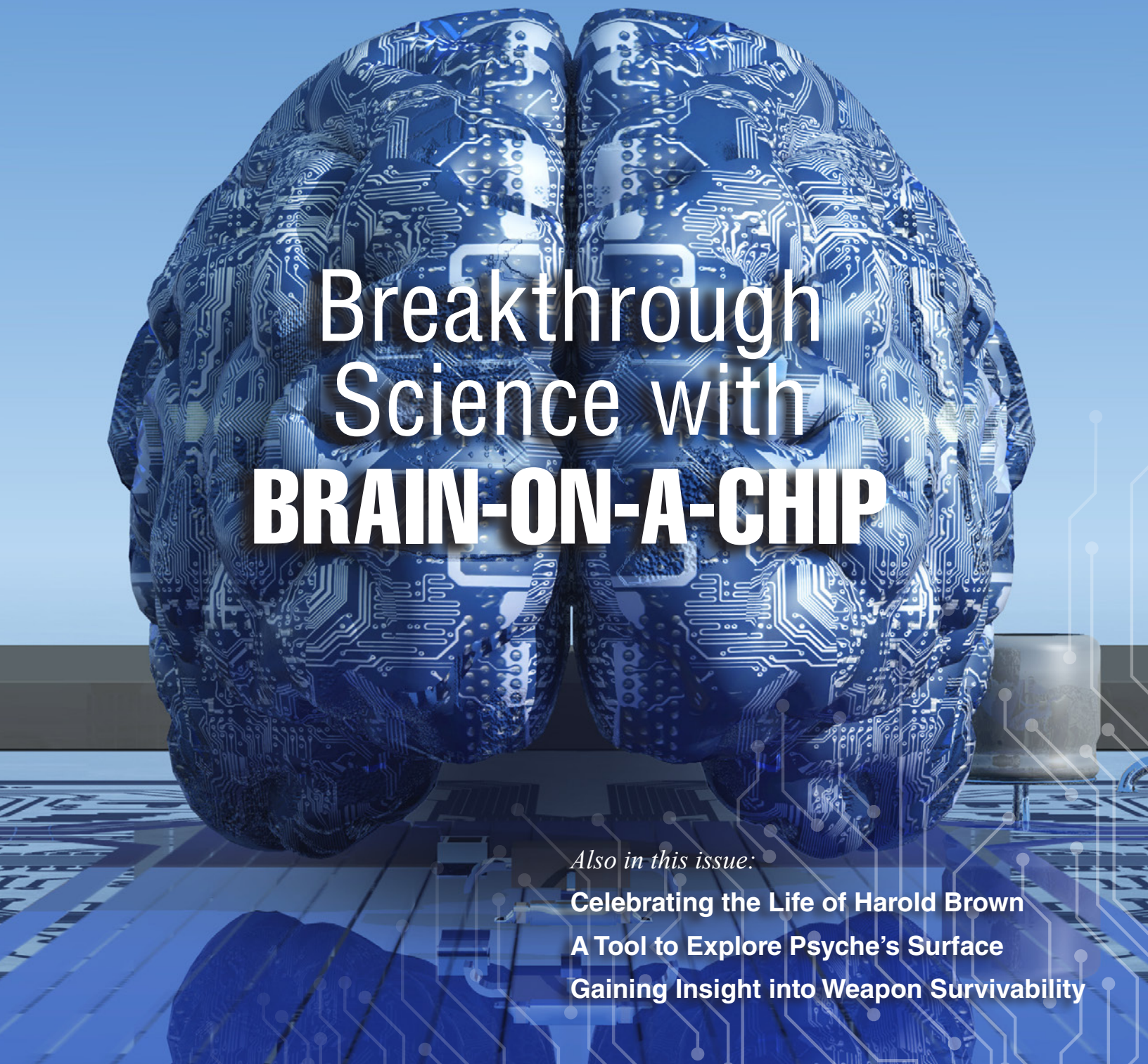
Lawrence Livermore National Laboratory

Science & Technology Review

May 2019



Breakthrough Science with BRAIN-ON-A-CHIP

Also in this issue:

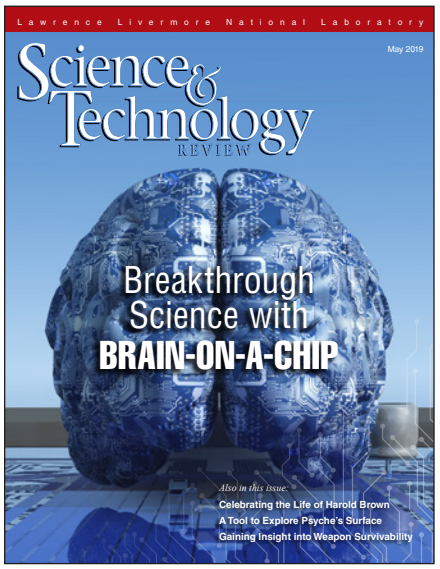
Celebrating the Life of Harold Brown

A Tool to Explore Psyche's Surface

Gaining Insight into Weapon Survivability

About the Cover

As the article beginning on p. 4 describes, the Laboratory's innovative brain-on-a-chip technology is the latest iteration of its iCHIP (in vitro chip-based human investigational platform) project. The brain-on-a-chip, which mirrors the structure and functions of human brain tissues, has broad applications. For example, it could be used to determine how soldiers are affected by exposure to chemical and biological weapons and the effectiveness of potential countermeasures and prophylactic pretreatments. The technology could also help predict the effects of promising new drugs designed to treat neurological disorders.



Cover design: Mary J. Gines

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.

The Laboratory is managed by Lawrence Livermore National Security, LLC (LLNS), for the National Nuclear Security Administration (NNSA), a semi-autonomous agency within the U.S. Department of Energy (DOE). LLNS is a limited liability company managed by Bechtel National, Inc.; the University of California; BWXT Government Group, Inc.; and AECOM Energy & Construction, Inc. Battelle Memorial Institute also participates in LLNS as a teaming subcontractor. Cutting-edge science is enhanced through the expertise of the University of California and its 10 campuses and LLNS' affiliation with the Texas A&M University system. More information about LLNS is available online at www.llnsllc.com.

Please address any correspondence (including name and address changes) to S&TR, Mail Stop L-664, Lawrence Livermore National Laboratory, P.O. Box 808, Livermore, California 94551, or telephone (925) 423-3893. Our e-mail address is str-mail@llnl.gov. *S&TR* is available on the Web at str.llnl.gov.

Prepared by LLNL under contract
DE-AC52-07NA27344

Science & Technology REVIEW

May 2019

Lawrence Livermore National Laboratory

Contents

S&TR Staff

Scientific Editor
Dawn A. Shaughnessy

Managing Editor
Ken Chinn

Publication Editor
Caryn Meissner

Writers
Lauren Casonhua, Arnie Heller, Dan Linehan, and Jeremy Thomas

Art Director
Mary J. Gines

Proofreader
Deanna Willis

***S&TR* Online**
Lauren Casonhua, Rose Hansen, and Pam Davis Williams

Print Coordinator
Diana Horne

S&TR, a Director's Office publication, is produced by the Technical Information Department under the direction of the Office of Planning and Special Studies.

S&TR is available on the Web at str.llnl.gov

Printed in the United States of America

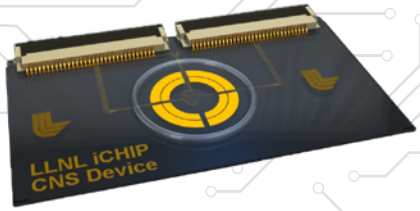
Available from
National Technical Information Service
U.S. Department of Commerce
5285 Port Royal Road
Springfield, Virginia 22161

UCRL-TR-52000-19-5
Distribution Category UC-99
May 2019

Feature

3 **At the Intersection of Engineering, Neurobiology, and Computation**
Commentary by Anantha Krishnan

4 **Small Brain-on-a-Chip Promises Big Payoffs**
Livermore's brain-on-a-chip may offer a faster, less expensive, and more effective way to evaluate the organ's response to human-made and natural threats.

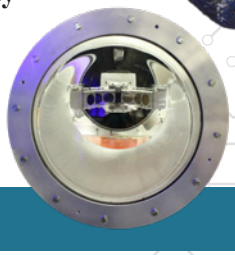


Research Highlights

12 **A Brilliant Mind Leaves an Indelible Legacy**
Lawrence Livermore celebrates the life and contributions of its third director, Harold Brown, whose career was truly one of service to the nation.

17 **"Mini" Device Set to Analyze Mysterious Psyche**
A space-bound gamma-ray spectrometer will explore the 16-Psyche asteroid, providing insights into the formation of Earth and other terrestrial planets.

20 **Energetic Laser Helps Test Weapon Survivability**
At the National Ignition Facility, researchers evaluate the ability of nonnuclear weapons' components to withstand extreme x-ray and neutron environments.



Departments

2 The Laboratory in the News

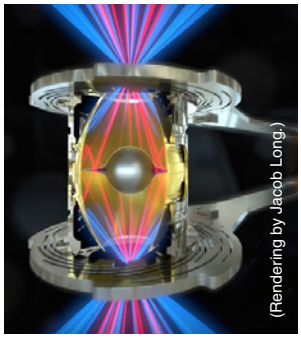
24 Patents and Awards

25 Abstract

Higher Energy Efficiency with Rugby Hohlraum

Using a hohlraum shaped like a rugby ball—rather than a typical straight cylinder—scientists conducting inertial confinement fusion (ICF) experiments at the National Ignition Facility (NIF) have significantly boosted the amount of laser-induced energy absorbed by the ICF fuel capsule. The research, which appears in the October 29, 2018, edition of *Nature Physics,* detailed how scientists from Lawrence Livermore and Los Alamos national laboratories increased the level of laser-induced energy absorption to about 30 percent, nearly double what was achieved with cylindrical hohlraums.

The research team used a single-shell, aluminum target capsule inside a gold rugby hohlraum, which is wider in the center and tapered toward the ends. (See image below.) The experiment was driven by 1-megajoule laser shots, which coupled about 300 kilojoules with the capsule. The hohlraum shape allowed for a capsule with a radius about 50 percent larger than usual, exposing more surface area to capture energy. In addition, the hohlraum's curved inner walls better directed x-ray energy to the capsule.


(Rendering by Jacob Long.)

Spherical capsules remain symmetrical during implosion, but perturbations and other imperfections degrade the fusion process and inhibit ignition—when more energy is produced than the amount of energy deposited by the lasers in the hohlraum. "If we have more energy available, then we can tolerate these defects better, and we will have more margin of error to achieve ignition," says Livermore physicist and lead author of the paper Yuan Ping. The team plans to gradually step up the total amount of laser energy while finding the right mix of energy, laser pulse shape, capsule size, hohlraum shape, and implosion symmetry to optimize energy delivery to the fusion fuel—providing a new path to ignition.

Contact: Yuan Ping (925) 422-7052 (ping2@llnl.gov).

Carbon Nanotubes Mimic Biology

Cellular membranes serve as an ideal example of a multifunctional, tunable, precise, and efficient biological system. However, until recently, these membranes have been difficult to reproduce in a laboratory setting. In research that appears on the cover of the December 17, 2018, online edition of the journal *Advanced Materials*, Lawrence Livermore scientists have now created polymer-based membranes with 1.5-nanometer carbon nanotube pores that mimic the architecture of cellular membranes.

The inner channel of a carbon nanotube is narrow, hydrophobic, and extremely smooth—all properties that mirror those of biological pores. Carbon nanotube porins (CNTPs) are short segments of carbon nanotubes (5 to 15 nanometers) that can transport protons, water, and macromolecules, including DNA. "CNTPs are unique among biomimetic nanopores because carbon nanotubes are robust and highly chemically resistant, which make them amenable for use in a wider range of separation processes, including those requiring harsh environments," says Aleksandr Noy, a Livermore materials scientist and senior author on the paper.

The team integrated CNTP channels into polymer membranes, mimicking the structure, architecture, and basic functionality of biological membranes in an all-synthetic architecture. Proton and water transport measurements showed that the CNTPs maintain their high permeability in the polymer membrane environment. Jeremy Sanborn, a Lawrence Scholar and co-author on the paper, says, "This development opens new opportunities for delivery of molecular reagents to vesicular compartments to initiate confined chemical reactions and mimic the sophisticated transport-mediated behaviors of biological systems."

