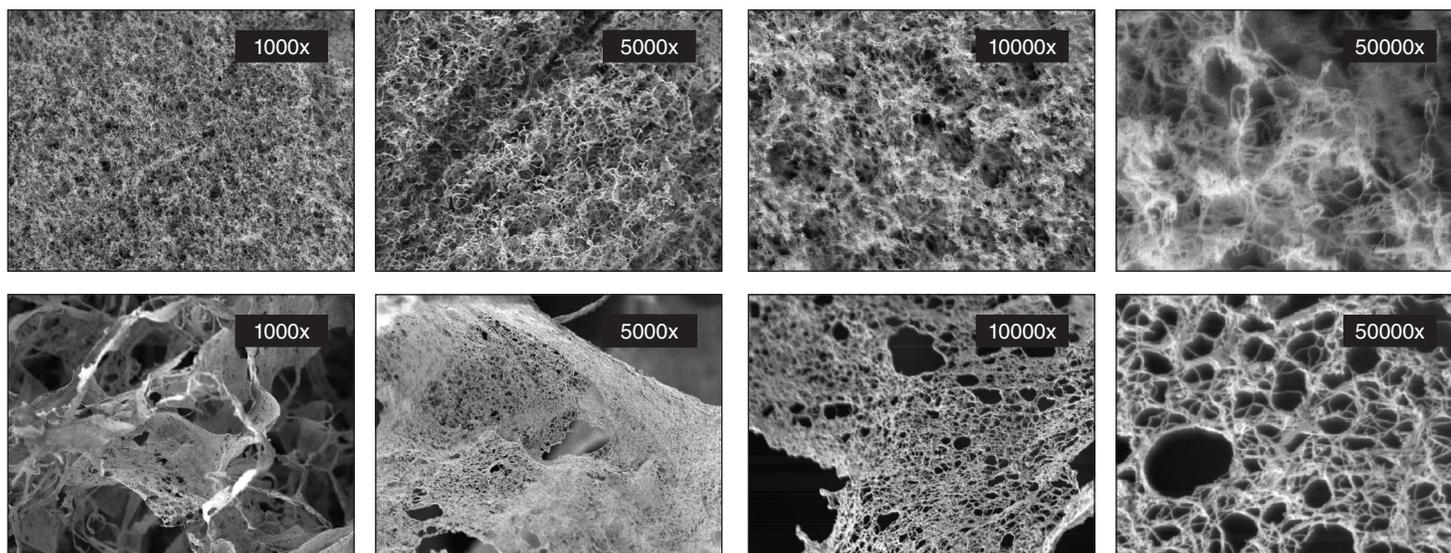
"By varying the concentration of nanowires in the suspension, we can fine-tune or custom-design the density of gold aerogel," says Bagge-Hansen. "We've achieved a range of densities, from 6 to 23 mg/cm^3 ." To control pore size, the team has several tools. They vary the speed of freezing: faster freezing results in smaller pores; slower freezing yields larger pores. They can also change the solvent liquid, and add inactive substances known as "excipients" that alter the freezing properties of the solvent without becoming part of the aerogel, so the purity of the aerogel remains high. Adding an excipient called tert-Butanol (tBA) to the suspension creates dramatically smaller ice crystals of uniform size.

Like a Breath of Metal Air

The lowest gold foam density the team achieved is 6 mg/cm^3 , or only 0.03 percent density, relative to full-density gold— 19.32 g/cm^3 . The foam's atomic density is 1.8×10^{19} atoms/ cm^3 , lower than the atomic density of air (2.7×10^{19} atoms/ cm^3) at room temperature and atmospheric pressure. "Producing millimeter-scale gold aerogels at this low density was quite unexpected and underscores the opportunities

A sample of a gold aerogel hangs from a single thread of spider silk, illustrating its unusually low mass. (Photo by Joshua DeOtte.)





presented by freeze-casting metal nanowire solutions,” says Bagge-Hansen. “It adds another capability to our toolbox.” The final product looks nothing like lustrous gold, because its physical properties metamorphose as the size of the gold particles approach the nanoscale. “A gold nanoparticle solution changes colors from purple to green to red as the nanoparticles’ size and aspect ratio change,” says Qian. “The nanowires have a unique structure that changes their light-scattering properties, ultimately giving the aerogel its black hue.”

With the gold-aerogel manufacturing process established, the team spent several months collaborating with National Ignition Facility (NIF) target fabrication scientists to calibrate and test protocols for storing, transporting, and successfully mounting the aerogel on targets at NIF. When NIF’s high-powered laser beams hit the material, the aerogel vaporizes and generates x-rays at particular energies useful for studying high-energy-density physics and examining the intersection of condensed matter physics, nuclear physics, astrophysics, and plasma physics. Researchers at the Laboratory initially developed these ultra-low density metal foams to give physicists better x-ray sources to employ in experiments that support NIF’s Stockpile Stewardship mission.

Initial samples of the ultralight gold aerogel had a frustrating tendency to fall apart or drift away with the slightest breath or change in air current, which presented a legitimate challenge. Eventually, the team determined how to create an aerogel that stays in place on the target when the laser burst hits. “These (next-generation) gold foams are mechanically stable, compared to early samples that were similar in strength to a long cigarette ash,” said Brent Blue, the National Security Applications program manager. “They can be squeezed or dropped, and they bounce back and hold their shape very well, which is a critical

Electron microscope images at different magnifications of gold aerogel generated from nanowires suspended in a water-based solution. Gold aerogel was generated in a mixture of water and tert-Butanol (tBA) (top row). It shows a more uniform pore size than those grown without tBA (bottom row).

quality for use as a bright x-ray source. This is an amazing feat given that, even though they look solid, they are 99.9 percent void, or 0.1 percent solid.”

