Lawrence Livermore National Laboratory

Science & Technology REVIEW

April/May 2013

Faster, Cheaper Pathogen Detection

Also in this issue:

- Novel Optical Fibers
- Megatons to Megawatts
- JASPER Fires 100th Shot

About the Cover

As described in the article beginning on p. 4, Lawrence Livermore researchers have developed a technology that within 24 hours can identify any known microbe whose genetic code has been sequenced (about 6,000 species and strains). Called the Lawrence Livermore Microbial Detection Array (LLMDA), the technology combines big data—innovative bioinformatics—with a tiny device called a microarray. LLMDA is being used to identify viruses and bacteria that are correlated with high cancer risk, vaccine safety, and defense against a bioterrorist attack.

Cover design: George A. Kitrinos

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 operated by Lawrence Livermore National Security, LLC (LLNS), for the Department of Energy's National Nuclear Security Administration. LLNS is a partnership involving Bechtel National, University of California, Babcock & Wilcox, Washington Division of URS Corporation, and Battelle in affiliation with Texas A&M University. 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) 423-3432. Our e-mail address is str-mail@llnl.gov. *S&TR* is available on the Web at str.llnl.gov.

National Nuclear Security Administration

Prepared by LLNL under contract DE-AC52-07NA27344

Science & Technology REVIEW

April/May 2013

Lawrence Livermore National Laboratory

Contents

S&TR Staff

Scientific Editor
A. J. Simon

Managing Editor
Ray Marazzi

Publication Editor
Pamela MacGregor

Writers
Monica Friedlander, Arnie Heller, Caryn Meissner, and Ann Parker

Art Director
George A. Kitrinos

Proofreader
Carolin Middleton

Print Coordinator
Charlie M. Arteago, Jr.

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.

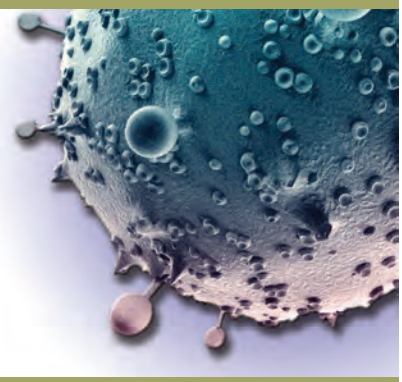
S&TR is available on the Web at str.llnl.gov

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-52000-13-4/5
Distribution Category UC-99
April/May 2013

Feature



Research Highlights

Departments

Uncovering the Biological Fate of Silica Nanoparticles

Livermore researchers Mike Malfatti, Heather Palko, Ed Kuhn, and Ken Turteltaub used accelerator mass spectrometry (AMS) measurements to investigate the relationship between administered dose, pharmacokinetics, and long-term biodistribution of carbon-14-labeled silica nanoparticles (SiNPs) in vivo. Because of their unique properties such as monodispersity, large surface area, and high drug-loading efficiency, SiNPs have been developed for a vast array of biomedical uses such as optical imaging, cancer therapy, targeted drug delivery, and controlled drug release for genes and proteins.

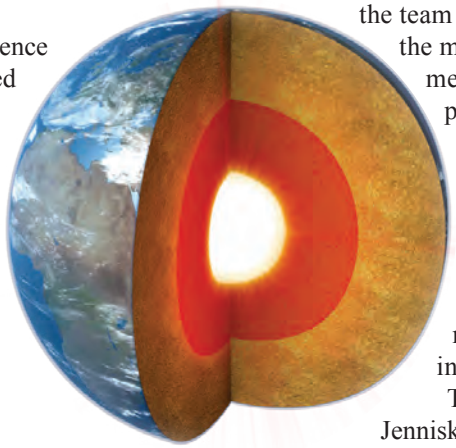
However, the increasing use of nanoparticles for a wide variety of commercial, industrial, and biomedical applications has led to safety concerns. Studies have shown that inhalation of microcrystalline silica may be linked with the pulmonary disease silicosis in humans. Chronic inhalation studies in rats have shown an association with pulmonary fibrosis and cancer, and exposure to microscale amorphous silica has been linked to inflammation, granuloma formation, and emphysema. Scientists want to better understand the interactions of SiNPs with biological systems.

The Livermore pharmacokinetics analysis showed that SiNPs were rapidly cleared from the circulatory system (the "central compartment" in pharmacokinetic models) and were distributed to various body tissues, where they persisted over the eight-week study. These results raise questions about the potential for bioaccumulation and associated long-term effects. The team's findings appeared in the October 17, 2012, edition of *Nano Letters*.

Contact: Mike Malfatti (925) 422-5732 (malfatti1@llnl.gov).

Oxygen to the Core

An international collaboration involving Lawrence Livermore has discovered that Earth's core formed under more oxidizing conditions than was previously predicted. While scientists know that Earth accreted from some mixture of meteoritic material, they have not been able to quantify precisely the processes that led to the separation of various chemical elements to form Earth's mantle and core. The new research defines how these materials may have been distributed and transported in the early solar system.



The team conducted a series of laser-heated diamond-anvil-cell experiments at high pressures (350,000 to 700,000 atmospheres) and temperatures (2,827 to 4,127°C). Results demonstrated that with increased oxygen, a slight reduction of siderophile elements (such as vanadium and chromium) and moderate depletion of nickel and cobalt would result during core formation, as inferred from geologic measurements. Livermore geophysicist Rick Ryerson says, "A model in which a relatively oxidized Earth is progressively reduced by oxygen transfer to the core-forming metal can reconcile both the need for light elements in the core and the concentration of siderophile elements in the silicate mantle. The model suggests that oxygen is an important constituent in the core."

Because core formation and accretion are closely linked, constraining the process of core formation allows researchers to place limits on the range of materials that formed our planet and determine whether the composition of those materials changed with time. Other teams members include Julien Siebert and Daniele Antonangeli (former Livermore postdoctoral researchers) from the Université Pierre et Marie Curie, and James Badro (a faculty scholar at Livermore) from the Institut de Physique du Globe de Paris. The research appeared in the January 10, 2013, edition of *Science Express*.

Contact: Rick Ryerson (925) 422-6170 (ryerson1@llnl.gov).

Meteorite Made Up of Rare Material

A consortium of scientists including Lawrence Livermore's Gary Eppich has determined that the Sutter's Mill Meteorite is the most pristine sample yet collected of the rare Carbonaceous-Mighei (CM) chondrite class of meteorites. CMs contain largely unaltered materials from the dawn of the solar system. The Sutter's Mill Meteorite had the force of 4 kilotons of TNT on its descent over the towns of Coloma and Lotus in northern California when it hit Earth on April 22, 2012.

Through a series of tests including x-ray and isotopic analyses, the team looked at 1 kilogram—the amount recovered on the ground in the form of 77 meteorites—of the 45,000-kilogram Sutter's Mill giant. Eppich's contribution focused on x-ray fluorescence spectrometry, which allowed the team to rapidly and nondestructively determine the major and trace element composition of the meteorite. This technique uses a powerful primary x-ray beam to cause the sample to produce secondary x rays, which are characteristic of the chemical composition of the sample. These data were useful in characterizing the meteorite on the basis of its chemical composition. "We believe we've identified the point of origin of these relatively pristine samples of solids formed in the early solar system," says Eppich.

The team, led by meteor astronomer Peter Jenniskens of the SETI Institute and the NASA Ames Research Center, believes a good candidate source region for CM chondrites is the Eulalia asteroid family, recently proposed as a source of primitive C-class asteroids in orbit that pass Earth. Team members concluded the meteorite was a composite of bits and pieces from different asteroids that collided in space. The research was reported in the December 21, 2012, issue of *Science*.

Contact: Gary Eppich (925) 422-5731 (eppich1@llnl.gov).

Commentary by Glenn A. Fox

Team Science Successfully Identifies 6,000 Bugs Simultaneously

SINCE its inception more than 60 years ago, Lawrence Livermore has earned a reputation for technical advancements made largely through "team science," a strategy successfully pioneered by E. O. Lawrence. In more recent times, this philosophy has been proven once again successful when biologists, engineers, and computer scientists teamed up to deepen understanding of human cells and their response to not only agents of disease (pathogens) but also environmental insults such as radiation and chemical agents.

Long before the biotechnology industry took off, Livermore multidisciplinary teams were designing high-speed electrophoresis systems for analyzing biological samples based on their size and electrical charge, developing automated high-speed flow systems for sorting and analyzing chromosomes, and unraveling the secrets of chromosome 19 as part of the Human Genome Project. More recently, multidisciplinary teams have simulated for the first time the electrophysiology of the human heart, developed an implantable retinal prosthesis, and formulated a West Nile Virus vaccine using Livermore's breakthrough nanolipoprotein technology.

As described in the article beginning on p. 4, the latest development by such a team is the Lawrence Livermore Microbial Detection Array (LLMDA). This compact system can detect and identify within 24 hours all bacterial, viral, fungal, and protozoan pathogens for which the genome is known—about 6,000 species and strains. LLMDA uses probes consisting of short stretches of RNA or DNA to help uniquely identify the pathogens contained in a clinical or environmental sample. These probes are selected using a set of algorithms developed by Livermore bioinformaticists.

LLMDA has a wide range of applications in such areas as public health, biodefense, and product and food safety. In particular, our bioinformaticists have been on the front lines of the nation's biodefense effort since 2001. Because early detection and unmistakable identification are crucial to limiting the potentially catastrophic human and economic costs of a bioattack, Livermore researchers have developed new methods to quickly identify pathogens that could be used to sicken or kill urban populations, livestock, or crops.