Contact: Aleksandr Noy (925) 423-3396 (noy1@llnl.gov).

Natural Variability Plays Role in Snowpack Stability

Spring snowpack in the mountains of the western United States has not declined substantially since the 1980s, despite an increase in temperature of 1°C during the same period. In research that appears in the December 17, 2018, edition of the journal *Geophysical Research Letters*, scientists at Lawrence Livermore, Oregon State University, and the University of Washington describe how the snowpack's apparent insensitivity to warming results from changes in atmospheric circulation caused by natural swings in the sea surface temperature over the Pacific Ocean.

For the study, the team looked at trends in sea surface temperature over a 35-year period and used a computational method called "dynamical adjustment" to quantify the influences of both natural variability and human-induced warming on snowpack changes. "Our results indicate that the contribution of global warming to western U.S. snowpack loss has in reality been large and widespread since the 1980s, but mostly offset by natural variability in the climate system," says Livermore scientist Stephen Po-Chedley, who co-authored the paper.

The results point to a faster rate of snowpack loss in coming decades as the phase of natural variability becomes less favorable for snowpack accumulation. Since 1950, the snowpack on April 1 (the typical peak in annual snowpack) has decreased by 15 percent over much of the western United States, as warmer temperatures have caused a shift from snow to rain, particularly at low elevations. Climate models indicate a further decrease in winter snowpack of approximately 60 percent by 2050, leading to a dramatic reduction in summer stream flows.

Contact: Stephen Po-Chedley (925) 422-3421 (pochedley1@llnl.gov).

Commentary by Anantha Krishnan

At the Intersection of Engineering, Neurobiology, and Computation

LAWRENCE Livermore has been at the forefront of many recent advances in innovative measurement methodologies and engineering platforms as well as computational models to elucidate critical aspects of neurobiology. As part of the Laboratory's mission of enhancing national security, one focus has been protecting warfighters who may be exposed to a multitude of advanced and even outlawed weapons, such as chemical and biological agents. As the article beginning on p. 4 describes, the Laboratory has developed a new "brain-on-a-chip" platform—a remarkable device the size of a microscope slide—that mirrors the structure and functions of human brain tissues. The motivation for this innovative technology is to improve our scientific understanding of the human neural system and how it responds to exposure to toxic compounds.

Obviously, the effects of chemical weapons, even at low doses, cannot be tested on human subjects. Moreover, testing on animals has proven to be unreliable in reproducing the human physiological response, as can be seen in pharmaceutical development. Producing a reliable model that accurately recapitulates the function of the human brain is a formidable challenge. Livermore's brain-on-a-chip is a promising solution, offering an advanced tissue model that incorporates the three-dimensional architecture of the neural system, the in vivo heterogeneity of cell and tissue types, and sensing modalities to observe neuronal function with high spatial and temporal resolution.

To realize the brain-on-a-chip, Livermore researchers devised a unique approach wherein they can precisely deposit different types of neuronal cells onto submillimeter regions of a multielectrode array embedded in a biocompatible chip a few centimeters long. Over time, the cells establish intricate networks and begin to communicate with one another. The embedded microelectrode arrays, which were fabricated at the Laboratory's Center for Micro and Nanotechnology, allow researchers to record these cellular communications. The brain-on-a-chip device can also be connected to a Livermore-developed blood–brain barrier designed to mimic the one found in the human brain, further improving the technology's efficacy.

Livermore's strong expertise in data analytics and statistical modeling is helping to process the vast information sent back and forth from neuron to neuron. By accurately recording these signals, the brain-on-a-chip is enhancing scientists' knowledge of how neurons process information and respond to compounds and environmental factors. Importantly, the measurements and data obtained from the device are being validated, including by exposure to select toxic chemicals in tests conducted at Livermore's Forensic Science Center.

Both the brain-on-a-chip and the associated blood–brain barrier are elements of Livermore's iCHIP (in vitro chip-based human investigational platform) project that aims to better understand and eventually predict the effects of pharmaceutical drugs as well as potentially harmful substances on human cells, tissues, and organs without the need for animal or human test subjects. Other subsystems of the iCHIP have included a platform with cultured heart cells and one with neurons comprising the peripheral nervous system.

For the warfighter, the brain-on-a-chip will potentially accelerate the development of effective countermeasures for exposure to chemical and biological agents. Down the road, the device may also provide a way to significantly speed up development of new pharmaceuticals—a process that now takes many years and several billions of dollars to accomplish. Indeed, Lawrence Livermore's unique multidisciplinary research focus, especially at the intersection of engineering, neurobiology, and computation, will continue to make important advances in enhancing the protection of the nation's warfighters—and its everyday citizens.

■ Anantha Krishnan is associate director for Engineering.

Small Brain-on-a-Chip Promises Big Payoffs

Livermore's new investigational platform could provide an innovative means for better understanding brain pathology and for developing countermeasures to chemical and biological warfare agents.

IN a telling example of Lawrence Livermore's pioneering marriage of biology and engineering, Laboratory researchers have developed a "brain-on-a-chip"—the newest embodiment of an integrated system designed to accurately evaluate the effects of potentially harmful chemicals, viruses, and drugs on humans without relying on animal or human test subjects. In conjunction with an artificial blood–brain barrier (BBB), the device simulates the central nervous system (CNS) by recording activity from multiple brain cell types deposited and grown onto a small platform embedded with microelectrode arrays.

The brain-on-a-chip holds significant promise for national security and broader applications. For example, the device could be used for determining how soldiers are affected by exposure to chemical and biological weapons and the effectiveness of potential countermeasures and prophylactic pretreatments. The technology may also offer a breakthrough means to more quickly predict the effects on the brain from candidate drugs developed to treat neurological disorders. Finally, it could help scientists understand how brain cells function, connect, and interact to combat neurological impairments and illnesses such as Parkinson's disease and epilepsy.

The device is part of the Laboratory's iCHIP (in vitro chip-based human investigational platform) project—a broad initiative at Livermore to advance human health with a focus on understanding, diagnosing, and potentially treating human neural problems and diseases. (See *S&TR*, March 2014, pp. 16–19.) The research effort applies Livermore core capabilities in bioscience, bioengineering, materials science, and high-performance computing as well as expertise in forensic science and microfabrication. Developed through an accomplished multidisciplinary team, which this year included 11 scientists and engineers, 5 postdoctoral researchers, and

5 summer students, iCHIP technologies are becoming a faster, less expensive, and more effective method for evaluating the body's response to human-made and various natural threats.

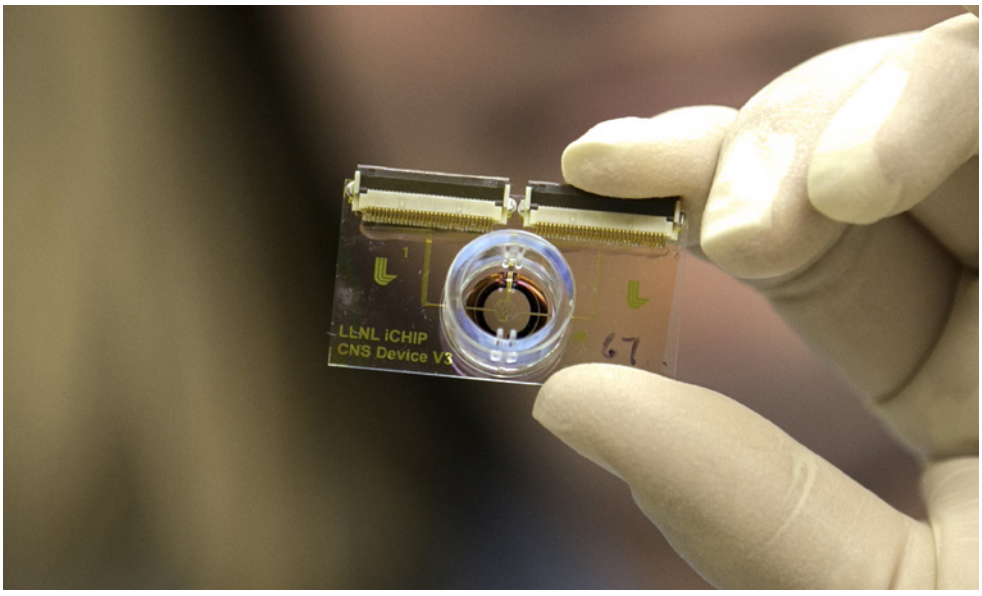
Initiatives Prove Fruitful

The Laboratory's Center for Micro and Nanotechnology is a dedicated fabrication and prototyping facility with extensive experience manufacturing biocompatible microelectrode arrays for recording (and optionally, generating) neural signals. Fabricated at the center's Biomedical Foundry, the arrays gained national attention as part of the first commercialized artificial retina, for which the Laboratory played an important development role. (See *S&TR*, October/November 2009, pp. 14–15.)

Since that time, the Laboratory Directed Research and Development (LDRD) Program has supported iCHIP projects by funding two Strategic Initiatives (SIs). This type of research investment aims to answer key science, technology, and engineering challenges. The first SI, which ended in 2015, allowed the research team to integrate the biocompatible microelectrode array technology into four separate organ-on-a-chip devices: CNS, BBB, peripheral nervous system (PNS), and heart (see the box on p. 10). The second SI, which will end in late 2019, focuses on further developing CNS and associated BBB platforms. According to biologist Kris Kulp, deputy division leader for Livermore's Biosciences and Biotechnology Division, "The first SI confirmed we could build biocompatible engineered systems that support a healthy culture of different cell types." With the platform built and validated, the aim in the second SI, says Kulp, is to discover "what kind of pressing biological questions can be answered with our engineered platform, especially with regard to examining the brain's response to chemical warfare agents."

Engineer Elizabeth Wheeler, a principal investigator (PI) for the first SI and a co-PI for the second one, notes that U.S. warfighters as well as civilian populations face a threat from exposure to chemical warfare agents. Although banned by international treaty, chemical weapons have been used sporadically in Mideast conflicts. Following exposure, these compounds quickly affect CNS, PNS, and other organs and can cause seizures, paralysis, and death. To streamline countermeasure development, researchers need an experimental model that produces more human-relevant data and measurements than do current assays.

According to biologist and co-PI Nick Fischer, a reliable experimental model must mirror human brain function. This type of model can be accomplished by carefully integrating key physiological parameters, such as a three-dimensional (3D) architecture, implementing human neurons, and incorporating neuronal "support" cells. The current brain-on-a-chip platform fulfills all of these requirements and is further complemented by a BBB component. In this way, the device offers the promise of more rapidly developing new antidotes to chemical (and biological) warfare agents without depending on unreliable animal testing. Indeed, more than 90 percent of candidate pharmaceuticals that pass animal studies fail in human trials. In addition, although simple human cell cultures provide basic insight, they are often too far removed from the complexities of the entire nervous system to accurately mirror the responses of the brain.



Livermore's iCHIP (in vitro chip-based human investigational platform) is a miniature external replication of a human organ, integrating biology and engineering with a combination of microfluidics and multielectrode arrays. The iCHIP team has developed platforms for four separate organs: central nervous system (CNS, shown here), blood–brain barrier, peripheral nervous system, and heart. (Photo by Julie Russell.)

Mimicking the Brain

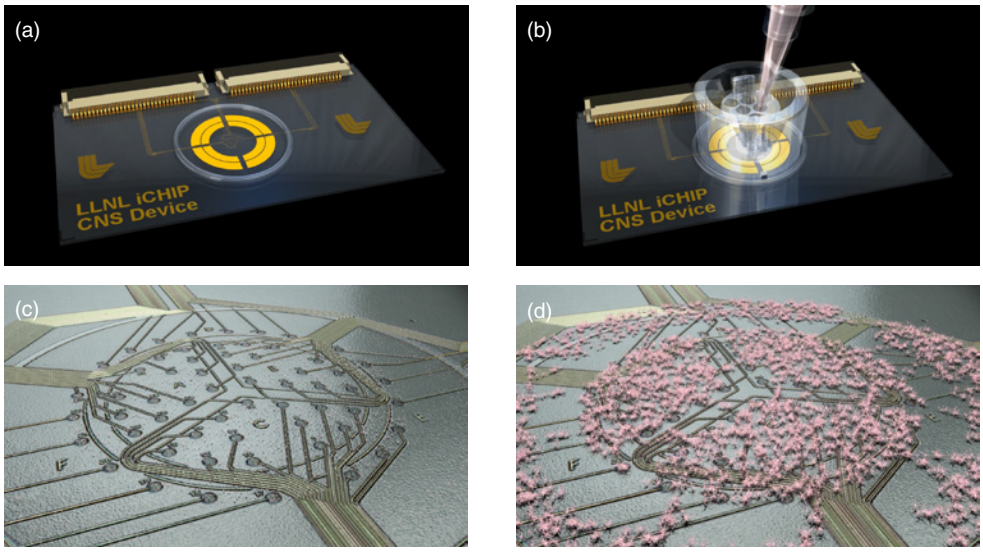
A key to the brain-on-a-chip is Livermore's ability to tailor the design and fabrication of the microelectrode arrays, which capture the patterns of neural cells' action potentials—the "bursts" or spikes of electrical energy that cells emit when communicating with each other. "The microelectrodes serve as 'microphones' that listen to the neurons," says biologist Heather Enright. The electrical signals are recorded from cells that are positioned on or near an electrode. The arrays

record changes in the neural cells' electrophysiology (electrical activity) and viability in response to chemical exposures.