Now, the research team has turned their focus to developing new methods for transforming any metal into an aerogel. “We’ve been working on tin for a while,” says Bagge-Hansen. “Making tin into nanowires and aerogels is a huge challenge. Its chemistry is so different from gold. The process will be even more difficult as we move from tin into the other transition metals of the periodic table.” The team has had discussions with potential private-sector partners to further explore industrial uses of metal aerogels. For all their insubstantiality, these mini metal monoliths stand to become bona fide heavyweights in scientific research and industrial materials of the future.

—Allan Chen

Key Words: aerogel, catalysis, cobalt, copper, excipient, freeze-casting, freeze-drying, gel, gold (Au), high-energy-density science, liquid nitrogen, monolithic aerogel, nanofoam, nanoparticle, nanoporous metal, nanowire, National Ignition Facility (NIF), nickel, silver, sonication, tert-Butanol (tBA), tin.

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TO this day, Lawrence Livermore continues to live up to its original mission as the “new ideas” laboratory. Ideas sparked at Livermore generate technologies for national security and publications about advancements in fields from biosciences to high-performance computing to manufacturing. Many Livermore ideas have commercial potential as well. With investment, they can be developed into products that benefit consumers, industry, and the U.S. economy.

Ideas are not in short supply, but funding for Department of Energy (DOE) national laboratory research often ends when a new scientific principle is proven experimentally. Industry partners and startups with the capacity to move technologies into the marketplace seek a high level of proof that an invention has commercial potential. As a result, efforts to connect a promising early-stage technology with a capable commercial partner often stop at the steep edge of the laboratory-to-market resource gap.

Money for additional development, such as building a full-size prototype or testing across a range of operating

conditions, has not been easy to obtain. “Technology maturation funding has long been the bane of technology transfer at national laboratories,” says Rich Rankin, Director of Livermore’s Innovation and Partnerships Office (IPO).

DOE, recognizing the need to bridge the gap between national laboratory research and industry investment, created the Technology Commercialization Fund (TCF). Unlike funding for basic science research, the TCF supports projects that demonstrate the potential of energy-related technologies to successfully reach the marketplace. DOE dedicates 0.9 percent of its applied energy research, development, demonstration, and commercial application budget each fiscal year to support the program, which is managed by its Office of Technology Transition.

In six funding rounds, from 2016 through 2021, the TCF program has awarded more than \$140 million to 399 projects across the national laboratory complex. The 29 projects awarded at Livermore include energy harvesting products, grid security



INDUSTRY GAP

systems, batteries, advanced manufacturing, and carbon capture technologies, among others. “The energy space may not seem like our primary focus, but applied-energy applications touch on many aspects of Livermore research such as materials and networked systems, in addition to fossil fuels and nuclear energy,” says Rankin.

Finding a Match

The TCF Program funds projects at two levels. Topic Area One projects, lasting 6 to 18 months, receive up to \$250,000 for technology maturation specifically designed to attract an industry partner. Topic Area Two projects receive up to \$1.5 million for a one- to three-year collaborative project with an industry partner. These longer-term, joint research and development efforts further boost a laboratory-developed technology’s chance to reach commercial users.

Each TCF award must be matched by non-federal funds. Livermore uses royalty revenues from successfully licensed

technologies to match Topic One awards. Livermore’s industry partners match Topic Two awards with cash or in-kind services and supplies. IPO’s Business Development Executives (BDEs) help connect researchers with industry partners and coach them in applying for the program. IPO also executes the Cooperative Research and Development Agreements (CRADAs) between Livermore and commercial partners, in the case of Topic Two projects.

Rankin stresses that the groundwork for a commercial partnership takes time to build. “Seeking a partner willing to commit \$1.5 million right before proposals are due is not a good idea,” says Rankin. “The first step is to develop a relationship with the IPO BDE working in the researcher’s area of expertise.”

BDEs build industry contacts for their technology portfolios by attending conferences and regional development forums, hosting company visits, and leveraging relationships with investors and research institutions such as the University of California and Stanford. “Commercialization is a contact sport,” says Rankin. “Interactions with industry are what lead to the next big thing.”

Building Long-Term Partnerships

In addition to paving the lab-to-market path for national laboratory technologies, the TCF Program forges partnerships between national laboratories and industry. “Many researchers are intrigued by the possibility of commercializing their research,” says Elsie Quaiter-Randall, IPO’s deputy director. “The TCF Program helps scientists learn about what industry is doing, commercially, in their area of research. This adds to scientists’ sense of satisfaction in their work.”