The concept of a computerized system to scrutinize a pathogen's genetic code and select telltale portions for identification began in 2000 when we laboriously developed a method for detecting the bacterium that causes anthrax. This work continued when we developed assays for detecting likely bioterrorism agents as part of a biosecurity system deployed by the Department of Homeland Security at the 2002 Winter Olympic Games in Salt Lake City. Our team reasoned that an automated method could compare targeted pathogen genomes against all other sequenced microbial genomes to reveal which regions of DNA were unique to the pathogens of interest. With Laboratory Directed Research and Development funding, scientists developed a computerized process that has now reached its fullest potential to date with the LLMDA system.

LLMDA dispenses with the need to wait days or even weeks for positive identification of one or many pathogens. Such speedy turnaround could save many lives in the event of a bioterrorist attack or a deadly pandemic such as the 1918 flu that killed more than an estimated 50 million people worldwide. The device also could realize significant cost savings in routine health care by readily identifying bugs causing the common cold, influenza, and other sicknesses.

The new detection system is a fine example of translational research, which applies basic science findings to practical applications that enhance human health. Our translational research portfolio is packed with similar efforts. For example, we are working on a radically different method to test the safety and effectiveness of potential medical countermeasures to biological or chemical attacks. Traditionally, promising new treatments are tested first in time-consuming animal tests. However, animal models are not always accurate predictors of human response. A team of engineers, chemists, and biologists is creating a system that combines human cells, tissue engineering, and microfluidics to reproduce the human physiological response to neurological toxin exposure. We call the device the In Vitro Chip-Based Human Brain Investigational Platform, or iCHIP, and it lays the foundation for the ultimate objective of using human tissue–based assays to rapidly assess new drugs.

Devices such as LLMDA and iCHIP represent Livermore's continual strive toward innovative applications of science and technology that make a difference for the nation.

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

A Faster and Cheaper Method to Detect Agents of Disease

Livermore's pathogen detection technology identifies nearly 6,000 different microbes within 24 hours.

SPEEDY, accurate identification of pathogens—the viruses, bacteria, and fungi that cause disease—is becoming increasingly important. Infectious diseases pose a growing threat to public health due to population growth, international air travel, bacterial antibiotic resistance, and other factors. In addition, forensic experts are increasingly concerned that pathogens, perhaps genetically engineered, could be released deliberately by terrorist organizations or rogue states.

While several techniques exist for identifying pathogens via their genetic code, most of these methods are too costly or slow to efficiently analyze clinical and environmental samples that may contain hundreds or even thousands of different microbes. Lawrence Livermore researchers have developed a technology that rapidly identifies any known microbe whose genetic code has been sequenced. Called the Lawrence Livermore Microbial Detection Array (LLMDA), the technology combines innovative bioinformatics (the discipline of analyzing biological data using computational tools) with a tiny device called a microarray.

Livermore scientists analyzed the genetic code of every microbe that has been sequenced (about 6,000 species and strains in all) and then selected the roughly 360,000 most important genetic markers. In one microarray configuration, 360,000 probes—short stretches of DNA or RNA that complement the isolated genetic markers—are arrayed in a microscopic square grid on a 2.5- by 7.5-centimeter glass slide. When a fluorescently labeled fluid sample containing the genetic material of microbes contacts the microarray's probes, only the squares with DNA or RNA unique to a particular organism are activated. The activated squares produce a fluorescent pattern, from which species present in the sample are identified. In this way, multiple pathogens are detected simultaneously, with typical processing times of less than 24 hours. The current-generation LLMDA can identify 3,111 viruses, 1,967 bacteria, 94 protozoa, 136 fungi, and 126 archaea (primitive bacteria).

In trials for government agencies, international researchers, and health-product companies, LLMDA has accurately

and rapidly identified bacterial and viral pathogens present in human and animal clinical samples, environmental samples, and product samples. Government agencies and private research centers are collaborating with Livermore's LLMDA team to identify viruses and bacteria that are correlated with high cancer risk, vaccine safety, and defense against a bioterrorist attack. If widely adopted, LLMDA could allow professionals in medicine, pharmaceuticals, law enforcement, product and food safety, public health, animal health, the military, and global disease surveillance to detect within 24 hours any virus or bacteria that has been sequenced and included among the array's probes.

Current sponsors of the pathogen detection effort include the Department of Defense and the Department of Homeland Security (DHS). Collaborators include the University of California at San Francisco; Blood Systems Research Institute in San Francisco, California; Moffitt Cancer Center in Tampa, Florida; University of Texas Medical Branch at Galveston; National Institute for Public Health and the Environment in Bilthoven, Netherlands; University of California at Davis; U.S. Food and Drug Administration (FDA); Centers for Disease Control and Prevention (CDC); Naval Medical Research Center; and Marine Mammal Center in Sausalito, California.

LLMDA was licensed in 2012 to MOgene, LC, a U.S.-based supplier of DNA microarrays and instruments. The Statens Serum Institut in Denmark has also licensed the device for use as its primary virus-screening tool. A number of other industrial collaborators have expressed interest in licensing LLMDA or in having samples analyzed with the device. Licenses include analysis software. However, licensees must provide their own computer for analyzing results.

Computer scientist Thomas Slezak, who leads Livermore's pathogen bioinformatics team, conceived of LLMDA in 2003 when he learned of an important advance in directly synthesized DNA microarray technology. While microarrays have been around for several years, their use has been limited because each probe was restricted to about 25 DNA or RNA bases. A technology breakthrough has permitted much larger probes (60 or more DNA or

RNA bases). About 10-percent variation in the probes has proven to be acceptable. If the DNA in a sample differs from a probe by up to six bases, the probe can still detect a match. "The earlier, smaller probes were too sensitive to withstand even a single mismatch variation," says Slezak. "Because pathogen strains circulating in nature contain variations in DNA that can differ from the strains already sequenced, it was imperative for us to use a technology that was robust to natural—or engineered—variation.

"Early sponsors were difficult to find," he adds, "because the concept of simultaneously testing for thousands of microbes seemed unrealistic." As a result, work on the first-generation LLMDA began in 2007 as a Laboratory Directed Research and Development project.

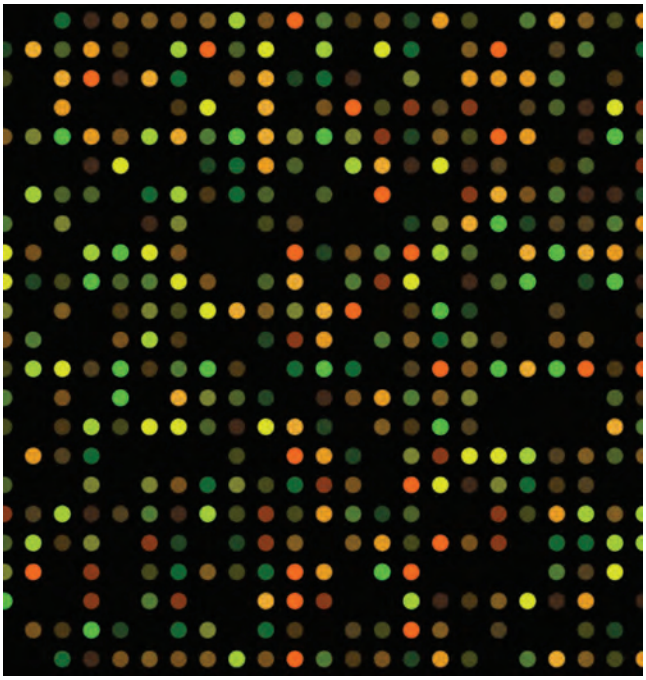
The current development team includes biologist Crystal Jaing, who leads the microarray laboratory work and manages collaborations; bioinformaticist Shea Gardner, who designed the array and probe selection effort; bioinformaticist Kevin McLoughlin, who designed the analysis software; and biologists James Thissen and Nicholas Be, who perform LLMDA experiments. Jaing, Thissen, and Be are part of the Applied Genomics Group of the Biosciences and Biotechnology Division, which has extensive experience in biodetection. Gardner and McLoughlin belong to Slezak's 12-member pathogen bioinformatics team, which develops advanced assays for detecting pathogens. In 2000, this team created the world's first automated pathogen DNA-signature detection system.

How LLMDA Works

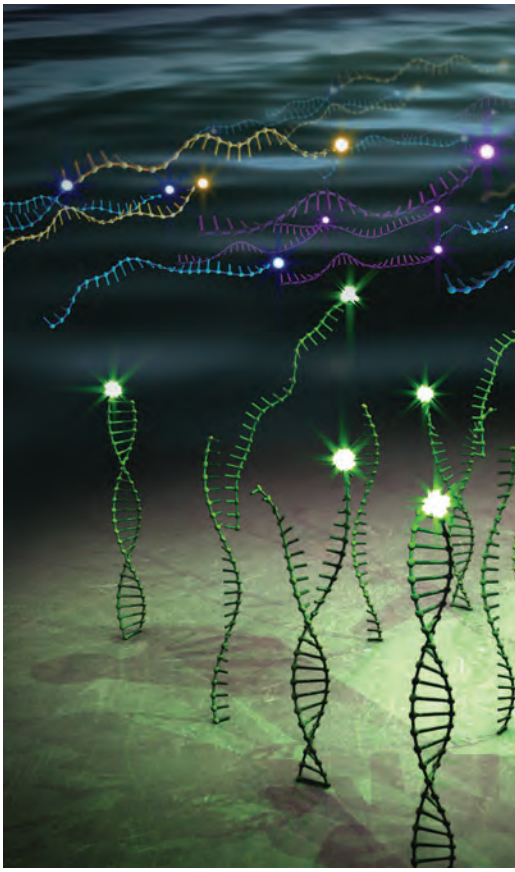
In the past few years, microarrays have attracted increased interest from clinicians, government agencies, and disease researchers because of their ability to analyze foods, pharmaceuticals, and complex clinical and environmental samples. While other nucleic-acid-based microarrays can detect certain classes of microbes, such as viruses, LLMDA is the only one that provides simultaneous characterization of both bacteria and viruses. Says Jaing, "LLMDA is sensitive and specific. It can detect very low concentrations of a particular microbe."