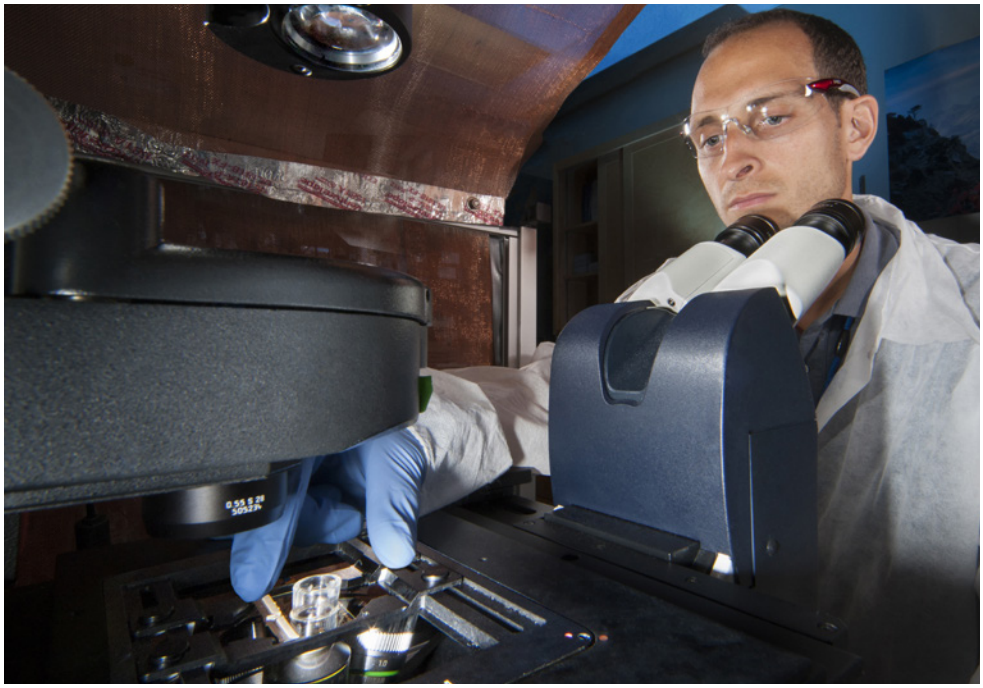
Cells are grown inside experimental wells that sit on top of the microelectrode arrays embedded in the platform. The platforms are designed to promote cell health and longevity, and their surfaces support cell growth and adherence. The cells' viability can be confirmed both optically by brightfield and fluorescent microscopy and electrophysiologically by the embedded microelectrodes. After 10 to 14 days, the microelectrodes start to pick up electrical signals, and by 21 days the cells form a functioning communication network.

As part of the first SI, the team built a CNS-based platform that simultaneously cultured rat brain cells from the cortex (the brain's outer layer of neurons) and hippocampus seeded in different sections at the bottom of the platform's well. To recreate different regions of the human brain, researchers positioned the cells on the platform based on their relative orientation in vivo.

Engineer David Soscia led a team that developed a microfabricated, funnel-like insert made for any type of chip platform or cell type. It enables precise placement of different cell populations onto smaller areas within the well and in closer proximity to neighboring populations. Cells are added to the insert with a micropipette and then settle via gravity flow through the insert for precise deposition onto the microelectrode array. Once the cells are deposited, the insert is removed and the cells become established, sending out long processes (axons and dendrites) to communicate with each other. The lack of physical barriers or chemically treated surfaces is unique to Livermore's "multiregion" CNS platform. Since no physical barriers exist, the hippocampal and cortical neurons can freely communicate not only with themselves, but with each other. Importantly, both cell types retain their



(a) Lawrence Livermore's brain-on-a-chip is designed to promote the health and longevity of multiple cell types. (b) A microfabricated, funnel-like insert enables precise placement of different cell populations onto small areas within a protruding "well." Cells are added to the insert with a micropipette and then deposit onto the (c) microelectrode array at the center of the platform. (d) The insert is removed, and the cells become established and begin to communicate with each other. (Renderings by Kwei-Yu Chu.)



Engineer David Soscia uses a microscope to examine cells established within the brain-on-a-chip. (Photo by Randy Wong.)

signature shape, viability, and function, despite being co-located.

The researchers analyzed the rodent brain cells' electrical activity for up to 30 days and found that the cells on the platform displayed the same physiological responses previously described by researchers using live animals. The Livermore team also showed that some features of hippocampal cells' electrical activity, such as the spiking rate, were significantly higher when cultured together with cells obtained from the cortex.

From Rodents to Humans

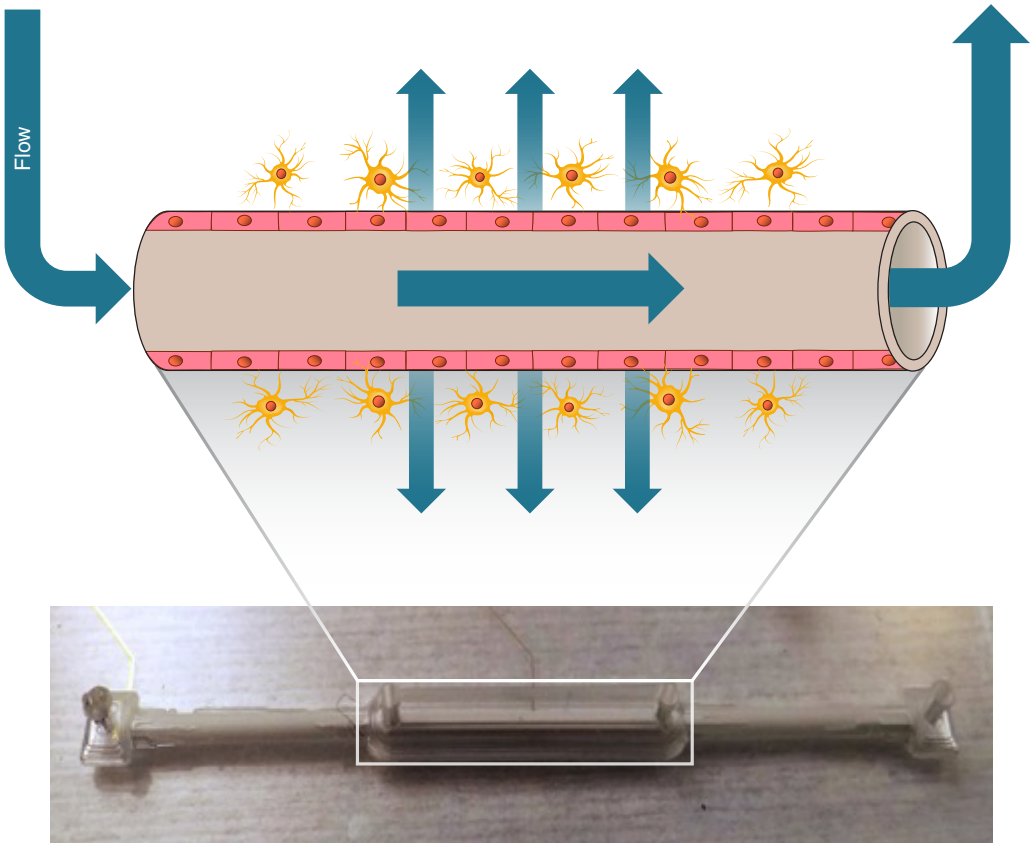
During the second SI, the team began building on their initial results and worked to more closely mimic the brain's two-dimensional cellular microenvironment by increasing the complexity of the cell culture to include neural support cells (astrocytes and oligodendrocytes). In collaboration with Stanford University, they also began experiments with human cells. Fischer explains that the human brain includes distinct but interconnected regions of neurons and supporting cells, and any accurate model must reflect that heterogeneity. Despite this requirement, most in vitro research platforms have focused on populations of a single type of cell or even individual human cells.

In the mixed-cell platform, astrocytes provide structural support, secrete growth factors, and modulate electrical transmissions. Oligodendrocytes produce the myelin that insulates neurons' axons, which carry electrical impulses away from the cell body. As expected, the cultures of neurons combined with astrocytes and oligodendrocytes to form robust neuronal networks exhibiting greater synchronized activity than simple cultures of neurons alone.

The researchers launched a significant effort to validate the technology and demonstrate that the cells on the engineered platforms could generate human-relevant data. They evaluated cell response to chemical agents, surrogates, and well-documented compounds known to affect CNS by either exciting or suppressing electrical activity. The work included use of surrogate chemical agents from biological laboratories at Lawrence Livermore as well as real chemical agents that are strictly controlled at the site's Forensic Science Center—one of two U.S. laboratories with international certification to handle chemical warfare agents.

The validation effort included a direct comparison between cultured rodent neurons and live animal models. An electrode array called the Livermore Flexible Probe (see *S&TR*, June 2018, pp. 4–11) was implanted into a rat's cortex by former Livermore engineer Anna Belle, who co-led the study. In parallel, rat cortical neurons were cultured with the brain-on-a-chip. Both in vivo and in vitro cells were exposed to various chemicals. In the case of an anesthetic dose of ketamine, both cell types showed repressed neural activity, as expected. However, cells on the in vitro platform did not completely mirror the response of the animal, likely resulting from complexities such as metabolic breakdown that are not captured in an isolated in vitro system. The team also tested the chemical atropine (a treatment for nerve agent exposure) and found that the results of the in vitro experiments were similar to those using in vivo cells.

Enright notes that although testing with rodent models and extrapolating the results to humans is not ideal, the ability to compare neuron responses in live animals to those in rodent brain-on-a-chip cells holds considerable value. Tests can also help determine the difference



The blood–brain barrier platform incorporates flow along and across a hollow fiber, which is coated with cultured human endothelial cells (pink rectangles) on the inside and astrocytes (yellow figures) on the outside.

between the responses of human and rodent brain cells cultured on Livermore platforms. By correlating data between both live animals and cell cultures and human and rodent cells, the team can more confidently predict where the platform may be most effective in studies to develop countermeasures.

The team is now working to evaluate complex, 3D neuronal cultures that allow noninvasive interrogation with microelectrodes. "Seeding human neurons in 3D gives us a more realistic morphology, especially when including support cells," says Fischer. "Neurons and other brain cells behave differently when in a 3D environment. Their firing patterns differ, including more synchronized bursts of electrical activity." Soscia leads the effort to develop the prototype 3D configuration in which microelectrode arrays are located vertically along biocompatible polymer pillars. Neuronal cells are seeded around the pillars in a biocompatible hydrogel matrix to provide structural support (an effort spearheaded by postdoctoral researcher Doris Lam). "We want a cell culture depth of approximately 500 micrometers compared to the 20-micrometer depth we have obtained thus far," says Fischer.

A Highly Selective Organ

Developing an artificial BBB model is an important complement to the brain-on-a-chip platform. Indeed, understanding which chemicals cross this highly regulated barrier has significant implications on their ultimate effect on the in vivo CNS. "The blood–brain barrier is the brain's first line of defense," comments biomedical engineer Monica Moya, who leads development of the specialized platform. "It decides what substances are allowed to pass through into the brain." For a drug (or toxin) to affect CNS, it must pass through the barrier. Conversely, BBB breakdown is involved in brain pathology and toxicology.