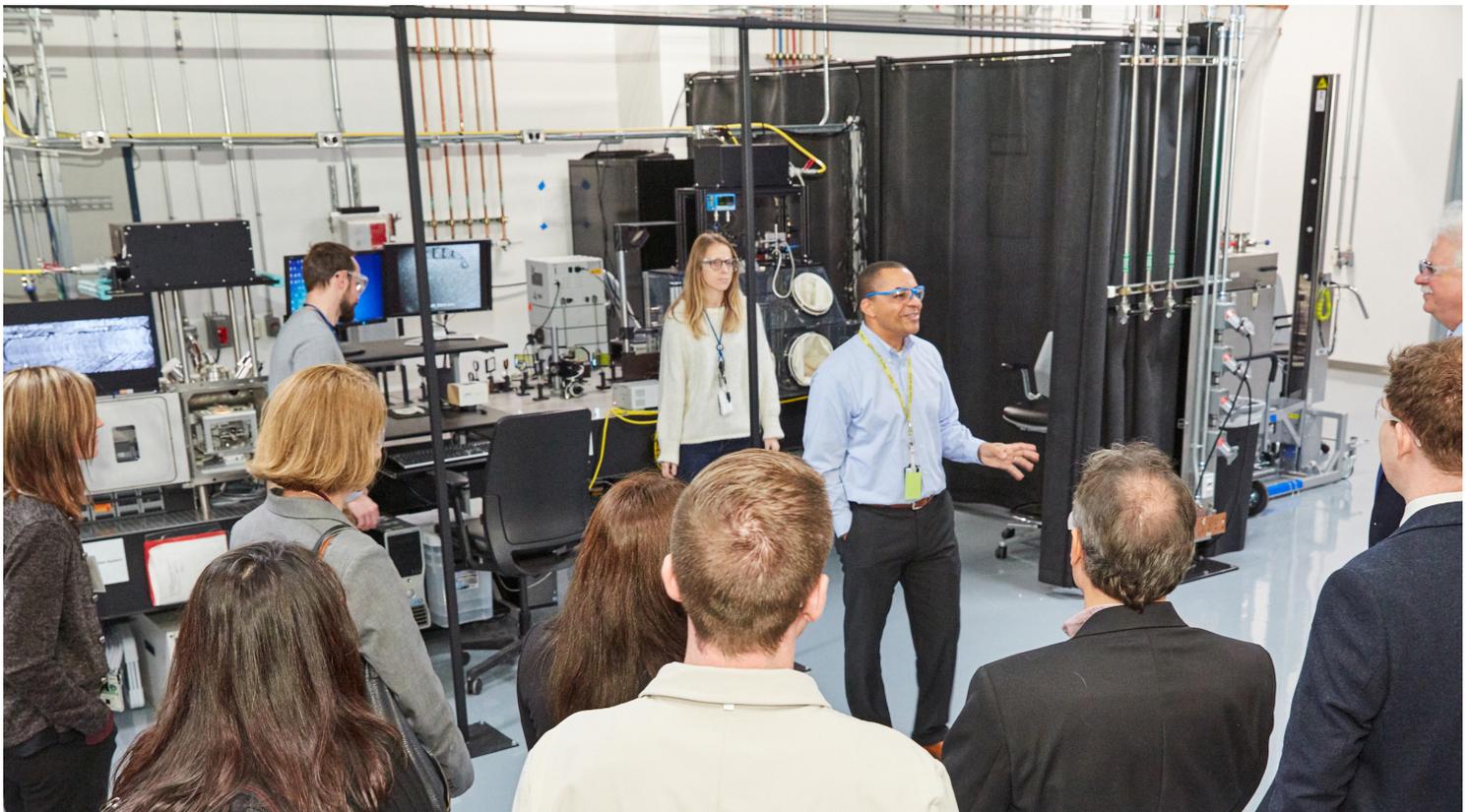
The Laboratory receives direct benefits from industry partnerships as well. For example, General Electric (GE) Global Research joined Livermore researchers on a TCF Topic Area Two project to advance high-quality, additively manufactured metal parts for commercial use. Livermore, National Nuclear

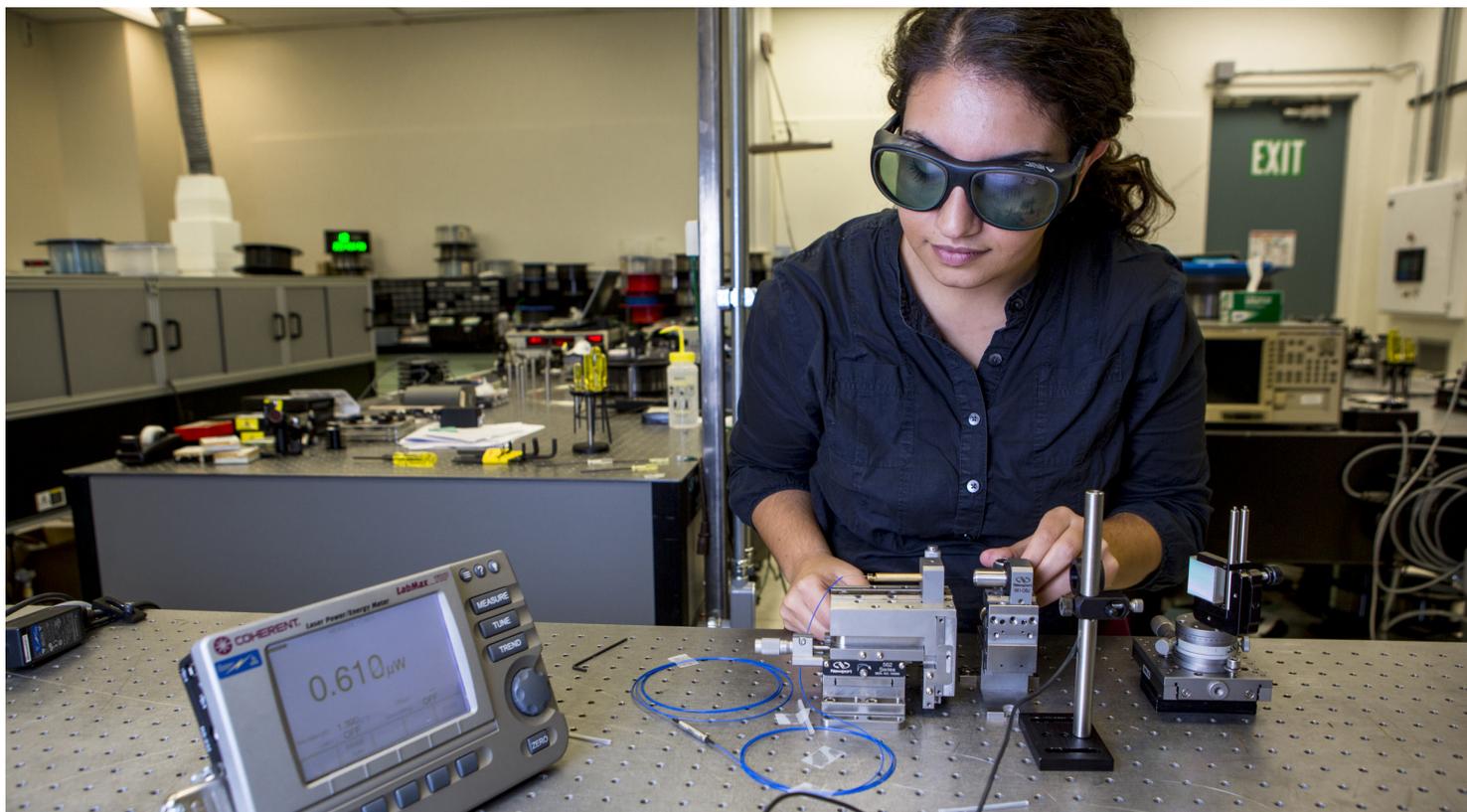
During a tour of Livermore’s Advanced Manufacturing Laboratory (AML), Materials Science Division leader Manyalibo “Ibo” Matthews (center) highlighted collaborative research conducted at the AML, such as a partnership with GE Global Research to explore new metal additive manufacturing processes. GE-supplied machines used in the project are now available for future research by Livermore and its partners.