The key principle behind LLMDA is hybridization between two complementary sequences of nucleic acids. The probes have sequences corresponding to segments of an organism's genome and are sprayed onto a glass slide in a manner similar to ink-jet printing. The probes can also be built using chemical photodeprotection technology. Each glass slide contains one or more aggregates of probes, and each aggregate features hundreds of thousands of squares arranged in a grid. Several dozen squares on the grid contain probes that correspond to unique genetic sequences from a single organism.

Several glass slide configurations are possible, ranging from one square grid containing all 360,000 probes for detecting any microbe previously sequenced, to



When a fluorescently labeled sample of fluid containing the genetic material of microbes contacts the Lawrence Livermore Microbial Detection Array's (LLMDA's) probes, only the squares with DNA or RNA unique to a particular organism are activated. The activated squares produce a fluorescent pattern, from which species present in the sample are identified. In this way, multiple pathogens are detected simultaneously, with typical processing times of less than 24 hours.



12 square grids on one slide, each with 135,000 probes. The latter is designed for human clinical purposes and allows for specimens from a dozen patients to be analyzed simultaneously.

The detection process begins with DNA and RNA (from microbes) extracted from a clinical or environmental sample. The DNA and RNA are amplified, if needed (for example, if a bacterium concentration is expected to be quite low, as from an aerosol sample). The genetic material is fragmented and labeled with a fluorescent dye and then applied to the microarray at 42°C for several hours, allowing the fragments to hybridize to their complementary probes. After unbound genetic material is washed off, only strongly hybridized pairs remain, which fluoresce brightly. An automated system, guided by Livermore software, examines the pattern of squares that light up to identify the virus or bacterium, sometimes down to the strain level.

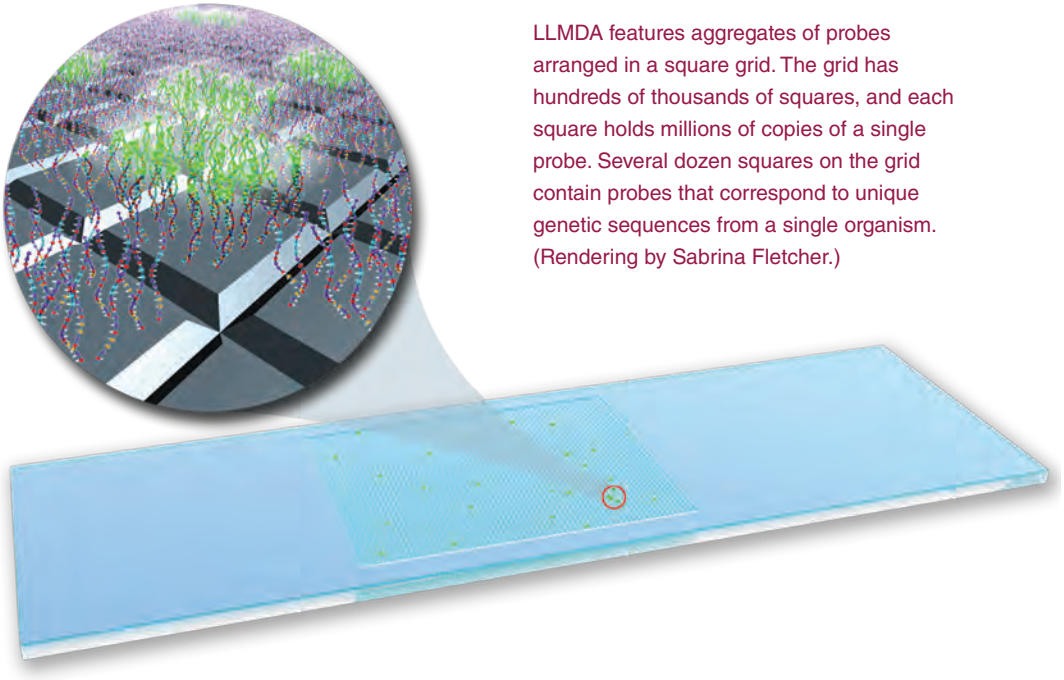
Jaing notes that when compared with the two main microbe detection technologies—polymerase chain reaction (PCR) and DNA sequencing—LLMDA is mid-range in cost, processing time, and sensitivity. PCR analysis is relatively inexpensive, fast, and sensitive for known organisms, but it can detect no more than about 50 different organisms at one time. The PCR assays are too limited for analyzing the thousands of species of pathogens that have been sequenced. In contrast, LLMDA can identify previously sequenced bacteria and viruses as well as new pathogens containing DNA sequences similar to those previously identified in other pathogens. At the other end, DNA sequencing provides the most comprehensive information about pathogens but is costly and can take several days to complete. LLMDA is much faster and cheaper than sequencing.

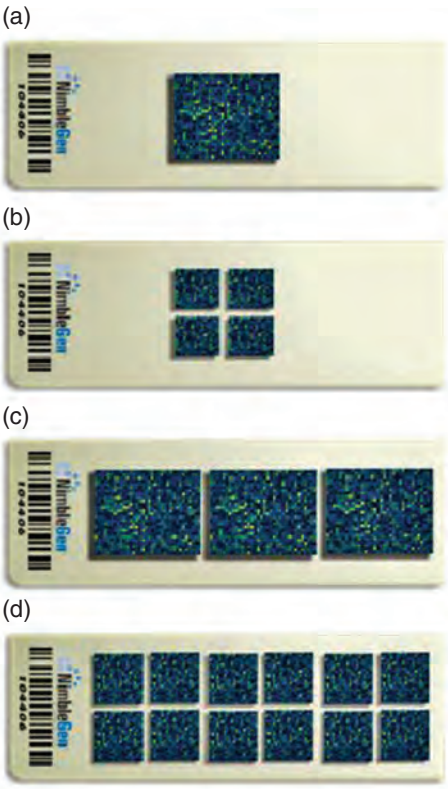
In the rendering below, viral RNA fragments fluorescently tagged from a sample hybridize to LLMDA probes. (Rendering by Kwei-Yu Chu.)

Designing 360,000 Probes

Key to the Livermore technology is the specificity of its 360,000 probes, each selected to help detect one microbe or a set of microbes. A probe consists of typically 50 to 65 nucleotides based on a region of RNA or DNA from the available viral, bacterial, fungal, protozoan, and archaeal genomes. More than 100 conserved and unique probes on average are selected per species. Says Gardner, "Unique parts discriminate one species or strain from another. Conserved parts are the same in all strains. Because conserved parts are so important to the organism, they don't mutate away." Gardner routinely updates the probes with new sequences of bacteria, viruses, and other microorganisms published in public databases as well as new sequences obtained from collaborators. However, the process is not yet automated and can take weeks to perform on an entire year's collection of new data.

LLMDA features aggregates of probes arranged in a square grid. The grid has hundreds of thousands of squares, and each square holds millions of copies of a single probe. Several dozen squares on the grid contain probes that correspond to unique genetic sequences from a single organism. (Rendering by Sabrina Fletcher.)





Several microarray configurations are possible on a single slide, including (a) a single square array containing all 360,000 probes, (b) four arrays of 72,000 probes each, (c) three arrays of 720,000 probes, and (d) for efficient human clinical use, 12 arrays on one slide, each with 135,000 probes.

Gardner developed a "software pipeline" to analyze every sequenced microbe and extract stretches of DNA and RNA that might make good probes. The task required hundreds of thousands of central-processing-unit hours (over about 45 days) using powerful Livermore cluster computers. The pipeline requires more than a dozen steps, each involving a different algorithm. For example, algorithms are used to calculate unique regions of nucleotides (while removing nonunique regions), search out conserved regions within a family, and predict how "sticky" a probe will be to its nucleic-acid complement in the sample.

The algorithms seek to balance the goals of conservation and uniqueness, prioritizing sequences that were conserved within the family of the targeted organism and are unique relative to other families. For example, selecting probes that correspond only to what makes this year's influenza virus unique will fail to identify the virus when it mutates, as viruses tend to do. As a result, Gardner looks for some stretches of genetic material that are conserved. The use of multiple probes also makes it possible to discriminate between strains of the same species. Probes are designed to have no significant matches to the human genome sequence.