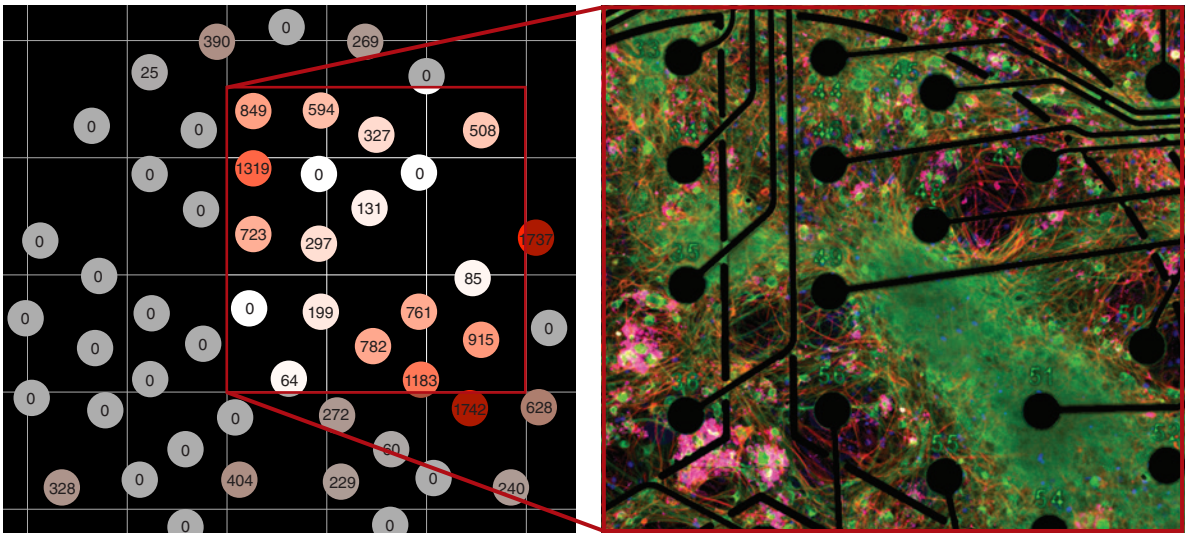
A critical task for the second SI has been to optimize and validate the BBB device. Human endothelial cells (that line blood vessels) are cultured on the inside of porous hollow fibers until a tight monolayer of cells forms, and astrocytes are cultured on the outside of the fibers as support cells. Fluid that contains nutrients continuously flows through the cell-coated fibers. Compounds travel through tight junctions between endothelial cells or through the cells themselves, while pumps rhythmically pass fluid along the cell monolayer, causing them to experience shear stress similar to what the in vivo BBB sustains.

Data from the device were validated by measuring the cell response to chemical compounds that are known to cross, disrupt, or be blocked by the barrier. Researchers used a variety of biological molecules to measure BBB function and permeability and demonstrated that key barrier features, for example drug efflux pumps, were active in the engineered device. Exposure to histamine and a cell-signaling protein increased permeability in vivo, and both chemicals disrupted the barrier's integrity, as expected.

Making Sense of Data

An essential element of the second SI is performing data analytics and computational modeling to help scientists better understand neuronal networks and how cells communicate. Computational models serve as a tool for predicting the effects of compounds on the brain and speeding development of therapeutic regimens for exposure to chemical agents.

Data scientist Ana Paula De Oliveira Sales and postdoctoral researcher Jose Cadena Pico are analyzing the data collected by the microelectrodes to study how neurons' electrophysiology changes over time and in response to environmental conditions and compounds. "Modeling the brain cell networks helps us make sense of all the data," says De Oliveira



(far left) Scientists map electrical activity hotspots (shades of red) to cell composition. (inset) The information is used to better understand communication between brain cells and cell types, as recorded by electrodes (black circles).

Platform Enables Study of Different Biological Systems

Lawrence Livermore's iCHIP (in vitro chip-based human investigational platform) holds promise as a tool for speeding development of medical countermeasures for biosecurity applications and improving the overall drug discovery process. iCHIP devices combine human cells, tissue engineering, and microfluidics to reproduce the body's physiological response under an array of conditions. In a project funded through a Laboratory Directed Research and Development Program Strategic Initiative, Livermore researchers have integrated the biocompatible microelectrode array produced in-house into four separate organ-on-a-chip platforms, including ones for the heart and peripheral nervous system (PNS).

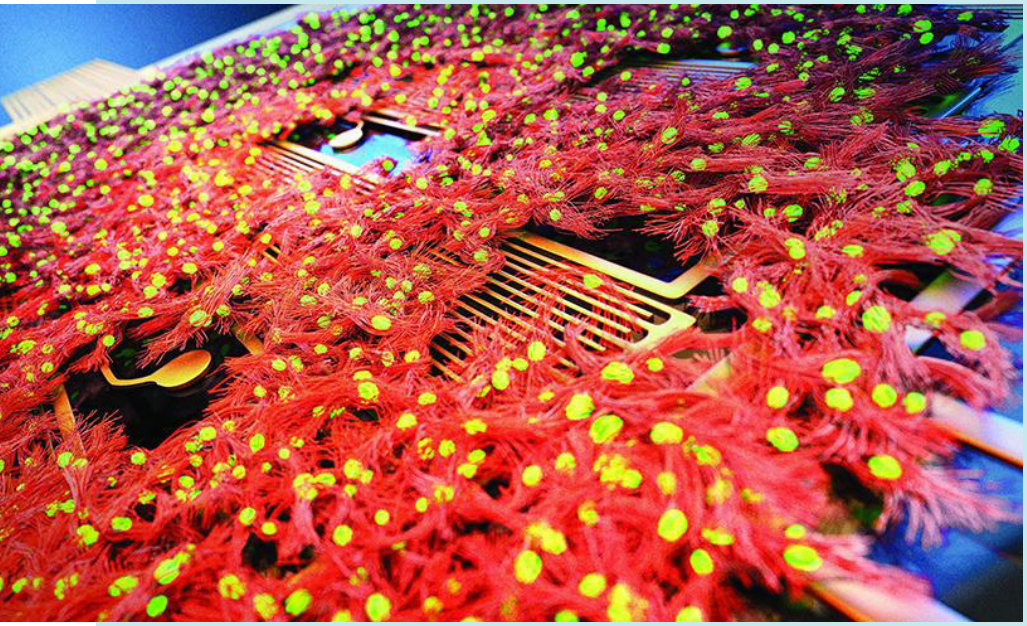
Livermore's heart-on-a-chip, developed by materials scientist Fang Qian, offers a noninvasive method for measuring the adhesion, health, and contractility of heart cells simultaneously in real time—a first in cardiac research. The platform's heart cells naturally grow into two-dimensional tissue that starts to beat after just two days in culture. One of two independent microelectrode arrays integrated into the device monitors the electrical activity of the cells, while the second array measures impedance, which correlates with contraction. In studies, when the cells were exposed to norepinephrine, a stimulant drug used to treat low blood pressure, both the electrical signal and firing rate increased, as happens in human hearts. In contrast, when researchers applied blebbistatin, an excitation–contraction decoupling compound, the cells stopped beating although the electrical signals continued, as expected.

Cardiotoxicity—damage to the heart cells—is a major cause of why promising drug candidates fail. The heart-on-a-chip could help assess the effects of candidate pharmaceuticals on heart tissue much earlier in the drug discovery process. Such a device would also decrease the time needed for new drug trials and ensure potentially lifesaving drugs are safe and effective while reducing the need for human and animal testing.

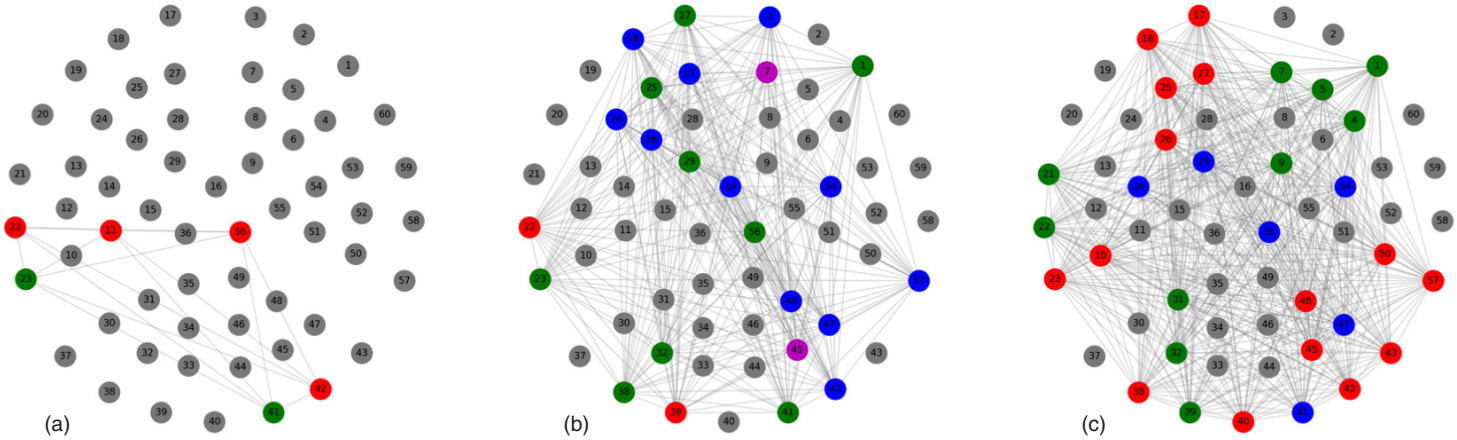
The effects of new drugs and toxins on PNS tissues, which connect the central nervous system to organs and limbs, are often investigated using neurons isolated from human dorsal root ganglia (DRG). Located along the spinal nerves, DRG are the cell bodies of sensory neurons, which have long axons (extensions) that are activated by pressure, temperature, and chemical stimuli. DRGs are also important for processing both acute and chronic pain. They thus serve as an excellent model for studying the neurotoxic effects of chemicals in the body.

PNS tissues were the first biological system components incorporated into an iCHIP. Biologist Kris Kulp says that previous studies using DRG neurons described changes in electrophysiology proceeding from variations in culture conditions and exposure to viral proteins, drugs, and chemicals. However, these studies used the traditional "patch-clamp" technique, which is used for investigating the electrophysiology of single neurons. As a result, the data obtained were limited to tens of single cells, making statistically relevant data impractical. In addition, the patch-clamp method disrupts the neuron's membrane, killing the cell and making chronic chemical testing impossible.

The PNS-on-a-chip device offers strong advantages over other models because it records results from hundreds of DRG neurons for long-term testing and evaluation of chemical and toxic effects. The team seeded human DRG neurons onto the platform and recorded the patterns of the tissues' action potentials with the embedded microelectrode array. The researchers also integrated pH sensors to indicate cell activity, metabolism, and general health. The cells were cultured for several weeks and tested for their response to various chemicals, including capsaicin (a compound found in chili peppers that triggers neural pain response), adenosine tri-phosphate (activates neuron receptors), and potassium chloride (causes neural membrane depolarization). Results of the tests were consistent with previously documented human-derived data.



The heart-on-a-chip measures the effects of various compounds on human heart cells. (Rendering by Ryan Chen.)



An array of 60 electrodes is either inactive (grey) or active and part of a specific community (shown in different colors) after (a) 16, (b) 23, and (c) 30 days in culture.

Sales. "Sometimes a neuron will emit a spike, which indicates that a message is being passed to one or several cells." The researchers' computational model attempts to illustrate how network activity can reflect the complexity of the culture and how this process evolves. "We are looking at cell communities that form and the chatter that goes on within them as well as communication with neighboring communities," she says.

De Oliveira Sales notes that the Laboratory has significant capability to examine the brain-on-a-chip cells using brightfield microscopy. Such analysis can reveal whether a cell is solitary, clumped with others, or appears healthy or diseased. The computational team is also developing methods to autonomously correlate appearance and apparent health of the cells with their recorded electrical activity.

Many Potential Benefits

Livermore researchers are showing that their iCHIP devices provide higher quality, more reliable human-relevant data than other investigative models. Enright says, "We have made considerable progress over the past few years. The brain-on-a-chip provides a unique capability."