Security Administration (NNSA), Kansas City, and GE established an additional partnership to demonstrate a Livermore-developed technology, supplying GE’s Concept Laser M2 machine to Livermore’s Advanced Manufacturing Laboratory. The machine supported the initial 3D metal printing project and is now available for future innovation by Livermore and industry partners. “The TCF Program catalyzed our ongoing relationship with GE and provided a tangible benefit for our laboratory and the NNSA,” says Quaiter-Randall. “GE and other partners value the Laboratory’s expertise as much as our researchers value industry perspectives.”

Forging the Lab-to-Market Path

Although smaller in scale, Topic Area One projects can help Laboratory-developed inventions make significant progress towards commercialization. Livermore researcher Leily Kiani, a physicist in the NIF and Photon Science Principal Directorate, has championed a neodymium-doped fiber amplifier that could double the capacity of information-carrying fiber-optic cables. This would improve internet bandwidth, an important proposition given the growing dependence on internet connectivity for work, school, and personal interactions. The amplifier research, initially funded by Livermore’s Laboratory Directed Research and Development program, identified the potential





for optical fibers to operate in a different transmission region, called the E-band, and double their information-carrying power.

To build on the technology's basic research, IPO awarded Kiani an Innovation Development Fund (IDF) grant. IPO's competitive IDF grant provides between \$35,000 and \$150,000 to develop technologies with commercial potential. With this boost, the fiber group reached the proof-of-concept stage, making their work more attractive for a TCF award. Kiani successfully applied for a Topic Area One TCF award and received \$150,000 for a one-year project to develop a prototype fully compatible with existing telecommunication architectures. "The TCF has been critical for us to demonstrate viability for a commercial product based on E-band amplifier technology," says Kiani. "Building a module with the features and performance that match conventional C-band amplifiers shows the technology can be taken out of the lab for real communications."

Entrepreneurial training from the National Lab Entrepreneurship Academy, managed by Livermore's IPO, has helped the researcher hone her pitch to potential investors. Telecom company input has informed Kiani's next stage of development—additional amplifying-fiber improvements to match commercial expectations. "IPO worked with our group to make invaluable connections to potential industrial partners, strengthen our proposals, and secure training in commercialization and entrepreneurship," says Kiani.

Leily Kiani's work focuses on increasing the capacity of fiber-optic cables with the help of the Department of Energy's Technology Commercialization Fund.

"That support will pay dividends when we present a clear picture of the commercialization path to new contacts."

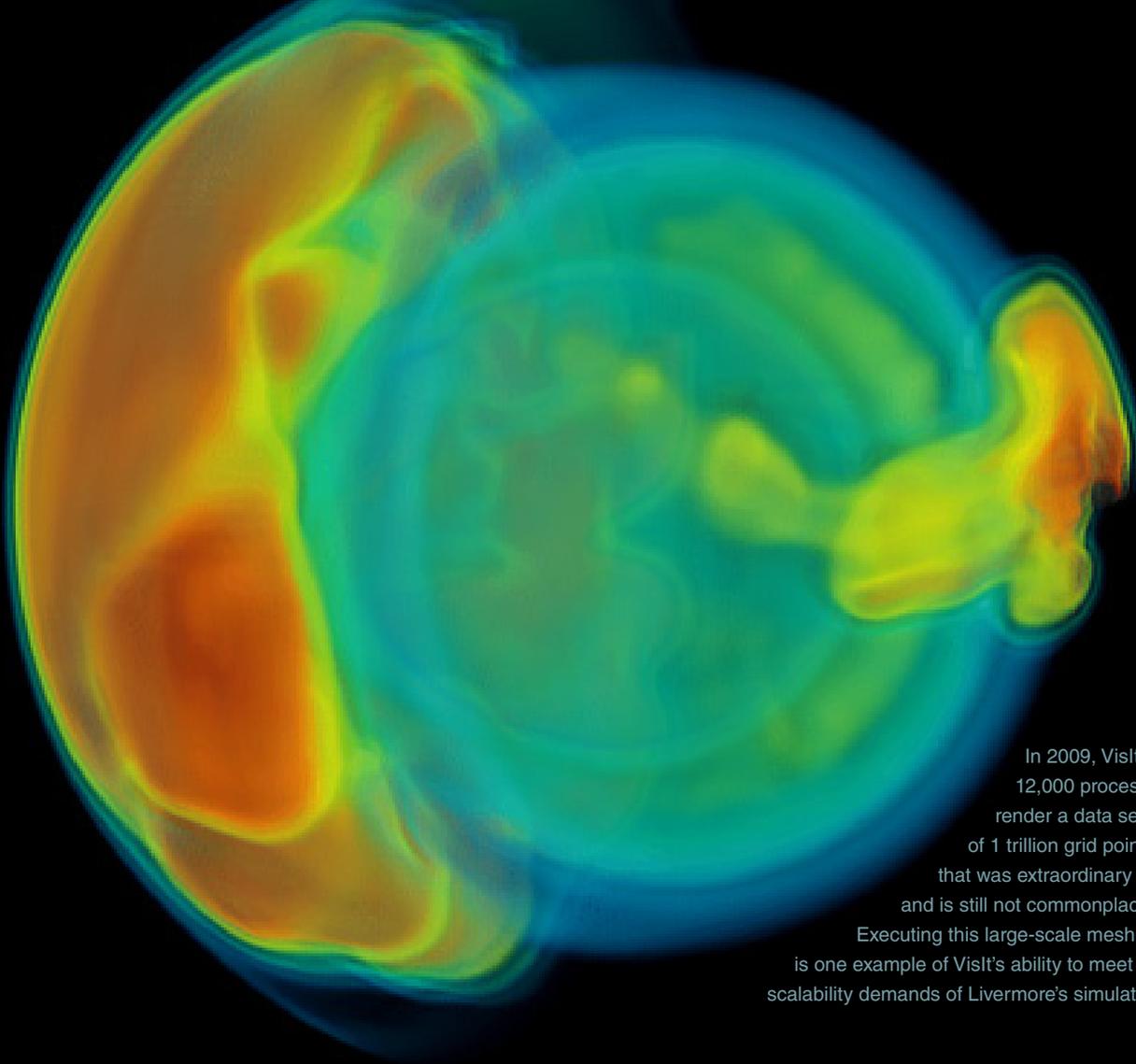
For the latest round of TCF awards announced in June 2021, five Livermore projects received a total of more than \$3 million in federal funding. "The program is about more than money," says Rankin. "The TCF advances DOE's goal to benefit society and the U.S. economy in a real way by improving our technologies' chances to reach the marketplace and by building long-term, mutually beneficial relationships with industry."