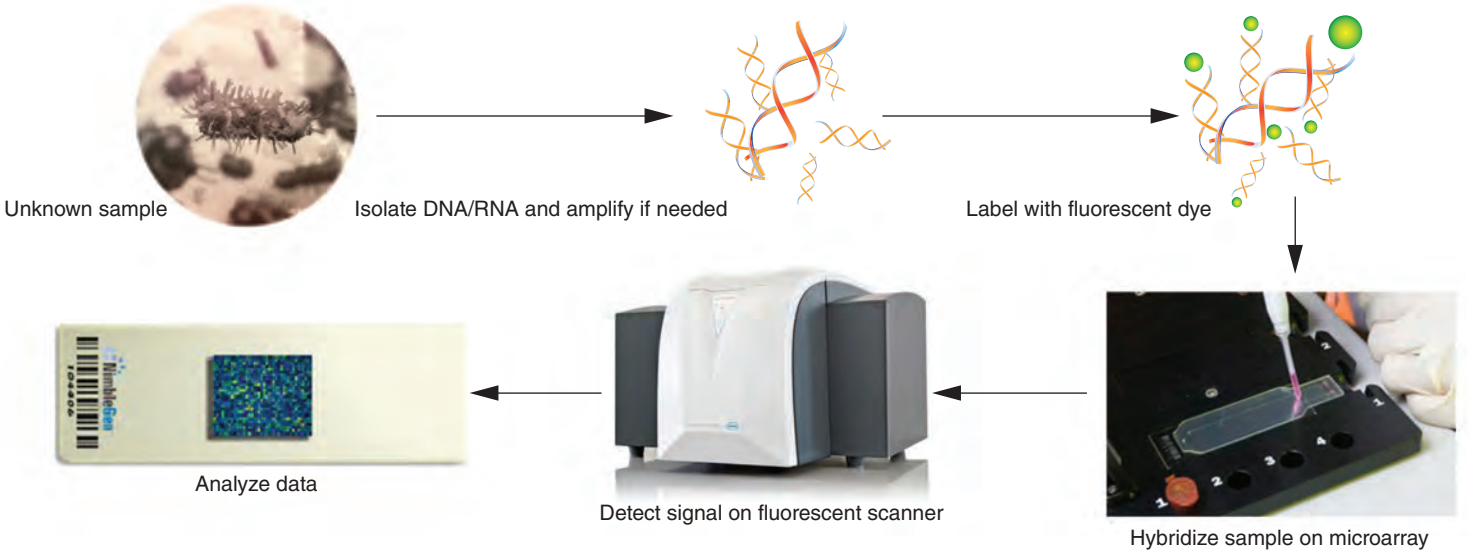
In addition, a set of 2,600 negative control probes has sequences that are randomly generated, but with length and content of cytosine and guanine (two nucleic-acid bases) that match those of the target-specific probes. The negative control probes establish a built-in background rate of fluorescence for each microarray analysis.

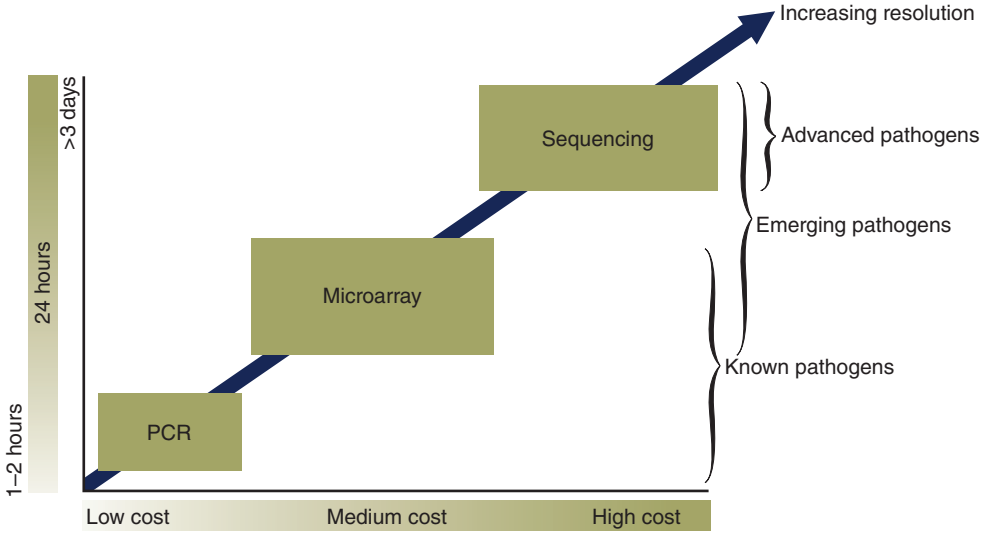
In all, the algorithms scan more than 20 billion bases comprising the genetic code of close to 6,000 species. Looked at another way, the task corresponds to searching through more than 666 million books and locating within each book at least 60 phrases unique to that book. Together, the probes contain data that make up a 60-megabyte file.

Detection Analysis

Analyzing the microarray results requires a workstation with 200 gigabytes

In the LLMDA analysis process, DNA and RNA are extracted from a sample, labeled with a fluorescent dye, and hybridized with the probes arranged on a microarray. After unbound genetic material is washed off, only strongly hybridized pairs remain, which fluoresce brightly. The microarray is then scanned, and the data are analyzed.





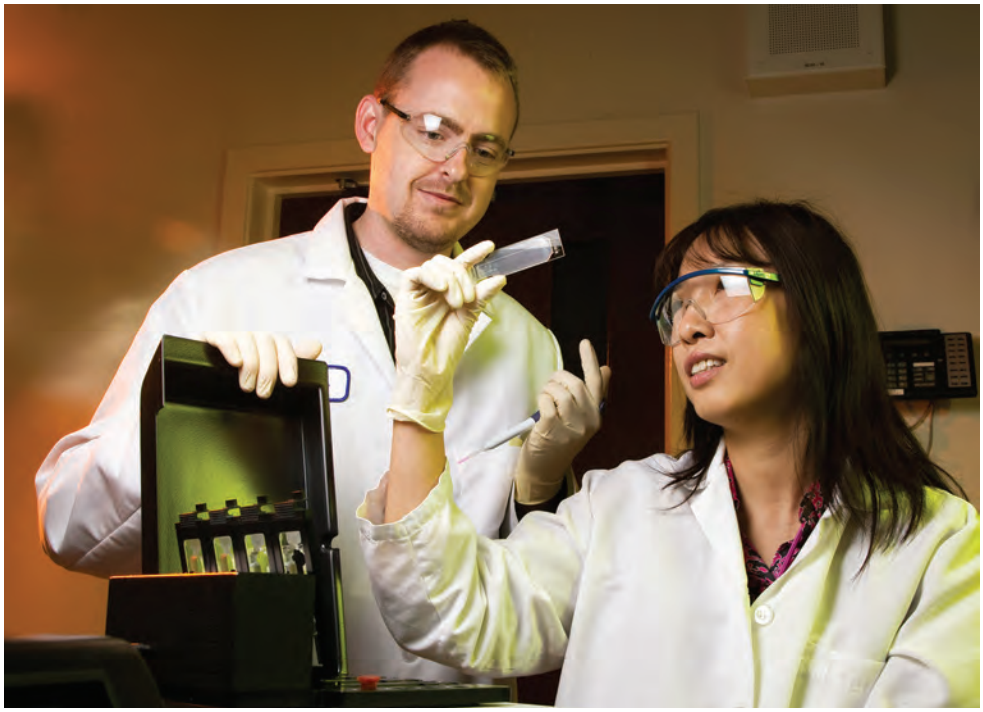
When compared with polymerase chain reaction (PCR) and DNA sequencing, microarrays such as LLMDA are mid-range in cost, processing time, and sensitivity. PCR analysis is relatively inexpensive, fast, and sensitive for known organisms, but it can detect no more than about 50 different organisms at one time. In contrast, LLMDA can identify thousands of previously sequenced bacteria or viruses, including new pathogens containing DNA sequences already identified in other pathogens. Although DNA sequencing provides the most comprehensive information about pathogens, it is costly and takes much longer to complete than LLMDA.

of memory and 12 processors as well as the Livermore-developed analysis algorithm that makes sense of the voluminous data produced by the scan. The analysis begins when the slide containing the hybridized probes is placed in a scanner. A laser scans across the slide's surface, and a photodetector picks up the fluorescing squares. Within a few minutes, an enormous image file of 100 megabytes is built up. Commercial software analyzes the image and produces a file quantifying the fluorescent intensity at each spot.

To identify the organisms that best explain the probe intensities recorded on the image file, McLoughlin developed the composite likelihood maximization algorithm. The computer program searches repeatedly through the database of all sequenced microbial genomes, at each iteration choosing the most likely pathogen to match the fluorescent pattern. In the first iteration, it looks for the target genome that explains the largest portion of the detected probe signals. In each subsequent iteration, the algorithm chooses the organism that explains the largest part of the signal not already explained by the first target. Computer scientists call this kind of algorithm "greedy" because it is always grabbing for the best explanation, then the next most likely explanation, and so on.

The microarray results, ready in 10 to 20 minutes, display a list of predicted targets organized by viral or bacterial family that reflects the most probable organisms corresponding to the detailed fluorescent pattern. For Livermore users, the results are automatically available online via a Web-based interface. After logging on, users can query any LLMDA test and request analysis in various ways. For example, a user may request a list of only the viruses present in a particular sample. When the analysis is complete, the user receives an e-mail with a link to the results.

A system for analyzing LLMDA results has been deployed at DHS's microbial



Biologists James Thissen (left) and Crystal Jaing work with an LLMDA slide that is used to detect nearly 6,000 different microbes.

forensics center. Another is deployed at the Statens Serum Institut, where the system is reportedly identifying viruses more efficiently than numerous PCR tests. This year, the Livermore team is supporting a large-scale evaluation of LLMDA at both CDC and the U.S. Army Medical Research Institute of Infectious Diseases.

Health, Biodefense Applications

In the area of biodefense, the LLMDA platform provides a "safety net" for rapid detection of known pathogens that might not be watched for in the first line of defensive systems (for example, BioWatch or the CDC's Laboratory Response Network). It also offers an orthogonal confirmation to PCR recognition of a known pathogen. And, unlike PCR, the platform can provide a rough guess as to the closest strain.