By recreating the microenvironment and function of brain tissues, the brain-on-a-chip allows the study of how cells form networks, how they communicate, and how that communication changes when cells are combined with, or located close to, a different cell type. The platform will also allow researchers to analyze how disease spreads through the brain and more accurately model epilepsy and other debilitating conditions. For example, the platform could aid the study of human seizure response—a reaction caused by some chemical warfare agents—to help physicians better understand how to treat the condition.

For protecting the warfighter, the device may greatly advance development of effective countermeasures for exposure to chemical (and biological) agents. For example, researchers could potentially predict how warfighters are likely to be affected by long-term, low-level exposure to chemical agents. The brain-on-a-chip may also help scientists determine if certain types of neurons are more susceptible to these toxins than others. Scientists could also screen compounds for prophylactic use before entering at-risk environments. Existing pretreatments for U.S. warfighters have unpleasant side effects. Therefore, development of alternatives that are equally effective but better tolerated is of significant interest.

Conventional development of new pharmaceuticals and antidotes to toxic compounds currently takes years, costs billions of dollars, and relies extensively on animal testing, which can lead to inaccurate predictions about the likely human response. Federal agencies need a faster, cheaper, more flexible method for addressing threats. The Livermore team has discussed follow-on funding with representatives from the National Institutes of Health and the Department of Defense. Fischer notes the brain-on-a-chip effort dovetails with Lawrence Livermore's overall mission of national and global security. In a few years, U.S. warfighters—as well as the general public—may have an improved tool for thwarting agents of chemical warfare and, quite possibly, agents of human disease.

—Arnie Heller

Key Words: blood–brain barrier (BBB), brain, brain-on-a-chip, Center for Micro and Nanotechonology, central nervous system (CNS), Forensic Science Center, heart, hippocampus, iCHIP (in vitro chip-based human investigational platform), Laboratory Directed Research and Development (LDRD) Program, microelectrodes, neurons, peripheral nervous system (PNS), Strategic Initiative (SI).

For further information contact Nick Fischer (925) 422-6144 (fischer29@llnl.gov) or Elizabeth Wheeler (925) 423-6245 (wheeler16@llnl.gov).

A Brilliant Mind Leaves an INDELIBLE LEGACY

A patriot, scientific genius, and nuclear deterrence pioneer, the Laboratory's third director played a pivotal role in U.S. policy and national security.

Harold Brown (pictured here in the 1950s) was the Laboratory's third director. He passed away on January 4, 2019, at the age of 91.

HAROLD BROWN, Lawrence Livermore National Laboratory's third director, was an intellectual giant. Born in New York City in 1927, Brown displayed a brilliant scientific mind early in life, graduating from the Bronx High School of Science at the age of 15 with outstanding marks. He studied physics at Columbia University, earning his bachelor's degree after just two years and holding the highest academic record of any Columbia undergraduate. Remarkably, he earned both his master's and doctorate degrees by the age of 21.

After a stint lecturing at Columbia and the Stevens Institute of Technology, as well as working at the University of California's (UC's) Radiation Laboratory in Berkeley, California, the Atomic Energy Commission (AEC) recruited Brown to be a research scientist at Lawrence Livermore (then a UC Radiation Laboratory offshoot) in 1952. In those freewheeling early days, Brown later recalled, the Laboratory was loosely organized, but operated under a tremendous sense of urgency to quickly develop new warheads capable of countering increasing Soviet aggression and technological advances. "It was exciting to work with (Ernest) Lawrence and (Laboratory Director Edward) Teller," said Brown during a visit to the Laboratory in 2013. "I learned something from their successes as well as their mistakes. I learned that you can get things done if you work hard enough and your ideas are good enough . . . By and large, we were very young and inexperienced, but we were able to try new ideas. We had the optimism of youth."

At just 31 years of age, Brown became then-Laboratory Director Teller's deputy, and after severe bouts of colitis befell both Teller and Lawrence, the responsibility of leading the Laboratory's weapons program fell squarely on the shoulders of the youthful physicists Brown and Johnny S. Foster, Jr., who would later succeed Brown as Laboratory director. To counter the perceived Soviet advantage of larger nuclear payloads, as Brown wrote in his memoir *Star-Spangled Security*, the U.S. needed to develop lighter, more easily deliverable thermonuclear weapons.

Early in his Laboratory career, in 1954, Brown led the development of a revolutionary lightweight warhead that could be delivered by a missile mounted inside a submarine, a feat thought nearly impossible at the time. The Polaris missile deployed in 1959, a significant achievement coming just two years after the Soviet Union had launched the satellite Sputnik—an event that heightened tensions between the two superpowers. Brown recalled, "Given complete autonomy, we developed the (Polaris) system in about three years by avoiding external nitpicking and sniping, constant reviews, and program revisions. The project succeeded in half the normal time."

Foster says Polaris represented a "heroic effort" by Livermore and Sandia engineers and scientists that tipped the scales of nuclear supremacy in favor of the United States. "It was a marvelous thing," recounts Foster. "We had the superiority in submarines, we had the standoff capability, and we had the thermonuclear warhead that could be delivered. It was revolutionary, and it made all the difference." Former Laboratory Director Bruce Tarter adds that Polaris helped prove the Laboratory's worth in its early stages and positioned it to eventually become the "creator and owner" of the nation's strategic stockpile in subsequent decades. "It made the Cold War cold," says Tarter. "All of a sudden the U.S. had a collection of nuclear weapons that were unfindable—giving substance to the word 'deterrence.'"

During his time at Livermore, Brown became a proponent of arms control, convinced that limiting the number of delivery systems, rather than constraining the development of weapons technology, was the most important element in maintaining nuclear balance. Working with Teller, he helped establish the AEC's Plowshare Program to explore nonmilitary applications of nuclear energy. He also advised U.S. delegates attending international conferences on the topics of nuclear test detection and test bans.

Former Laboratory Director John Nuckolls, who joined the Laboratory in 1955, remembers working as an assistant to Brown in the Megaton Group (later known as A Division) that designed thermonuclear explosives and experiments. Nuckolls developed computer codes and made calculations for Brown's designs, and the two men worked together on multiple projects, including high-efficiency thermonuclear weapons, designs for a cannon that could fire a projectile into orbit, a new computer code to calculate the effects of underground nuclear explosions, and a below-ground nuclear explosion power plant as part of Plowshare.

Johnny S. Foster, Jr. (left), met Brown while conducting graduate work at the University of California Radiation Laboratory in Berkeley, California, and came to Livermore with him as part of a contingent of postdoctoral researchers who were transferred to the new sister facility. Foster, who would later succeed Brown as Laboratory director, worked closely with his colleague in the 1960s.

Nuckolls remembers his former supervisor as a "shy genius" and a "great teacher." Nuckolls says, "Harold was very good at encouraging people to do what they thought they wanted to do."

In 1960, Brown succeeded Teller (at Teller's recommendation) as Laboratory director, presiding for about nine months during a moratorium on nuclear weapons testing. As director, Brown continued to advocate for the importance of a nuclear deterrent, balancing the role of nuclear weapons with other elements of national security. George Miller, who served as Laboratory director from 2007 to 2011, says that Brown strongly believed the national laboratories should have a continuing role in arms control and nonproliferation, weighing policy goals with technical realities and playing a substantial role in intelligence.

Tarter notes Brown was an "extraordinary early leader" who, along with the Laboratory's first director Herbert York, Teller, and Foster, set the institution on a course to prominence. He calls Brown a "prodigy," who succeeded not only because he had a technical mind but because he could also play the political game.

The Polaris missile represents the success of Livermore's efforts to develop small, efficient thermonuclear weapons that could be carried by submarine. Polaris's success was critical in establishing U.S. nuclear deterrent capability.

"He could balance all the pros and cons and provide cogent arguments . . . People respected him. He wasn't just a policy person or someone running a large organization, he was his own intellectual bodyguard, which is pretty rare. He had enough of both sides to make a big impact," says Tarter.

Brown and his wife Colene, who married in 1953, left Livermore for Washington, D.C., in 1961. Brown moved to the Pentagon, where he served as director of defense research and engineering from 1961 to 1965 under Defense Secretary Robert McNamara, briefing President John F. Kennedy on nuclear weapons. As one of McNamara's "whiz kids" and the Department of Defense's third-highest ranking civilian, Brown was responsible for weapons development and cemented his reputation for having both technical expertise and a gift for strategic thinking.

Later, President Lyndon B. Johnson appointed Brown as secretary of the U.S. Air Force, where he assisted in planning for the Vietnam War and helped develop precision-guided weapons. In 1969, Brown became president of the California Institute of Technology (Caltech) in Pasadena, California, where he served for the next eight years and was instrumental in admitting the school's first female undergraduates.

"Whenever he was given an assignment, he would assess the situation and identify the instant problems, then he would implement corrections for those problems," says Foster. "Harold also looked at the future of the organization, whether it was at Livermore, the Air Force, or Caltech, and at the same time he would consider his alternative futures. In doing so, he ended up contributing in many ways to different organizations, committees, and advisory groups."

Brown continued his service to the country as a member of the U.S. delegation to the Strategic Arms Limitation Talks (SALT I), an arms control pact signed in 1972 by President Richard Nixon and Soviet Premier Leonid Brezhnev. In 1973, he became a member of the Trilateral Commission, where he joined leaders from Europe, North America, and Japan to promote political, economic, and security cooperation. Brown later became President Jimmy Carter's choice for U.S. secretary of defense from 1977 to 1981, the first scientist to hold the position. As secretary, Brown devised a new plan for nuclear deterrence, the "countervailing strategy," a significant departure from the doctrine of "mutually assured destruction" that had reigned since the earliest days of the Cold War. Brown thought the U.S. should develop the capability, through its delivery systems, accuracy, and intelligence, of responding to a Russian provocation by attacking the country's nuclear forces and government, instead of its cities and population centers.

Brown's tenure would see the Russian invasion of Afghanistan, a revolution in Iran that resulted in the capture of 52 U.S. hostages, and the signing of the Camp David Peace Accords. He was the first U.S. secretary of defense to visit China, helping to normalize relations between the two countries.

On March 23, 1962, President John F. Kennedy visited the University of California's Lawrence Radiation Laboratory in Berkeley, California, to express his thanks and appreciation for the important national security work being conducted by the scientists at Livermore and Los Alamos. Brown (far right), who was then director of defense research and engineering at the Pentagon, accompanied the president.

He played a central role in the Panama Canal Treaties and in talks that led to SALT II—a 1979 agreement to restrict Soviet and U.S. missiles and warheads. Although signed by both Carter and Brezhnev, the pact, which Brown saw as vital to a détente with Russia, was never formally ratified by the U.S. Congress and was essentially scrapped after the Soviets invaded Afghanistan. However, the two countries voluntarily adhered to conditions of the agreement throughout the 1980s.

Near the tail end of the Carter Administration in 1980, Brown was involved in planning a rescue of the U.S. hostages held in Iran. Brown called the failed attempt, which resulted in the loss of eight U.S. servicemen, "the worst night of my life." Faced with pressure to reduce the defense budget, Brown nonetheless oversaw a budget increase, as well as technological advances in ballistic and precision-guided cruise missiles, stealth aircraft, satellite surveillance, and communications and intelligence systems. In his farewell address as secretary of defense, Brown said, "These past four years have been rewarding and challenging. But much has been achieved. Most satisfying of all is that for four years our nation remained at peace despite the world tensions and turmoil that constantly pose challenges to our interests and peace." President Carter awarded Brown with the Presidential Medal of Freedom in 1981, the highest honor afforded to a U.S. civilian.

After leaving the Pentagon in 1981, Brown began a 30-plus year career in the corporate sector and academia. He taught at the Johns Hopkins University School of Advanced International Studies for several years, and from 1984 to 1992 chaired the school's Foreign Policy Institute. He also became a trustee (and later trustee emeritus) of the RAND Corporation and joined the Center for Strategic and International Studies as a counselor and trustee in 1992. "Apart from his obvious technical contributions, Harold leaves behind a legacy of promoting the integration of science and technology with political and policy goals," says Miller. "The ability to bring his detailed, logical thought to the interface between those different disciplines was one of his rare skills." In 1993, President Bill Clinton presented Brown with the Department of Energy's Enrico Fermi Medal, one of the most prestigious awards in science and technology, citing him for his "outstanding contributions to national security, leadership in development of nuclear weapons and in formulating nuclear deterrence policy during the difficult Cold War period, and ongoing counsel."