—Suzanne Storar

Key Words: commercialization, Cooperative Research and Development Agreement (CRADA), Energy I-Corps, entrepreneurship, industry partnership, Innovation and Partnerships Office (IPO), Innovation Development Fund (IDF) grant, Laboratory Directed Research and Development (LDRD), lab-to-market, National Lab Entrepreneurship Academy, prototype, Technology Commercialization Fund (TCF), technology maturation funding, technology transfer.

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VISUALIZATION SOFTWARE Stands the Test of Time



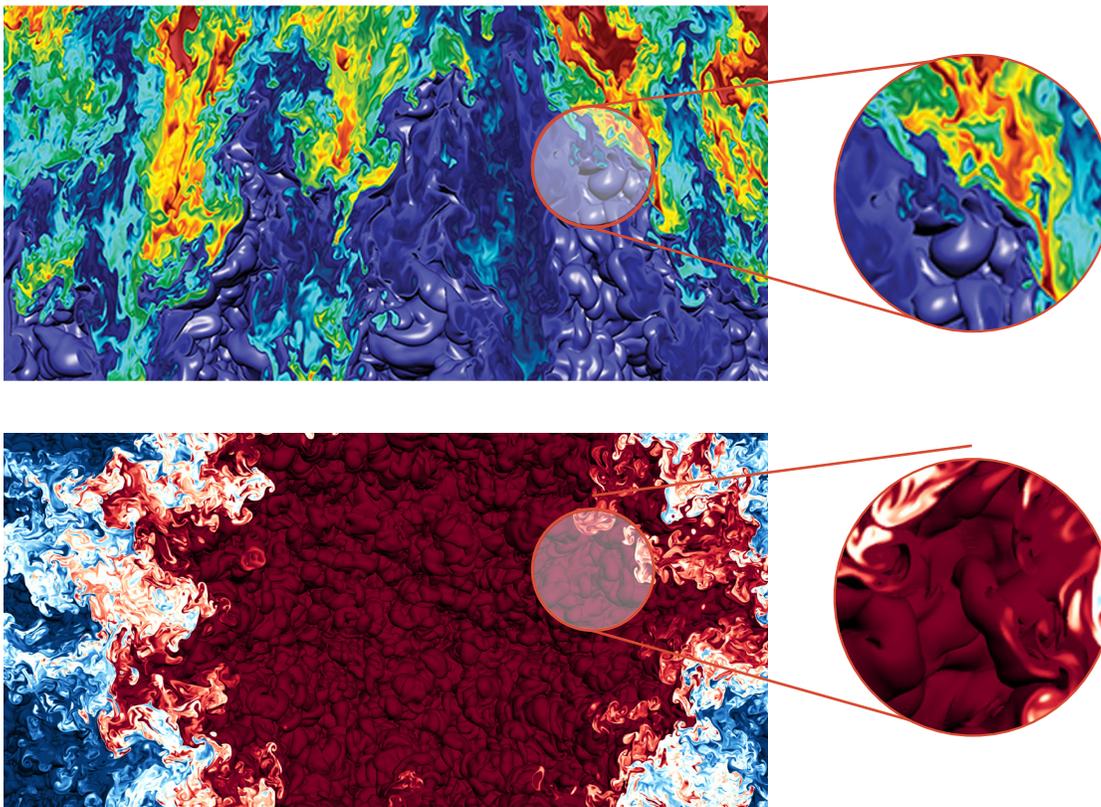
In 2009, VisIt ran on 12,000 processing cores to render a data set consisting of 1 trillion grid points—a feat that was extraordinary for its time and is still not commonplace today.

Executing this large-scale mesh visualization is one example of VisIt's ability to meet the scalability demands of Livermore's simulation codes.

In the decades since Lawrence Livermore's founding, the technology used in pursuit of the Laboratory's national security mission has changed over time. For example, studying scientific phenomena and predicting their behaviors require increasingly robust, high-resolution simulations. These crucial

tasks compound the demands on high-performance computing (HPC) hardware and software, which must continually be maintained, upgraded, or replaced.