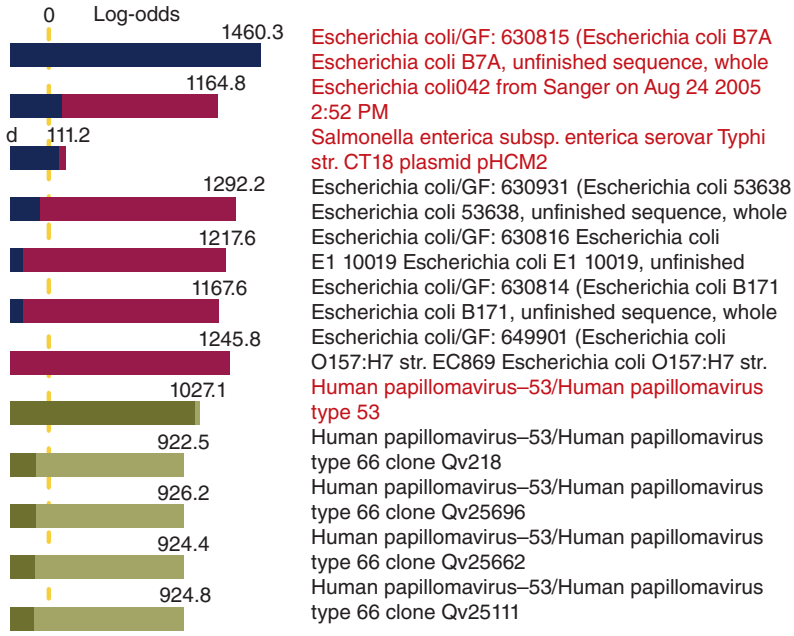
The Livermore team has developed other customized biodefense arrays for DHS that can recognize genes involved in known virulence or antibiotic resistance pathways, detect genetic engineering vectors, and provide very high-resolution phylogenetic strain typing for many key bacterial and viral threat agents. These arrays have been transitioned to the DHS National Biodefense Analysis and Countermeasures Center.

Jaing says LLMDA could prove particularly useful to CDC for tracking emerging diseases, wether they are recently discovered or previously known but causing a new outbreak, such as severe acute respiratory syndrome, or SARS. CDC is now testing a hierarchy for diagnosing unknown pathogens. The center will first use PCR to identify a microbe. If that technique is unsuccessful, the center will turn to LLMDA. If LLMDA does not identify it, meaning the microbe's genetics have not yet been sequenced, the center will use DNA sequencing. CDC has sent researchers to Livermore for training with LLMDA.

The Livermore team is also working with Department of Defense agencies such as the Naval Medical Research Center to identify pathogens in combat-wound samples and the microbial pattern predictive of wound infection and healing. LLMDA has detected clinically relevant pathogens from wound samples more rapidly and accurately than traditional microbiological techniques such as culturing a sample to see if a bacterial colony forms.

In addition, LLMDA has identified viruses and bacteria that are correlated with a high cancer risk to aid in early detection and prevention strategies. For example, LLMDA detected human papillomavirus 16 from cancer samples. The virus causes about 70 percent of cervical cancers and is the leading cause of oral cancer.

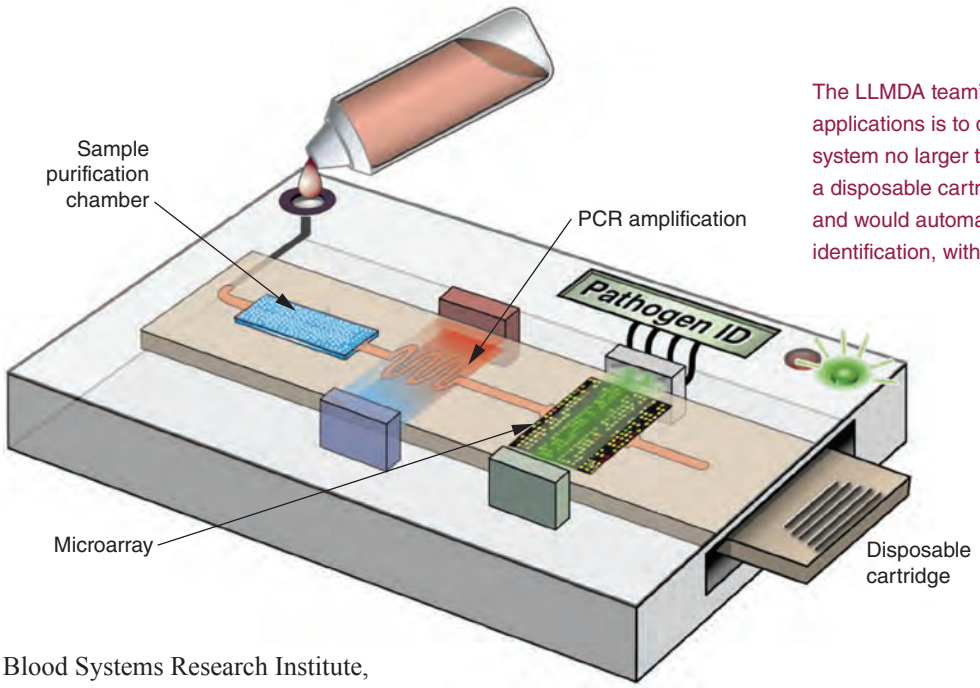
Finally, samples of DNA associated with the remains of Black Death victims from the Middle Ages are being studied with LLMDA to identify the pathogens that may have caused the disease. The LLMDA research team, along with Livermore bioscientist Monica Borucki, is conducting the study in collaboration with colleagues at McMaster University in Canada.



The composite likelihood maximization algorithm identifies the organisms that best explain the probe intensities recorded on an image file. The analytic results, ready in 10 to 20 minutes, are listed by viral and bacterial family in order of the most probable organisms that correspond to the detailed fluorescent pattern. Pathogens are listed within families in decreasing order of likelihood (log-odds) scores. Targets predicted most likely to be present are indicated in red text. The lighter- and darker-colored portions of the bars represent the unconditional and conditional scores, respectively. That is, the darker-colored portion shows the contribution from a target that cannot be explained by another, more likely target above it, while the lighter-colored portion illustrates that some very similar targets share a number of probes, so multiple targets may be consistent with the hybridization signals.

Ensuring Vaccine Safety

An important potential application for LLMDA is ensuring vaccine safety by testing live, attenuated viral vaccines for any potential contaminant viruses. The process of creating vaccines uses components derived from animals and runs the risk of contaminating the vaccine with other viruses (called adventitious). Working with the San Francisco–based



The LLMDA team's goal for biodefense and human and health applications is to develop an extremely compact, fully integrated system no larger than a cell phone. This portable device would feature a disposable cartridge holding an environmental or clinical sample and would automate every task, from sample preparation to pathogen identification, within 1 hour.

Blood Systems Research Institute, Livermore researchers used LLMDA in 2011 to evaluate seven live, attenuated viral vaccines: oral poliovirus, rubella, measles, yellow fever, varicella-zoster (herpes), multivalent measles/mumps/rubella, and rotavirus. The institute's team tested for the presence of adventitious viruses by sequencing all genetic material in the vaccines. LLMDA confirmed the institute's findings (without knowing the sequencing results), but much faster and at much lower cost.

Obstacles Still Remain

Many experts foresee that microarrays will eventually become a popular means for identifying pathogens present in clinical samples as well as ensuring quality control for food and biological products. An LLMDA system containing probes for all human pathogens could replace hundreds of individual PCR assays and eliminate the need for a clinical hypothesis regarding a suspected pathogen. Jaing notes, however, that the capabilities of LLMDA are limited by the genome sequence information available. Many species and strains of known microbial pathogens have not yet been sequenced.

Slezak adds that nontechnical obstacles exist to widespread adoption of LLMDA such as issues associated with medical product regulation, intellectual property, the culture of U.S. medicine, and health insurance. FDA does not have defined protocols for evaluating a device that simultaneously tests for thousands of microbes. Likewise, the U.S. Patent Office does not have experience dealing with such a device.

Also, U.S. physicians do not currently focus on the precise diagnosis of an infectious disease. "The task of the primary physician is to determine if the infection is viral or bacterial. If the infection is bacterial, antibiotics are prescribed," says Slezak. He also notes, "The basic insurance model is one patient, one test, one result, one payment. Insurance companies are unsure how to deal with a test that can detect many different pathogens." However, further enhancements to LLMDA, combined with organizational innovations in medical care, could lead to the widespread use of the device and improve diagnosis speed while reducing costs.