Throughout the 1990s and into the 2000s, Brown was a partner at the New York private equity firm Warburg Pincus and served as corporate director for more than a dozen businesses, including Mattel, IBM, and Cummins. Until his death, on January 4, 2019, Brown continued his involvement in government as a member of the Defense Policy Board, which advises sitting secretaries of

Brown (seated at left) visited the Laboratory in 2013 after he published his memoir *Star-Spangled Security*. He met with former Laboratory directors including (clockwise from left) Foster, John Nuckolls, Michael May, Bruce Tarter, George Miller, Michael Anastasio, and Penrose "Parney" Albright (seated).

defense on strategic, military, and international political issues, and participated in various government commissions involving military strategy, intelligence, innovation, and terrorism. Current Laboratory Director William Goldstein says, "From director of this Laboratory, to his years working for Presidents Kennedy, Johnson, Nixon, and Carter, Harold will always be remembered for his leadership, his intellect, and his commitment to the security of our nation."

Brown's memoir *Star-Spangled Security* was published in 2012, and the following year he visited the Laboratory to discuss the book. Addressing modern national security challenges, Brown said the greatest threats were internal, warning that the waning notion of U.S. exceptionalism, the increasing gap between rich and poor, and political partisanship could all undermine morale. In the book's conclusion however, Brown waxed optimistic about the future of the U.S. as a world leader because of its unique geographic position, natural resources, diversity, and flexible political system.

"We have the ability to address what we must to remain strong and prosperous," wrote Brown. "It is no small challenge, but we are not a nation of small aspirations. We are a nation of people who get things done. We have brought the flag through perilous fights. Now, it falls on each of us to join in protecting our interests abroad while guarding values that embody the rights and duties of each of us at home. Let's do it."

—Jeremy Thomas

For further information contact Jeremy Thomas (925) 422-5539 (thomas244@llnl.gov).

"Mini" Device Set to Analyze **Mysterious Psyche**

The Psyche mission will allow scientists to observe, for the first time, a planetary body made of metal rather than rock or ice. (Image courtesy of NASA's Jet Propulsion Laboratory.)

A few hundred million kilometers from the Sun orbits a large, metal mass that may answer the age-old question of how planetary bodies formed. The mass is the 16-Psyche asteroid, named in 1852 after the Greek goddess of the soul and its recognition as the 16th asteroid discovered in space. Psyche resides in the asteroid belt between Mars and Jupiter, and unlike typical asteroids that are composed of rocky materials, Psyche appears to be metal—mostly iron and some nickel.

Scientists are eager to explore the asteroid because its unique metal exterior suggests something phenomenal. "Theoretically, the best explanation for a 200-kilometer iron ball to be floating around in space is that it could be the remnant core of an early planet," explains Livermore physicist Morgan Burks. As part of a NASA Discovery Program mission, Burks is leading a team to develop an instrument for analyzing Psyche's composition. "Exploration of Psyche may increase our understanding of the hidden, inaccessible cores of Earth, Mars, Mercury, and Venus," says Burks. The research could also provide insight into how a planet's layers, such as crusts and cores, separate.

The Psyche mission, which includes project lead organization Arizona State University, NASA's Jet Propulsion Laboratory, and the Johns Hopkins Applied Physics Laboratory, marks the first time scientists will explore a "world made of metal," rather than ice or rock. Livermore scientists are designing and building a gamma-ray spectrometer, called GeMini-Plus—one of several key instruments that together will help determine the asteroid's elemental makeup as well as its gravitational field, magnetic field, and geological features. GeMini-Plus will be combined with a neutron spectrometer developed by Johns Hopkins to characterize the asteroid. "Psyche's surface releases a large number of gamma rays that are induced by cosmic-ray bombardment," says Burks. "Each element gives off a unique gamma-ray signature. By measuring the energy of the gamma

rays with high resolution, we could determine the composition of the asteroid's surface." GeMini-Plus will be the second gamma-ray spectrometer designed and built by the Laboratory for space exploration within the past 15 years.

Origins of a Novel Spectrometer

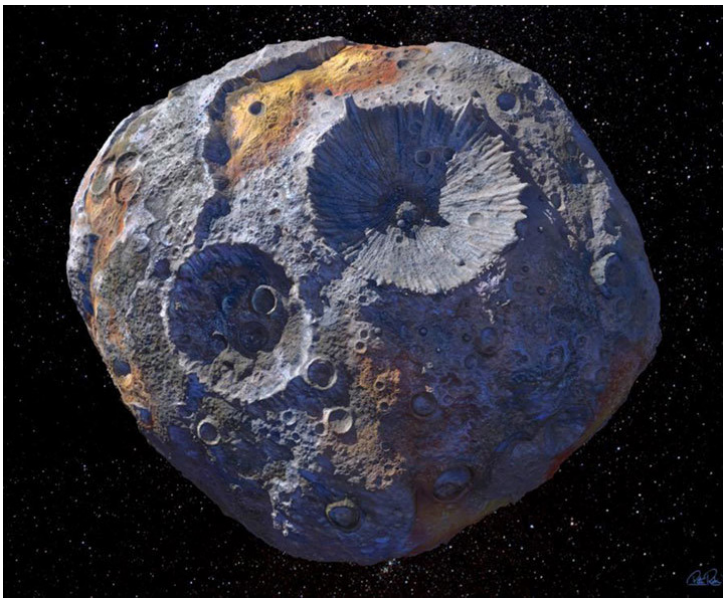
The original GeMini, developed by Burks, uses a germanium detector (hence the "Ge" in GeMini) to identify and analyze gamma rays emitted by radioactive materials for determining their elemental and isotopic composition. (See *S&TR*, October/November 2009, pp. 8–9.) Compared to other substances that can be used to detect gamma rays, germanium offers the best resolution. However, in the past, this resolution came at a cost, because the germanium must be cooled to extremely low temperatures (around -200°C) using liquid nitrogen. "Although liquid nitrogen is readily available in a laboratory environment such as at Lawrence Livermore, the substance is impractical or even impossible to obtain in the field, especially in an emergency situation," says Burks.

To overcome this challenge, Livermore scientists combined an innovative ultraminiature cooling system (hence the "Mini" in GeMini) with an infrared shielding mechanism. This mechanically cooled system, the first of many innovations that culminated in the advanced detector, does not require liquid nitrogen and is both fieldable and highly effective. Other features include rugged construction, low power consumption, automated operation, and small size—characteristics that are needed for both handheld devices and space applications. Burks says, "A synergy exists between the gamma-ray spectrometer we send to space and an instrument we use to try to prevent radioactive material from being smuggled into the country."

GeMini's predecessor was successfully tested in space in 2004, when NASA launched the MESSENGER spacecraft to Mercury. MESSENGER's goal was to characterize Mercury's surface and answer key questions about the solar system's second-densest planet. A first of its kind, the Livermore-developed gamma-ray spectrometer had to be rugged to survive the extremely high temperatures at its destination, among other requirements. The mission produced new insights about Mercury, such as its naturally occurring radioisotopes and extensive volcanic activity. Burks transitioned the gamma-ray spectrometer on MESSENGER to the commercially fieldable GeMini for national security applications and, more recently, the GeMini-Plus.

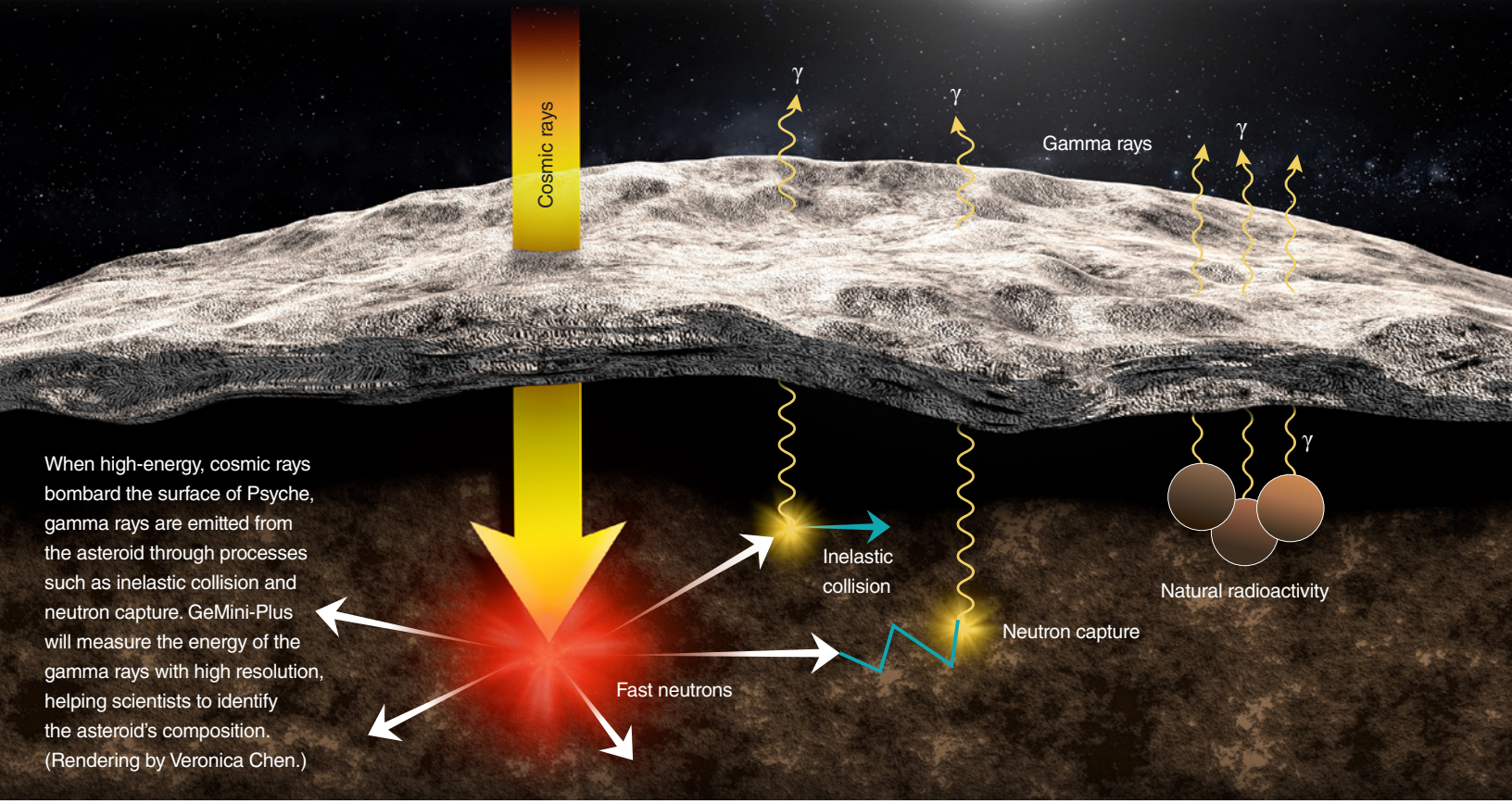
Mission to Psyche

Although the gamma-ray spectrometer onboard MESSENGER had to be optimized for Mercury's harsh environment, the same requirements were not necessary when planning a visit to Psyche. The asteroid's location much farther from the Sun freed scientists from the stringent thermal-shielding requirements of the previous mission. "Compared to its predecessors, GeMini-Plus has an



Psyche is hypothesized to be an exposed planetary core containing iron, nickel, and other metallic elements. (Image courtesy of NASA's Jet Propulsion Laboratory.)

GeMini-Plus is an improved, simplified, and more rugged version of the original GeMini gamma-ray spectrometer. The enhancements make the device more versatile than its predecessor.



When high-energy, cosmic rays bombard the surface of Psyche, gamma rays are emitted from the asteroid through processes such as inelastic collision and neutron capture. GeMini-Plus will measure the energy of the gamma rays with high resolution, helping scientists to identify the asteroid's composition. (Rendering by Veronica Chen.)

improved, simplified, and more rugged design, allowing for greater versatility," says Burks.

Once in space, GeMini-Plus will measure gamma rays emitted from the surface of Psyche as a result of cosmic-ray bombardment. The gamma rays will interact with the germanium inside the detector, liberating electrons in proportion to the gamma rays' energy. GeMini-Plus will collect the emitted electrons using an electric field applied to the germanium, and the data will be sent for analysis via specialized electronics to scientists on Earth, who will use the information to identify the material emitting the gamma rays.