Perhaps no other software project has adapted to such evolving needs as well as Livermore's VisIt, which has become



Rayleigh–Taylor instability occurs when fluids of different densities mix, such as in inertial confinement fusion. Livermore’s hydrodynamics codes depend on visualization software like Visit to reveal contours, flows, eddies, and other physical processes on large-scale meshes. These images were generated with Visit on Livermore’s Blue Gene/L (2006) and Sierra (2018) supercomputers and demonstrate Visit’s resolution improvements during the 12-year period. The 2018 Sierra calculation (bottom) was 60x the size of the 2006 calculation (top), revealing greater detail.

a trusted tool since its development began in 2000. VisIt—a portmanteau of *visualize* and *it*—is open-source software that enables researchers to rapidly visualize, animate, and analyze scientific simulations. It is the Laboratory’s go-to software for scalable visualization as well as graphical and numerical analysis of both simulated and experimental data sets.

Project leader Eric Brugger, who has worked on VisIt since its inception, states, “Our software is used broadly throughout the Department of Energy (DOE) complex, at universities, and at other supercomputing centers. It’s running on some of the world’s most powerful machines. VisIt strikes a balance between application support and capability development that appeals to the larger HPC community.”

A Dynamic History

Initially developed for the DOE’s Advanced Simulation and Computing program, VisIt is in many ways a microcosm of the Laboratory’s tradition of technological advancement through collaboration. It grew from a prototype in 2000 to its first major release in 2002. The project was soon released as open source and won an R&D 100 Award in 2005 (see *S&TR*, October 2005, pp. 10–11). Incremental feature releases followed regularly to enhance VisIt’s performance and capabilities.

The Livermore team originally shared project-hosting responsibilities with Oak Ridge National Laboratory (ORNL), the National Energy Research Scientific Computing Center (NERSC), and commercial company Intelligent Light. While Livermore handled VisIt’s developer documentation and website, nightly testing, and user hotline, ORNL managed issue tracking and the user email listserv, and Intelligent Light contributed the user documentation, forum, and an anonymous Subversion mirror. In addition to hosting VisIt’s nightly testing dashboard, NERSC hosted the source code, as it did for much of the DOE Office of Science’s open code development in the early 2000s.

As VisIt’s source code grew in size and functionality, the team moved it from a ClearQuest version-control platform behind Livermore’s firewalls to Subversion, hosted at NERSC. Today, most of the software’s services reside on the open-source platform GitHub—a move that enables more community development, interaction, and visibility than ever before. According to team member Mark Miller, the GitHub migration led to many workflow enhancements in continuous integration testing and issue tracking. “GitHub has improved the way we develop,” he says.

Brugger emphasizes that VisIt’s development has always been a team effort. He notes, “The Laboratory’s environment

makes stability and collaboration possible.” Alongside Brugger and Miller, the current team of computer scientists and software developers includes Kathleen Biagas, Cyrus Harrison, Matt Larsen, Alister Maguire, and Eddie Rusu. Livermore alumni include Hank Childs (original VisIt software architect and now a contributor affiliated with the University of Oregon), Sean Ahern (formerly of ORNL, now with ANSYS), Jeremy Meredith (formerly of ORNL, now with Google), and Brad Whitlock (currently at Intelligent Light). Other collaborators include Dave Pugmire (ORNL), Allen Sanderson (University of Utah), and Gunther Weber (Lawrence Berkeley National Laboratory).

The team’s expertise, passion for customer service, and commitment to excellence have ensured VisIt remains relevant to DOE goals, which in turn has earned sustained funding. Miller points out, “Visualization tools and the people who support them are at the nexus of vastly different data-handing requirements coming together in a common tool to help advance science. We have to be creative in our solutions. There’s never a dull moment.”

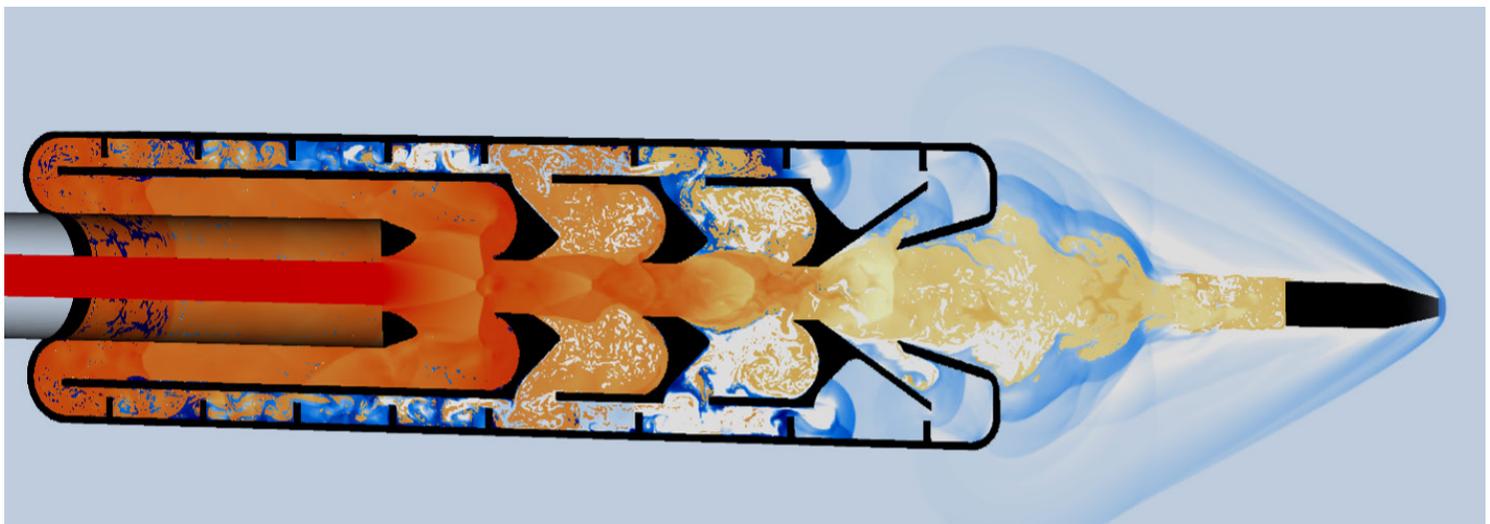
Foresight and Luck

From the outset, VisIt was designed to support future evolution. Harrison says, “No software solution is perfect, but a solid foundation was established early on.” Miller adds, “VisIt’s long-term success is due to a mix of foresight and luck regarding

how technology would change.” For example, the team has kept pace with the latest versions of programming models, as well as containerization technology that modularizes and automates the software’s continuous integration testing and deployment.