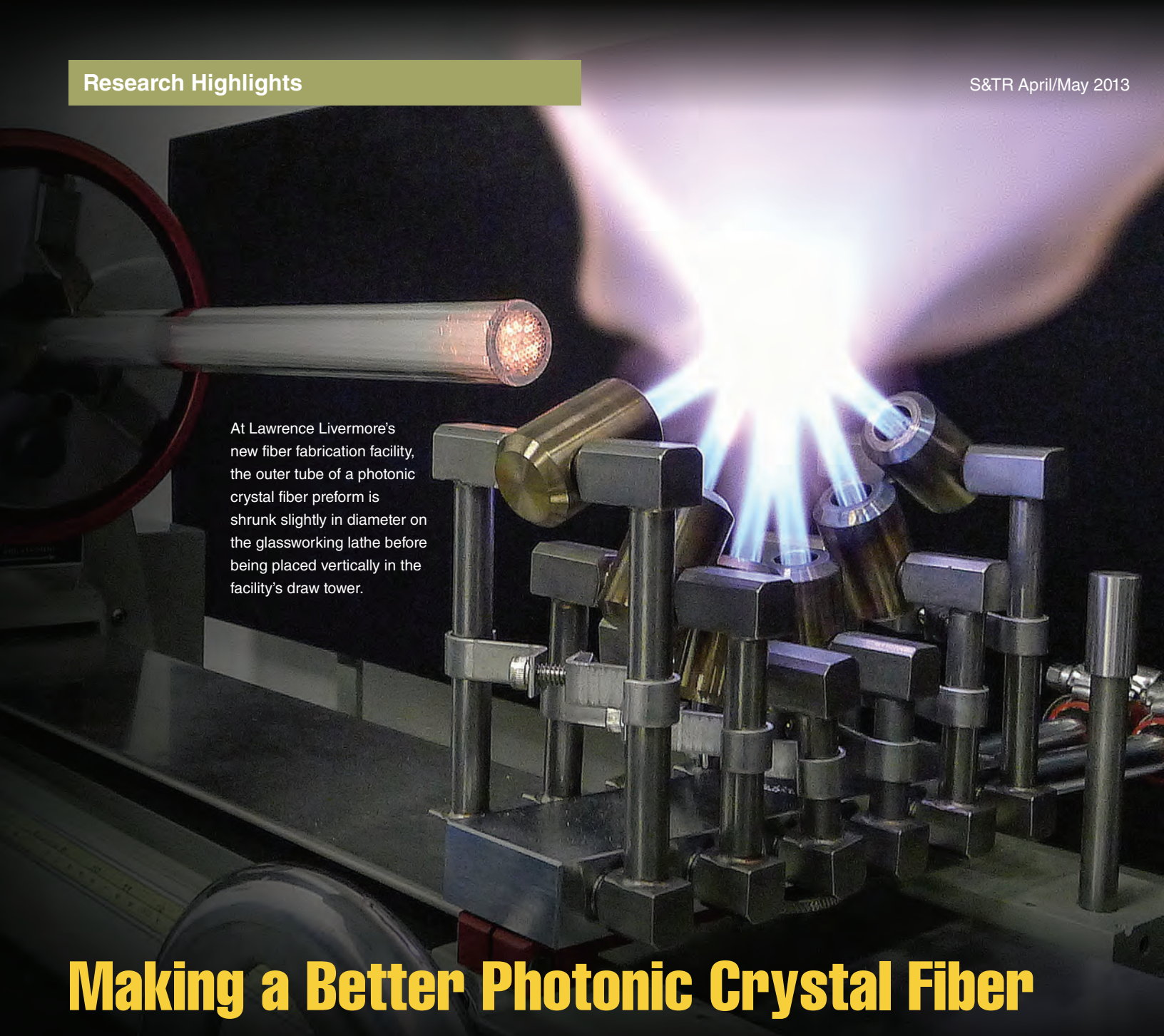
The Livermore team's long-term goal for biodefense and human and animal health applications is to develop an extremely compact, fully integrated system no larger than a cell phone. This portable device would feature a disposable cartridge holding an environmental or clinical sample and would automate every task, from sample preparation to pathogen identification. Such a device would be extremely useful if, for example, a white powder were discovered that looked suspiciously like anthrax. First responders could expect highly reliable results within 1 hour. (Current rapid field tests for pathogens have unacceptably high error rates.)

LLMDA encompasses clever algorithms, microtechnology, and innovative thinking. It is poised to provide a powerful new weapon to fight disease, ensure the safety of vaccines and food products, and provide increased protection from a bioattack.

—Arnie Heller

Key Words: bacteria, bioattack, bioinformatics, Blood Systems Research Institute, Centers for Disease Control and Prevention (CDC), composite likelihood maximization algorithm, Department of Defense, Department of Homeland Security (DHS), Lawrence Livermore Microbial Detection Array (LLMDA), microarray, pathogen, polymerase chain reaction (PCR), sequencing, Statens Serum Institut, U.S. Food and Drug Administration (FDA), virus.

For further information contact Crystal Jaing (925) 424-6574 (jaing2@llnl.gov).



At Lawrence Livermore's new fiber fabrication facility, the outer tube of a photonic crystal fiber preform is shrunk slightly in diameter on the glassworking lathe before being placed vertically in the facility's draw tower.

Making a Better Photonic Crystal Fiber

CULMINATING several years of successful modeling and experimentation with novel optical fibers, scientists at Lawrence Livermore have succeeded in fabricating ribbonlike photonic crystal fibers (PCFs) and using them to create optical lasers, amplifiers, and oscillators. These accomplishments were made possible by the installation of a fiber fabrication facility within the National Ignition Facility (NIF) and Photon Science Principal Directorate. The facility features an 8.2-meter-high draw tower with a furnace capable of temperatures above 2,000°C and offers a unique capability within the Department of Energy (DOE) complex.

In addition to the tower and its furnace, the facility also includes a computer-controlled mechanism for pulling the fibers and a glassworking lathe. With this new capability, Livermore scientists can produce custom optical fibers with intricately detailed cross sections. Unlike the bulk fibers produced by the telecommunications industry, which are completely solid and circularly symmetric, the rectangular-shaped Livermore fibers are manufactured with asymmetric patterns of holes and various materials that run the length of the fiber. These filaments of glass are just a few hundred micrometers thick but sturdy enough to withstand the extreme experimental conditions in high-power,

high-energy lasers. The fiber fabrication facility enables fundamental fiber laser research for future laser missions, such as defense and basic science, and the development of fibers for sensor, medical, and communications applications. Scientists predict a multitude of other applications as advancements are made in the technology.

Withstanding Extreme Conditions

Lasers being developed by Laboratory scientists for missions in defense and basic science typically require high-quality beams that are diffraction-limited and operate at average power (more than 1 kilowatt) and high energy (more than 10 millijoules). For a long time, experimental studies showed that even lasers made of PCFs would fall short by two orders of magnitude for many applications. This limitation, it turned out, lies partly in the circular symmetry of optical fibers first developed in the 1970s for the telecommunications industry. To overcome this obstacle, Livermore scientists created an entirely new waveguide geometry: the ribbonlike PCF. (A waveguide is a device that confines and directs the propagation of electromagnetic waves such as light.) The researchers computationally modeled and tested the concept, and they met many technical challenges, including fabrication and mode-conversion techniques and scalability issues. (See *S&TR,* June 2011, pp. 16–18.)

The light-guiding portion of a ribbon fiber is rectangular with a high width-to-height aspect ratio—similar to a ribbon of light. “By breaking from the telecom norm and making these ribbonlike fibers, we improve our lasers,” says Livermore physicist Mike Messerly, who fabricates the fibers. “The rectangular core increases the surface area for heat removal, thus extending the thermal limit for power scaling.”

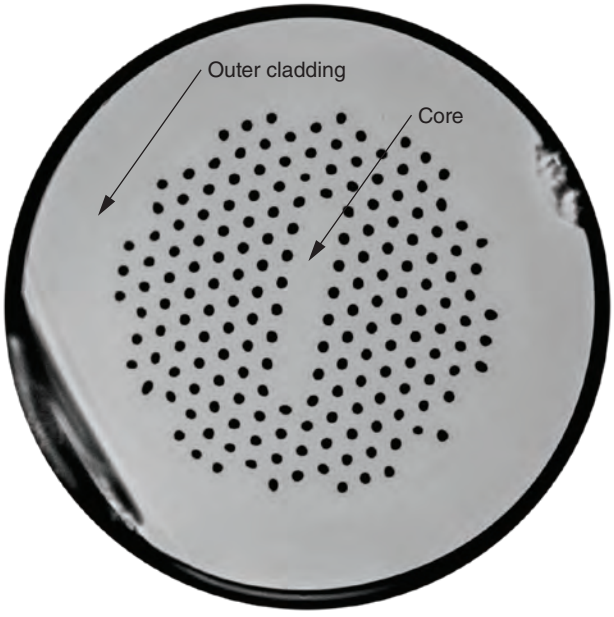
PCFs, a relatively new class of optical fibers, have a built-in microstructure consisting of a series of closely spaced holes that run along the length of the fiber and guide the light while blocking it from exiting the sides. PCFs derive their properties not from the glass composition but rather from the diffractive configuration of the optical holes. The fibers can be fabricated from a single material—pure silica—so they are more resistant to radiation than traditional optical fibers. The configuration of holes can be designed for the specific needs of each application. PCFs can confine light using lower-refractive-index cores or even hollow cores. The hollow-core fibers are particularly useful for Laboratory applications. The hollow replaces glass that can melt and fracture, so the fibers have a higher damage threshold at high temperatures.

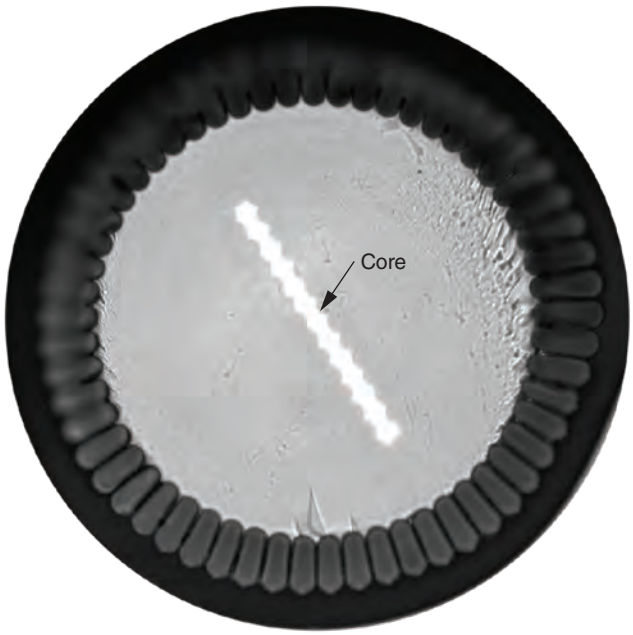
The 8.2-meter-high fiber draw tower gives the Laboratory the capability to manufacture custom optical fibers.

Most importantly, these fiber lasers can scale up to higher laser powers than previously achieved. "The scalability of the new structure is much higher than that of earlier designs," says physicist Jay Dawson, who leads the multidisciplinary team working on developing, fabricating, modeling, and testing the fibers. "We met our goal to demonstrate we could amplify a single, higher-order mode and convert that back to a single beam."

One application for the technology is for use in injection-seed lasers. "For example," says Dawson, "NIF is essentially a giant amplifier. A laser shot begins with a small laser from which a pulse is carved and then amplified in a series of amplifiers until the pulse becomes very powerful." Ideally, Dawson would like to see these fibers used more extensively in injection-seed lasers. He believes future laser facilities would benefit by incorporating the improved power and energy capability enabled by the novel fibers.