The Psyche mission will launch in 2022, with a projected arrival to the asteroid in 2026. To ensure GeMini-Plus is ready for the long trip, Livermore scientists will conduct various quality assurance tests: vibration testing to check the device's ability to survive a rocket launch that generates 35 G (gravitational forces), thermal testing to validate that it can operate in a range of temperatures, and performance testing to check its resolution. Livermore will then release the detector to Johns Hopkins researchers for integration with spacecraft flight electronics, after which it will be sent to NASA for further testing. Says Burks, "Designing an instrument for a deep-space mission requires incredible attention to detail. The instrument will be hundreds of millions of kilometers away when it is turned on, and it must work. Unlike a terrestrial instrument, we have no way to repair the hardware in space."

Coincidentally, the Psyche spacecraft will arrive at the asteroid at approximately the same time as another planned NASA spacecraft utilizing GeMini-Plus—one that is part of a 2024 mission to the moons of Mars. The goal of the mission is to gather information about the moons' surfaces and how they originated, but with an exciting addition. The Mars probe will procure a sample from one of the moons that will be brought back to Earth for analysis.

A Foreign Frontier

According to NASA scientists, the Psyche mission "offers a unique window into the violent history of collisions and accretion that created terrestrial planets." As it happens, Lawrence Livermore's expertise in gamma-ray spectroscopy offers a valuable capability for looking through that window. Livermore is currently the only laboratory that can obtain the necessary high-resolution data with such a low-mass, low-power device. "The technologies we are developing have a wide range of applications on Earth and in space," says Burks. "Devices produced for basic science research can also be applied to important national security applications. In turn, the national security advances we achieve help us further basic science."

From the gamma-ray spectrometer for MESSENGER, to GeMini, and finally GeMini-Plus, gamma-ray detection technology has given a boost to national security and made charting new territories possible. With its launch on the horizon, the Psyche spacecraft, incorporating GeMini-Plus, will provide a closer look at a remarkable planetary body and its origins, helping scientists to potentially solve some of the biggest mysteries about the formation of planets in our universe.

—Lauren Casonhua

Key Words: 16-Psyche, asteroid, gamma-ray spectrometer, germanium, GeMini, GeMini-Plus, NASA, planetary core, space.

For further information contact Morgan Burks (925) 423-2798 (burks5@llnl.gov).

Energetic Laser Helps Test **Weapon Survivability**

ESTABLISHED after the halt of underground nuclear testing, the Stockpile Stewardship Program is a critical element of the National Nuclear Security Administration's mission to ensure the safety, security, and effectiveness of the U.S. nuclear deterrent. As part of this program, scientists are tasked with guaranteeing nuclear weapons' survivability—that is, ability to function—under hostile conditions, such as those that could result from a pre-emptive strike by an adversary, or when a conventional war may be fought in a nuclear environment.

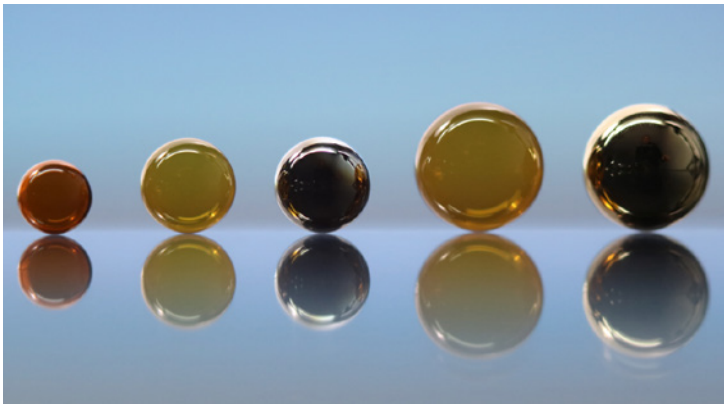
In the absence of nuclear testing, high-energy-density (HED) facilities, such as Lawrence Livermore's National Ignition Facility (NIF), have become a key tool for testing the survivability of nuclear weapon components. NIF allows researchers to subject nonnuclear parts, such as electronics and other materials, from weapon systems to intense radiation from x rays and neutrons and to probe material properties at extreme pressures and temperatures—conditions that mimic what systems may face in a real-world nuclear environment. Brent Blue, the National Security Applications program manager at NIF, says, "Survivability is a chess game. The moves an opponent will make are unknown as are their capabilities. Trying to predict what an adversary might do now, let alone 30, 40, or 50 years out, during the lifetimes of these systems, is incredibly challenging. An effective survivability strategy requires one to account for myriad possible 'what-if' scenarios both now and in the future."

Blue is part of a team at NIF that is implementing innovative methods for improving survivability experiments. For example, new target designs are serving as more intense sources of neutrons and x rays for maximizing the energy fluence through a test sample. In addition, specialized systems have been implemented for fielding samples closer to radiation sources, and novel diagnostics are recording essential data for determining how test materials are affected. These capabilities are providing new insights into weapon systems' durability and are also enhancing several national security programs.

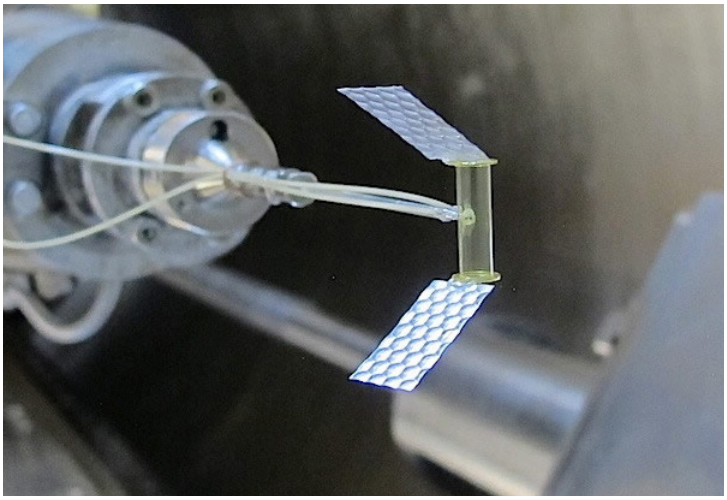
Targets Produce Intense Radiation

After a nuclear blast, an enormous flux of high-energy neutrons and x rays are emitted by the fusion reaction. NIF enables researchers to recreate this environment in a laboratory setting. "NIF is the most energetic laser in the world, which makes it capable of generating exceedingly bright sources of x rays. NIF is also the only facility that can generate intense sources of 14 megaelectronvolt (MeV) neutrons, which are characteristic of deuterium and tritium fusion," says Blue. The 14 MeV neutrons penetrate deep into materials and deposit large amounts of energy that heat materials throughout. X rays, on the other hand, are used to rapidly heat the surface of a test material, generating a shock wave that travels through to the rear of the sample.

The effects of neutrons and x rays on weapon components are studied in separate experiments that use different types of targets. This approach allows the source of either product to be optimized for generating the maximum fluence—that is, the number of neutrons or x rays flowing through a sample per unit area.

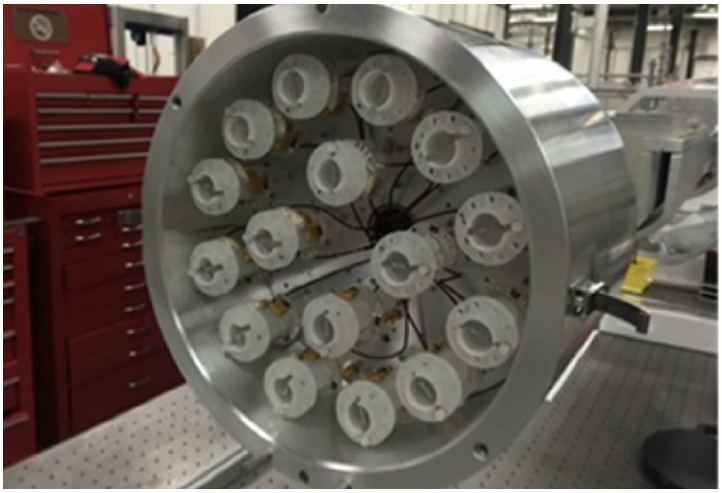


Direct-drive targets are gas-filled capsules ranging in size from 2 to 4 millimeters that contain room temperature deuterium and tritium. When heated by the laser, these capsules generate powerful 14-megaelectronvolt neutrons for survivability experiments. (Photo courtesy of General Atomics.)

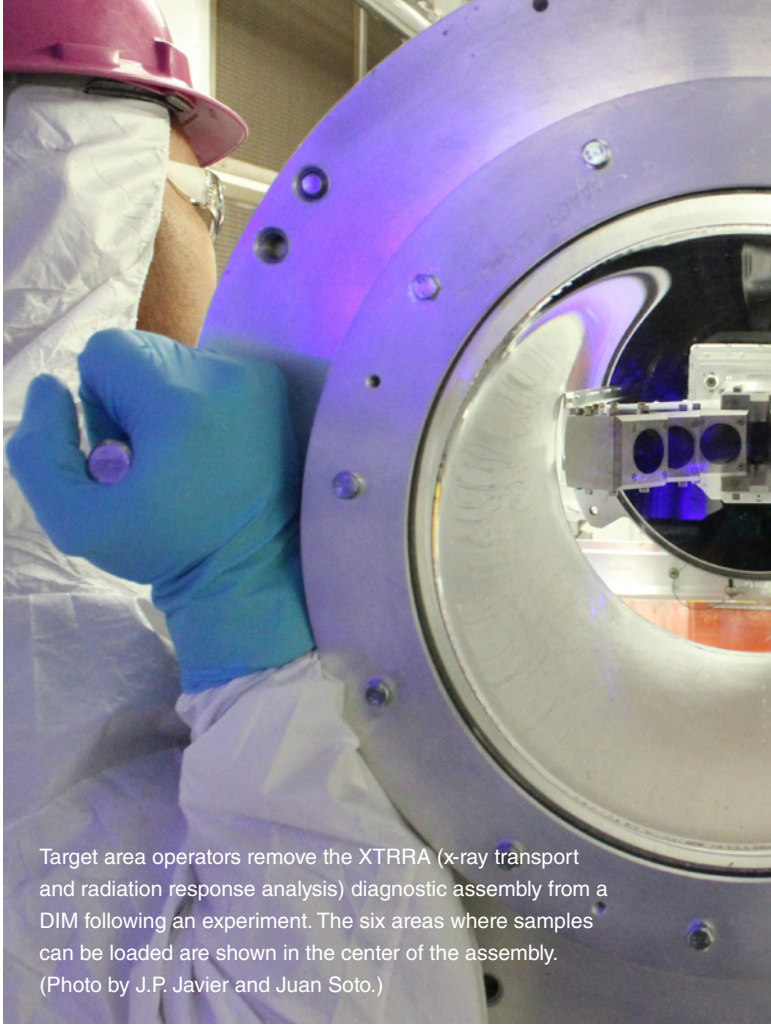


A thin-walled gas pipe positioned at the end of a target positioner is used as a source for high-energy x rays.

(left) A technician at the National Ignition Facility (NIF) prepares to load a sample into a specialized holder that will extend into the 10-meter-diameter target chamber for testing. (Photo by Brent Blue.)



The Sentinel diagnostic is a 16-channel line-of-sight x-ray spectrometer mounted in a diagnostic instrument manipulator (DIM). During an experiment, it measures x-ray output from a source at the target's equator.



Target area operators remove the XTRRA (x-ray transport and radiation response analysis) diagnostic assembly from a DIM following an experiment. The six areas where samples can be loaded are shown in the center of the assembly. (Photo by J.P. Javier and Juan Soto.)

In neutron-generating experiments, scientists use direct-drive targets—tiny plastic spheres ranging in size from 2 to 4 millimeters that contain room temperature deuterium–tritium gas. NIF's powerful laser beams are focused directly onto the target to "drive" the fusion reaction by rapidly heating the capsule's outer surface. Compared to other experiments that use an indirect means of heating the capsule, direct-drive targets are easier to field and can be positioned closer to a test sample, which allows higher fluence levels to be achieved.