Extensibility and scalability are also key reasons for VisIt’s longevity. The tool’s capabilities can quickly and easily expand through the use of plug-ins, which allow new features to be added without rewriting the entire code base. The team has built more than 250 plug-ins to handle a wide range of data formats, operators, and plots. “Plug-ins have given VisIt flexibility and widespread applicability,” explains Miller, who notes that careful management of third-party dependencies has also been an important part of the decision process. For instance, Brugger states, “We leverage the open-source VTK (Visualization Toolkit) and OSPRay software libraries to maximize VisIt’s modeling and image-rendering features.”

Not every development choice is obvious or easy. In the early 2000s, developing simulations in the C++ programming language was challenging due to wide variation in language features supported in compiler programs, which caused issues with applications’ portability and performance. Miller recalls, “We heavily constrained how VisIt used C++ to minimize the chances that a compiler wouldn’t be able to compile VisIt. We built a fallback implementation if the compiler’s exception handling was problematic.” By the mid-2000s, C++ had matured



Livermore researchers use VisIt with a multiphysics code to simulate propellant flow in a firearm suppression device. In 2019, the Lassen supercomputer produced this image during a run of 1.1 billion grid points. After refining the suppressor’s design through iterative simulations, the Laboratory created a prototype that performed as required. For U.S. soldiers using automatic weapons in training and combat situations, the suppressor design minimizes blowback and reduces the hearing loss associated with operation near the ear.

“The Laboratory’s environment makes stability and collaboration possible.”

– Eric Brugger, VisIt project leader



and become more prevalent, so VisIt’s compatibility with it evolved accordingly. In general, Miller summarizes, “We have been conservative about introducing new dependencies and features, making room for them without requiring them. VisIt must work on Linux, macOS, Windows, and DOE HPC platforms, so we carefully manage any choices that can impact any of those environments.”

Ultimately, Brugger says, “We’ve made some good technology decisions that have paid off.” VisIt’s development scope broadened as the software gained traction among other researchers, both at the Laboratory and externally. Harrison, who joined the team in 2007, adds, “Seeing VisIt used in new ways helps us determine where to go next. We learn a lot from users.” The team’s experience and customer dedication have helped guide development of another Livermore software project called Ascent, which processes visualizations while a simulation code is running, also known as *in situ*.

The Proof Is in the Picture

VisIt’s feature development is driven by the DOE’s mission, for which scalable, high-resolution computer simulations on HPC systems are of paramount importance. For instance, VisIt has long enabled hydrodynamics code teams to explore computationally intensive phenomena. One such phenomenon is the Rayleigh–Taylor instability that occurs when fluids mix—a key process in inertial confinement fusion. To visualize it, VisIt’s development focuses on parallelization for large data sets, implementation of custom data analysis routines, handling of non-standard data models, and a flexible, easy-to-use interface.

Among its many features, VisIt enables users to analyze structured and unstructured meshes, animate two- and three-dimensional data, and manipulate a range of geometric objects. The tool’s visualization algorithms easily process large data sets serially or in parallel, and users can query different points and variables within the results. VisIt’s latest major release included compatibility with new file formats, upgrades to the user

interface and documentation, and support for graphics processing units, which accelerate a machine’s computational performance.

Users can run VisIt on personal laptops, supercomputers, and everything in-between—including the more than two dozen HPC systems the Laboratory has brought online since 2000. The software is running on Livermore’s Sierra and ORNL’s Summit supercomputers. “Prioritizing portability to as many platforms as possible has come with certain tradeoffs,” states Brugger. “But it was the right decision given the increasing number of groups we work with and their diverse applications.”

As HPC processing power turns the corner toward a new era, VisIt is a key post-processing tool in the DOE’s Exascale Computing Project and Livermore’s RADIUSS project (Rapid Application Development via an Institutional Universal Software Stack) (see *S&TR*, February 2021, pp. 4–11). “We are excited to participate in these project portfolios,” says Harrison. When the Laboratory’s first exascale supercomputer, El Capitan, comes online in 2023, he adds, “VisIt will be ready.”

With 20 years of service behind it, VisIt continues to offer meaningful capabilities to the scientific community and remains Livermore’s flagship visualization software. Back in 2000, Brugger did not imagine he would still be developing VisIt today. He says, “The work continues to be challenging and interesting. Technology always changes, so there’s no time to get bored.”

—Holly Auten

Key Words: C++, data analysis, Department of Energy (DOE), high-performance computing (HPC), inertial confinement fusion, Intelligent Light, National Energy Research Scientific Computing Center (NERSC), Oak Ridge National Laboratory (ORNL), open-source software, programming, Rayleigh–Taylor instability, scientific code, simulation, VisIt, visualization.

For further information contact Eric Brugger at (925) 423-1293 (brugger1@llnl.gov).

In this section, we list recent patents issued to and awards received by Laboratory employees. Our goal is to showcase the distinguished scientific and technical achievements of our employees as well as to indicate the scale and scope of the work done at the Laboratory. For the full text of a patent, enter the seven- or eight-digit number in the search box at the U.S. Patent and Trademark Office's website (www.uspto.gov).