When fabricating the fiber, the type of light that it will guide is a major consideration. For basic science applications, pulses of light are needed to create bursts over a very short period of time—a mere 10 nanoseconds of ultraviolet light for inertial-confinement-fusion missions. Even shorter periods are needed for applications in high-energy physics, medicine, and fundamental materials research and development. Transporting these pulses turns out to be challenging for scientists. "If the bursts are energetic enough to melt a target, they might also be energetic enough to melt the fiber," Messerly says. Ultraviolet light, in particular, tends to dissociate the molecules that make up glass. "We need to have a fiber that has a large light-guiding region to prevent that from occurring. We are working on special fibers that can transport extremely high-power lasers and high-pulse energy lasers." These fibers will enable new applications for lasers by allowing light to be efficiently delivered into hard-to-reach places.





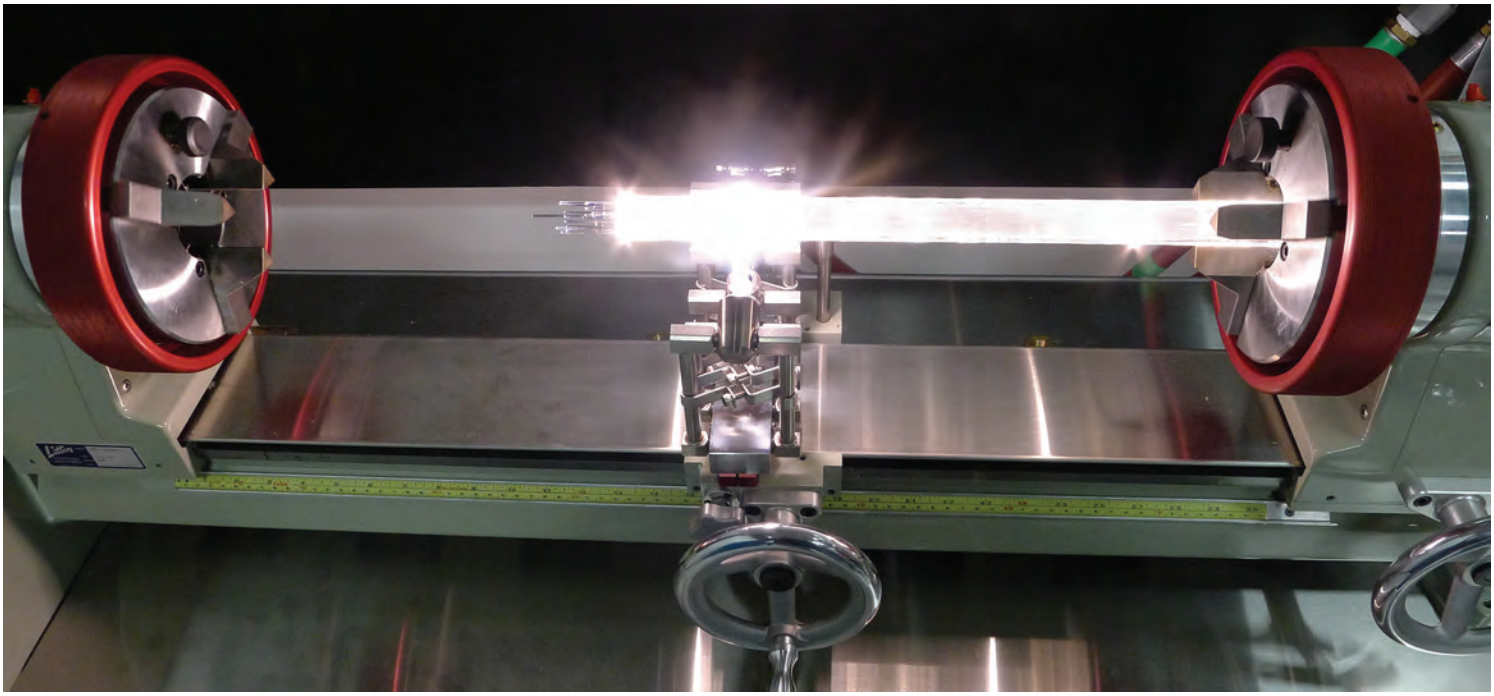
Some of the novel optical fibers being drawn at Livermore have intricate cross sections. They derive their properties from a series of closely spaced holes that run the fiber's length. The configuration of these holes is customized for each application. As shown in these microscope images, the light-guiding portion (core) of a ribbon fiber is rectangular.

A Towering Achievement

First envisioned three years ago, the tower began drawing fibers in the fall of 2011. About two stories high, the tower is small compared to the 10-story-high towers used in the telecommunications industry, whose fibers must span continents. "We do not require such a high tower because the fibers we fabricate for lasers are shorter—about 10 meters long," says Messerly. Researchers have since used the fabrication tower to draw hundreds of kilometers of custom fibers and have produced fiber lasers that are theoretically scalable beyond the limits of conventional circular-core fibers.

In the fiber fabrication process, a glass preform is fed through a tube at the top of the furnace. As the glass drops, it melts and is drawn out. The initial product looks almost like a teardrop-shaped Christmas ornament, but the control system quickly regulates the width of the strand to a constant diameter. The faster the glass is pulled, the thinner and more flexible it becomes.

The fibers are made in a two-step process: First, a hollow tube of glass a few centimeters wide is pulled down to form hollow capillaries about 2 millimeters in diameter. Next, about 200 of these capillaries are stacked together in an array and drawn through the furnace again, this time to a diameter of a few hundred micrometers. Further steps follow to create the ribbon fibers and



Manufacture of the Livermore optical fibers involves multiple steps. Here, a circular, sleeved stack of rods and tubes, already drawn through the tower mechanism, is placed in a glassworking lathe to be tightened and prepared for its next round in the draw tower. The finished fibers will be just a few hundred micrometers thick.

ultimately the laser, which is made with rare-earth-doped glass incorporated into the core.

Future Applications

Scientists have been producing ribbon fiber amplifiers since last summer, providing timely support to the Laboratory's missions. They are now working toward two important nonlaser applications: transport fibers and optical fiber sensors.

Guide star lasers are an example of an application for transport fibers, and the Laboratory has already provided lasers used at the Lick and Keck observatories. A flexible fiber could simplify the transport of guide starlight from the source to the launch point. Existing conventional fibers cannot transport the required power over the required distance. In the field of medicine, hollow-core PCFs could help perform robotic surgery by transporting short pulses of light from a laser into a patient.

Optical fiber sensors may need more research and development before they become feasible on a large scale, but the possible applications are virtually endless. Fiber sensors have already been deployed in downhole oil and gas sensing, and ultralight, ultraprecise fiber-optic gyroscopes are guiding aircraft and drones. In the future, optical fiber current sensors could be used to measure high voltages.

Furthermore, DOE and scientists at SLAC National Accelerator Laboratory have expressed interest in laser-based particle accelerators. "Traditional accelerators based on radio-frequency technology would be scaled down to optical wavelengths by taking a hollow-core optical fiber and shooting light into it to make an accelerator," Dawson says. He believes the technology needs some two decades of further research, and he is on the organizing committee to create a road map for the application of lasers to accelerators.

While some applications of these novel materials are still many years away, Dawson and his team have demonstrated the Laboratory's capability to stay ahead in the area of fiber optics. The unconventional fiber waveguides being developed at Livermore are of great interest to the Department of Defense and DOE for laser missions, and they promise to dramatically change accelerator design for scientific research in this century.

—Monica Friedlander

Key Words: draw tower, fiber laser, ribbonlike photonic crystal fiber (PCF), SLAC National Accelerator Laboratory, waveguide.

For further information contact Jay Dawson (925) 422-1617 (dawson17@llnl.gov).

A Transparent Success
"Megatons to Megawatts" Program

IN 1993, the U.S. and the Russian Federation signed a historic nonproliferation agreement designed to permanently eliminate excess uranium from dismantled Russian nuclear weapons by "recycling" it into fuel for U.S. power plants. Now, just months away from its 20th anniversary, the 1993 U.S.–Russian Highly Enriched Uranium Purchase Agreement is within sight of its negotiated finish line: the conversion of 500 metric tons of highly enriched uranium (HEU)—an amount equivalent to approximately 20,000 nuclear warheads—into low-enriched uranium (LEU). The effort yielded enough reactor fuel to supply 10 percent of the annual electricity in the U.S. since 2000.

The agreement, which demonstrates the commitment of the two countries to their nuclear disarmament obligations as delineated in the Treaty on the Non-Proliferation of Nuclear Weapons, is an unqualified success, and many organizations and individuals deserve plaudits for its achievements. The Department of Energy/National Nuclear Security Administration (DOE/NNSA) and the Russian State Atomic Energy Corporation (Rosatom) negotiated and signed the purchase agreement and the associated implementation documents. The United States Enrichment Corporation (USEC) in the U.S. and Techsnabexport (TENEX) in Russia act as Executive Agents to the agreement and implement the commercial aspects of the program. The national laboratories, including Lawrence Livermore, also play key roles in this international effort, most notably in the monitoring activities that ensure the nonproliferation objectives of the agreement are being met.

Transparency from "Soup to Nuts"

Early in the agreement's history, both countries realized it was vital to set up a process for building confidence that the HEU weapons material was actually being converted to LEU and then further refined into a form suitable for nuclear power. Such an effort required that the conversion processes and the flow of materials be transparent to both countries. DOE/NNSA and Rosatom established the HEU Transparency Program to develop and implement the necessary protocols.

According to Dan Decman, Livermore's program manager for the HEU Transparency Program, Laboratory personnel coordinate the presence of the U.S. monitoring team and the U.S. equipment required to verify the irreversible conversion.

The U.S. monitoring team includes Livermore staff, and the Laboratory is the repository for monitoring data gathered by the team. Additionally, Livermore is responsible for providing health and safety (H&S) support for all U.S. team members.