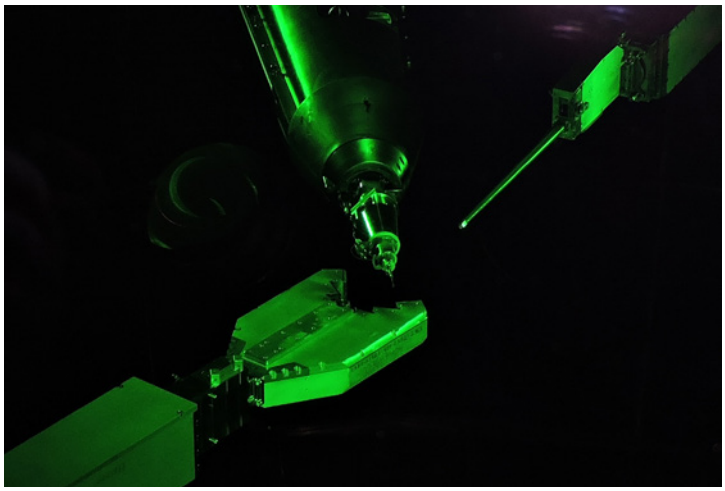
Targets used as x-ray sources are typically low-mass, thin-walled gas pipes containing materials that give off specific x-ray energies. "When the laser heats a target material, the x-ray energies emitted from the source are dependent upon what atomic element was used to make it," says Blue. For example, krypton gas predominantly gives off x rays at 13 kiloelectronvolts (keV). Argon and xenon generate x rays in the 4 to 5 keV range, and silver rises to approximately 22 keV. Researchers step through experiments with different x-ray energies to systematically evaluate x-ray effects on a sample. Together, data gathered from both neutron and x-ray experiments provide researchers with a comprehensive look at how weapon components may respond within an intensely radiative environment.

Diagnostics Are Key

Inside NIF, a wide range of diagnostics is used to measure and record experimental data. Blue and a team of NIF physicists and engineers recently added to the suite of instruments when they developed and implemented the Sentinel diagnostic—so named because of its resemblance to the squid-like "search-and-destroy" machines in the "Matrix" films. "To obtain the measurements we needed, we had to make a new diagnostic," says Blue, who along with the team, designed, built, and deployed the tool in just three months.

Sentinel is a 16-channel line-of-sight x-ray spectrometer mounted in a diagnostic instrument manipulator (DIM) on the equator of the NIF target chamber. (A DIM is a two-stage telescoping system for positioning a diagnostic package within the target chamber and enables diagnostics to be exchanged for different experiments.) The instrument works in conjunction with the Dante diagnostics—two broadband, time-resolved x-ray spectrometers that measure the x-ray flux emitted by the target. Throughout an experiment, Sentinel measures x-ray output at the target's equator, while the Dante systems are permanently located off the equator toward the target chamber's north and south poles. X-ray diodes within the detectors determine the x-ray yield from the targets, and each diode is filtered to record the x-ray power in a specific part of the spectrum.

When fielding an experiment, test samples are placed in the XTRRA (x-ray transport and radiation response analysis) diagnostic assembly, which can carry up to six exposed samples in a single shot. XTRRA is attached to the "snout" of a target and instrument manipulator (TANDM)—a combination diagnostic inserter and target positioner. The snout is the end of the instrument positioned closest to the source. Behind each sample is a stress gauge and an interferometer that help determine peak



This setup for a survivability experiment inside the NIF target chamber shows the XTRRA diagnostic assembly containing the samples (bottom), the target positioner (top center), and a time-resolved x-ray spectrometer for recording data (top right). (Photo by Dan Linehan.)

stress and ablation pressure in the material generated by the x rays produced during the shot. The assembly also contains three calorimeters that measure the total x-ray energy.

Sample positioning within the NIF target chamber is always a tradeoff. Samples close to the source receive a larger dose of radiation and must be smaller in size to ensure even irradiation. Moving the sample farther away allows for more uniformity but sacrifices fluence. Unlike typical fusion and HED experiments that have timescales of interest in the nanosecond (billionths of a second) range, for survivability experiments, scientists are concerned with timescales 1,000 to 1,000,000 times longer. As a result, data are recorded just before the laser is fired to a second or more after, allowing for observations of the materials as they heat up and cool down.

Survivability Is Essential

Although survivability experiments subject samples to exceedingly high neutron and x-ray yields, precautions are taken to ensure the samples remain intact. "The very nature of weapons' survivability is ensuring that the systems still function long after the engagement," says Blue. "Similarly, in experiments, we do not want the test samples destroyed. Rather, the samples are recovered for post-test analysis." Once a sample is retrieved, its strength and deformation can be evaluated, and researchers can inspect cross sections of the samples for microstructural changes.

Experimental and post-testing data also serve as critical input for computational models that are used to evaluate, validate, and visualize what happens during a test. The test–model cycle continues as additional tests are conducted, and thus more data become available. "Computer models are always approximations, but what we want to know is how good the answers are and whether they are good enough," says Blue. "Experimental facilities, such as NIF, allow us to test the models and push them beyond their limits. Learning comes from achieving a slightly different answer and then figuring out the reason behind it." Soon Blue will have plenty more data with which to push those models. In 2015, nearly 20 NIF shots were dedicated to survivability, while in 2019, that number will almost triple to 59 planned shots.

As the nation's stockpile continues to age, survivability testing will remain a key component for stockpile stewardship to ensure that these decades-old components and systems will remain safe, reliable, and effective. "To provide a credible strategic deterrent, nuclear weapons and delivery systems must be survivable against current and future offensive and defensive threats," says Blue. "Survivability and HED science are vitally important to national security."

—Dan Linehan

Key Words: fusion, high-energy-density (HED) science, laser, material properties, National Ignition Facility (NIF), neutron source, nuclear weapon, Stockpile Stewardship Program, survivability, target, x-ray source.

For further information contact Brent Blue (925) 423-0730 (blue3@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 (http://www.uspto.gov).

Patents

Intrinsic Use Control for System and Use Controlled Component Security
Mark Miles Hart
U.S. Patent 10,102,382 B1
October 16, 2018

Graphene Aerogels
Peter J. Pauzauskie, Marcus A. Worsley, Theodore F. Baumann, Joe H. Satcher, Jr., Juergen Biener
U.S. Patent 10,106,418 B2
October 23, 2018

Bidirectional Shape Memory Device
John E. Marion, III, Jane P. Bearinger, Thomas S. Wilson, Ward Small, IV, Duncan J. Maitland
U.S. Patent 10,107,270 B2
October 23, 2018

Methods for Making Graphene-Supported Metal Oxide Monolith
Marcus A. Worsley, Theodore F. Baumann, Juergen Biener, Monika M. Biener, Yinmin Wang, Jianchao Ye, Elijah Tylski
U.S. Patent 10,109,845 B2
October 23, 2018

Pulse-Train Drive System for Electrostatic Generators and Motors
Richard F. Post, Edward G. Cook
U.S. Patent 10,110,146 B2
October 23, 2018

Electrochemical Production of Metal Hydroxide Using Metal Silicates
Gregory Hudson Rau
U.S. Patent 10,113,407 B2
October 30, 2018

Awards

Former Lawrence Livermore Director **John Nuckolls**, who for more than 60 years has dedicated his career to advancing science and technology in support of national security, became the fourth recipient of the **John S. Foster Jr. Medal**. Established by **Lawrence Livermore National Security, LLC**, and bestowed on an annual basis by the director of Lawrence Livermore National Laboratory, the medal recognizes an individual for exceptional leadership in scientific, technical, and engineering development and policy formulation in support of U.S. nuclear security.

Nuckolls joined the Laboratory in 1955 as an aspiring young physicist from Columbia University. Fourteen years later, he received the E.O. Lawrence Award for his contributions to the development of high-efficiency thermonuclear explosives. During that same period, he explored novel methods for thermonuclear ignition, and following the invention of the laser in 1960, he pursued the possibility of using high-power lasers to achieve that goal. In 1983, Nuckolls was selected as associate director for Physics. In that role, he helped establish Lawrence Livermore as a state-of-the-art research institution as well as an outstanding nuclear laboratory. In 1988, he became the seventh director of the Laboratory, leading the institution through one of its most difficult periods as the Cold War gradually ended, nuclear testing ceased, and major reductions were made in the nuclear weapons budget. He began transitioning the nuclear weapons program from one that included full-scale nuclear testing to one that relied on laboratory experiments, enhanced simulation, and scientific understanding.

Since stepping down as director in 1994, Nuckolls has been involved with many advisory boards in defense, energy, and applied science. He has also received awards from the secretaries of the Department of Defense and Department of Energy, adding to his earlier Lawrence Award, Edward Teller Medal, and James Clerk Maxwell Prize.

Camille Bilodeau, a Lawrence Fellow and graduate student at the Rensselaer Polytechnic Institute in New York, won a **Best in Biotechnology** award from the **American Chemical Society** at its March 2018 national meeting in New Orleans, Louisiana, for her talk on how small molecules interact with proteins. Bilodeau, who is pursuing her Ph.D. in chemical engineering and is supported by a fellowship from the Laboratory's High Performance Computing Innovation Center and Advanced Simulation and Computing Program, later that year won **first place** in the poster competition at the 31st **International Symposium on Preparative and Process Chromatography** in Baltimore, Maryland, and the **Best Young Investigator Poster Award** at the **Gordon Research Conference on Water and Aqueous Solutions** in Holderness, New Hampshire. The two most recent awards were for her work designing multimodal chromatographic resins for separation of biological products and using classical molecular dynamics simulations to look at small molecule–protein interactions, which have applications in vaccines and drug design.

Abstract

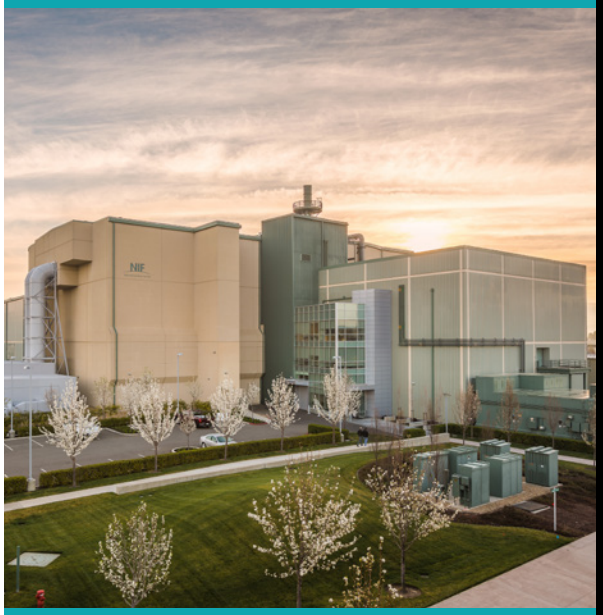
Small Brain-on-a-Chip Offers Big Payoffs

Lawrence Livermore's "brain-on-a-chip" is designed to predict the effects of potentially harmful chemicals, viruses, and drugs on humans without relying on animal or human test subjects. In conjunction with an artificial blood–brain barrier, the device simulates the central nervous system by recording activity from brain cells grown onto a small platform embedded with microelectrode arrays. The brain-on-a-chip holds significant promise for national security and broader applications. For example, the device could be used to determine how soldiers are affected by exposure to chemical and biological weapons and the effectiveness of potential countermeasures and prophylactic pretreatments. The technology could also help predict the effects on the brain from promising drugs designed to treat neurological disorders. The brain-on-a-chip is the latest iteration of the Laboratory's iCHIP (in vitro chip-based human investigational platform) project—a broad initiative at Livermore to advance human health with a focus on understanding, diagnosing, and potentially treating human neural problems and diseases.

Contact: Nick Fischer (925) 422-6144 (fischer29@llnl.gov) or Elizabeth Wheeler (925) 423-6245 (wheeler16@llnl.gov).

U.S. Government Printing Office: 2019/670-075-20003

Laser Facility Celebrates Milestone Anniversary



Over the last 10 years, the National Ignition Facility has made important contributions to the Stockpile Stewardship Program, national security, and high-energy-density science.

Also in June

• The Laboratory's Ambassador Lecture Series brings cutting-edge research to University of California campuses.

• A Livermore-invented, autonomous raft-based system helps the Department of Defense test the readiness of its delivery vehicles for the nuclear stockpile.

• Livermore scientists have developed a promising nerve-agent antidote that permeates the notoriously protective blood–brain barrier.

www.llnl.gov

Coming Next Issue

Science & Technology Review
Lawrence Livermore National Laboratory
P.O. Box 808, L-664
Livermore, California 94551

PRSRT STD
U.S. POSTAGE
PAID
San Bernardino, CA
PERMIT NO. 3330