Patents

Modular Gradient-Free Shaped Charge

Dennis Willard Baum
U.S. Patent 10,731,955 B2
August 4, 2020

Transparency and Color Tunable Electro-Optical Device Using Colloidal Core/Shell Nanoparticles

Jinkyu Han, Megan Carey Freyman, Thomas Han
U.S. Patent 10,732,480 B2
August 4, 2020

Click-Chemistry Compatible Structures, Click-Chemistry Functionalized Structures, and Materials and Methods for Making the Same

Patrick Campbell, Eric Duoss, James Oakdale
U.S. Patent 10,732,502 B2
August 4, 2020

Texture-Inducible Substrate

Andrew Pascall
U.S. Patent 10,733,906 B2
August 4, 2020

System and Method for Forming Material Substrate Printer

James A. Demuth, Andrew Bayramian, Bassem S. El-Dasher, Kevin J. Kramer
U.S. Patent 10,737,324 B2
August 11, 2020

3-Dimensional X-Ray Imager

Bernard J. Koziowski, Nobuhiko Izumi, Julia K. Vogel, Louisa A. P. Pickworth
U.S. Patent 10,741,297 B2
August 11, 2020

Cooler for Optics Transmitting High Intensity Heat

James A. DeMuth, Eric B. Duoss, Joshua D. Kuntz, Paul A. Rosso, Christopher M. Spadaccini
U.S. Patent 10,747,033 B2
August 18, 2020

Shape Memory Polymer Nanocomposites and Uses Thereof

Sayyeda Marziya Hasan, Jennifer Nicole Rodriguez, Pooja Singhal, Thomas Stephen Wilson, Duncan J. Maitland
U.S. Patent 10,751,063 B2
August 25, 2020

System and Method for Plasmonic Control of Short Pulses in Optical Fibers

Eyal Feigenbaum, Graham S. Allen, Jay W. Dawson, Mikhail A. Noginov
U.S. Patent 10,756,503 B2
August 25, 2020

System and Method for Forming Activated Carbon Aerogels and Performing 3D Printing

Swetha Chandrasekaran, Theodore F. Baumann, Marcus A. Worsley
U.S. Patent 10,767,062 B2
September 8, 2020

Awards

A team of current and former Lawrence Livermore and IBM scientists won the annual **Test of Time award** at the 2020 **Supercomputing Conference** on November 19 for a 2002 paper outlining the Laboratory's Blue Gene/L supercomputer. The paper was the first peer-reviewed overview article to disclose details of Blue Gene/L, including its nodes, system packaging, and software support. Among the paper's co-authors were Livermore physicist **Pavlos Vranas** and former Laboratory employees **Lynn Kissel, Mark Seager, R. Kim Yates, and Jeffrey Vetter**.

The Test of Time award recognizes a paper from a past Supercomputing Conference that has deeply influenced the high-performance computing (HPC) discipline, made a historical impact, and changed HPC trends. It has been awarded annually since 2013.

In January 2021, the the Institute of Electrical and Electronics Engineers (**IEEE**), the world's largest technical professional organization, announced the elevation of **Bronis de Supinski** to the rank of **fellow**, recognizing Livermore Computing's chief technology officer for his leadership in the design and use of large-scale computing systems.

The prestigious IEEE fellow distinction is the highest grade of membership in IEEE. Fewer than 0.1 percent of voting members are selected annually by the organization's fellow committee for the honor.

As chief technology officer, de Supinski formulates the Laboratory's large-scale computing strategy and oversees its implementation, frequently interacting with HPC leaders and collaborating with industry and academia. In 2005 and 2006, de Supinski won the prestigious Gordon Bell Prize as well as two R&D 100 awards, including one for leading the development of a novel scalable debugging tool.

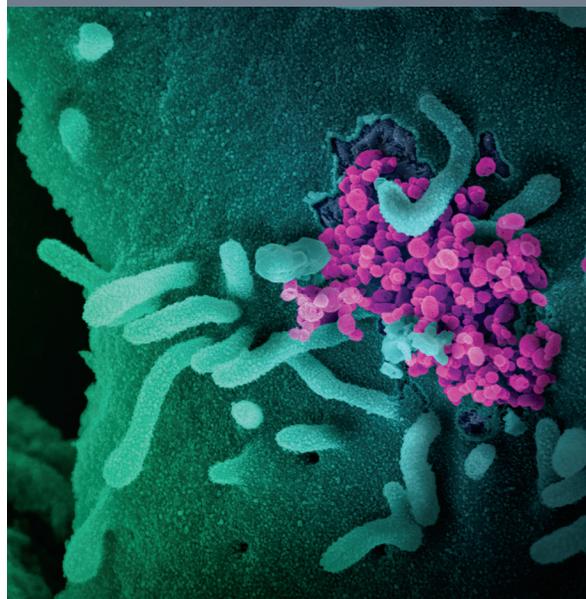
Abstract

Broadening the Landscape of Cancer Research

Lawrence Livermore has been on the forefront of cancer research for over 60 years. Early interest in cancer statistics stemmed from the nature of work, particularly how radiation affects humans. The Department of Energy funded research to investigate the effects of radiation on workers with long-term exposure. This research quickly morphed into a wider breadth of cancer research topics, including the use of advanced computational models to investigate mutations in genes. Livermore is regarded as a leader in cancer research, from the Human Genome Center to its participation in the National Cancer Institute's "Moonshot" project. The highly interdisciplinary Laboratory unites research in one more example: bringing together cancer biology, 3D printing, high-performance computing, big data, and materials science to address this pressing medical challenge.

Contact: Kris Kulp (925) 422-6351 (kulp2@llnl.gov).

Tackling the COVID-19 Pandemic



Livermore interdisciplinary teams and partners quickly addressed urgent national challenges during the COVID-19 pandemic.

Also in this upcoming issue...

- *Genomic analysis and machine learning predict wound-healing outcomes and lay the groundwork to potentially save lives.*
- *An advanced manufacturing innovation opens the door to faster 3D printing in a greater range of materials to meet consumer needs.*
- *Livermore statisticians and materials scientists refine a method for assessing sources of uncertainty in material strength experiments.*

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