"The HEU Transparency Program requires that both Russian and U.S. monitors have access to the uranium-processing facilities of each other's countries," says Decman. Russian monitors are allowed access to the Portsmouth Gaseous Diffusion Plant in Piketon, Ohio (which was used by USEC for processing the Russian uranium until May 2001), the Paducah Gaseous Diffusion Plant near Paducah, Kentucky (which was used for uranium enrichment after Portsmouth), and four U.S. fuel fabrication facilities. In turn, U.S. monitors are allowed access to four Russian Federation facilities: Siberian Chemical Enterprises in Seversk, Mayak Production Association in Ozersk, Ural Electrochemical Integrated Enterprise in Novouralsk, and Electrochemical Plant in Zelenogorsk. For Decman and others, several trips to Russia are required each year to verify the material conversion and flow of uranium. The duration of a trip is typically one week, but some past visits have been as long as two months.

The U.S. team is involved in monitoring the entire process in Russia, from "soup to nuts." (See the figure on p. 18.) The Russian HEU starts its journey through the HEU Transparency Program when it arrives in sealed containers at Seversk and Ozersk from the Russian weapons dismantlement sites. The material is in the form of actual weapons parts, so the U.S. monitors must interrogate the contents of the containers and determine what materials are inside as well as the percentage of fissile uranium (uranium-235) without breaking seals or otherwise breaching the containers. Decman says, "We inspect these initial containers, including their seals and receipt documents, and nondestructively analyze the uranium inside to confirm its weapons-grade status." These analyses are performed using a Livermore-developed nondestructive assay (NDA) system (described in "Getting the Assay" below).

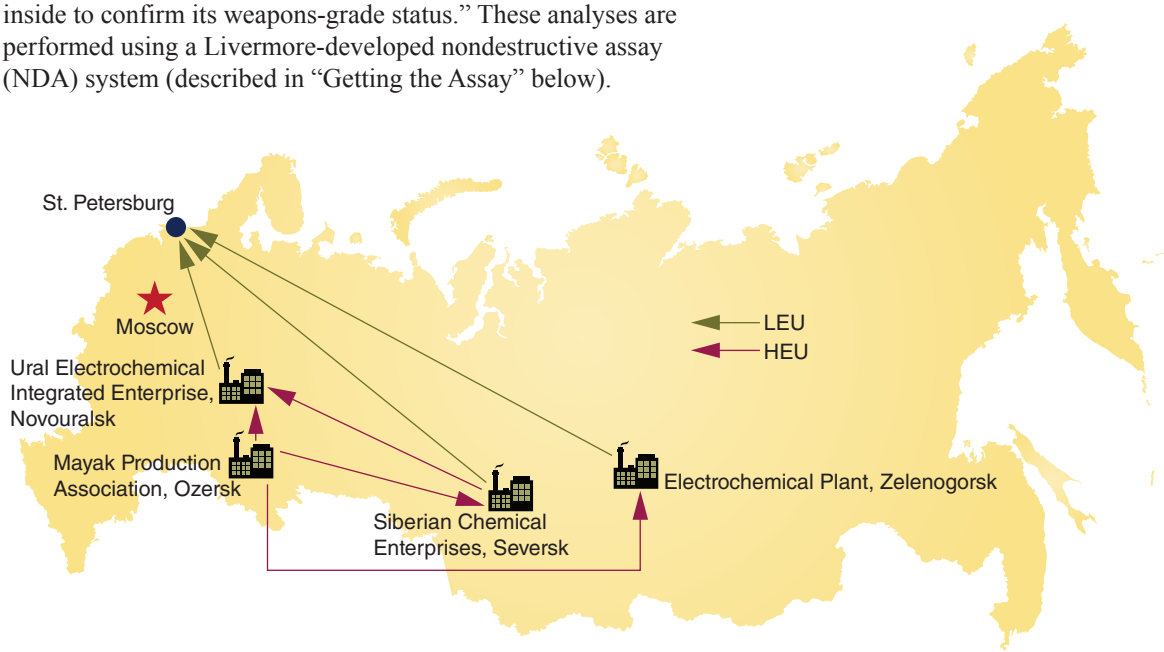
The HEU material, without the container, is machined into shavings, and the shavings are then assayed. "This step ensures that the percentage of HEU in the shavings is consistent with our initial measurements of HEU in the containers," explains Decman.

Next, the shavings are burned in gloveboxes to create oxides. The U.S. monitors can observe the entire oxidation procedure—from the initial feed into and withdrawal from the oxidation equipment to the final analysis of the withdrawn oxides. The monitors apply U.S. tags and seals to the oxide canisters, which are then shipped to Novouralsk or Zelenogorsk for fluorination and blending down. Fluorination and blending down also occur onsite at Seversk.

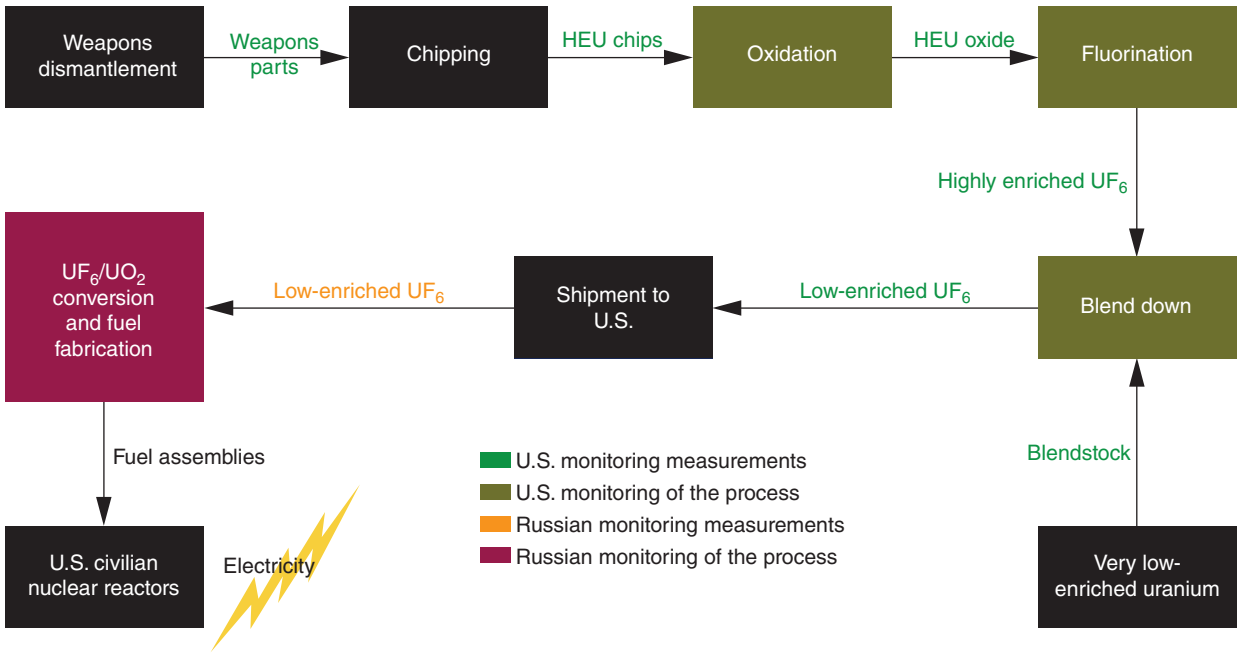
In the fluorination process, the oxides are converted into uranium hexafluoride gas. This gas is combined with "blendstock" LEU, which is very low-enriched uranium containing 1.5 percent of uranium-235. The end result is an LEU product that contains 5 percent or less of uranium-235 and is suitable for reactor fuel. The original HEU is about 90 percent uranium-235.

Getting the Assay

Collecting the data that demonstrate how much uranium-235 exists at each step in the process is challenging. In 1996, the U.S. and Russia agreed on the use of NDA equipment to provide uranium enrichment meter measurements for the HEU Transparency Program. In the enrichment meter method, the enrichment of a sample is proportional to the rate of the 186-kiloelectronvolt gamma rays emitted by the uranium-235. The method, which has been in use since the 1970s, works well for measuring bulk, homogeneous uranium samples. It is the standard technique for uranium enrichment measurements for the



Under the U.S.–Russian Highly Enriched Uranium Purchase Agreement, Russia processes highly enriched uranium (HEU) from dismantled Russian nuclear weapons at four sites: Mayak Production Association, Siberian Chemical Enterprises, Electrochemical Plant, and Ural Electrochemical Integrated Enterprise. HEU is processed into low-enriched uranium (LEU) for peaceful use in the U.S.



The conversion process of Russian HEU into LEU suitable to fuel U.S. nuclear power plants is monitored by teams from the U.S. and Russia at key points in the process. (UF_6 is uranium hexafluoride, and UO_2 is uranium dioxide.)

International Atomic Energy Agency and has a well-established track record.

Livermore's portable NDA system uses a collimated sodium iodide scintillation detector, a portable multichannel analyzer, and a laptop computer. Each NDA system is calibrated with uranium standards either at Livermore or at the Y-12 National Security Complex in Oak Ridge, Tennessee. The U.S. monitors have used these systems since 1997, taking between 2,500 and 3,000 measurements annually.

Since 1999, the program has also used NDA equipment to continuously monitor the blend-down process. The blend-down monitoring system (BDMS), developed by Oak Ridge and Los Alamos national laboratories, measures the enrichment and uranium-235 mass flow rate of the uranium hexafluoride gas as it is mixed with blendstock-LEU and then blended down to form product-LEU. "The blend down is a critical step in the process, and monitoring this material transition satisfies one of the primary nonproliferation goals of the HEU Transparency Program," says Decman.

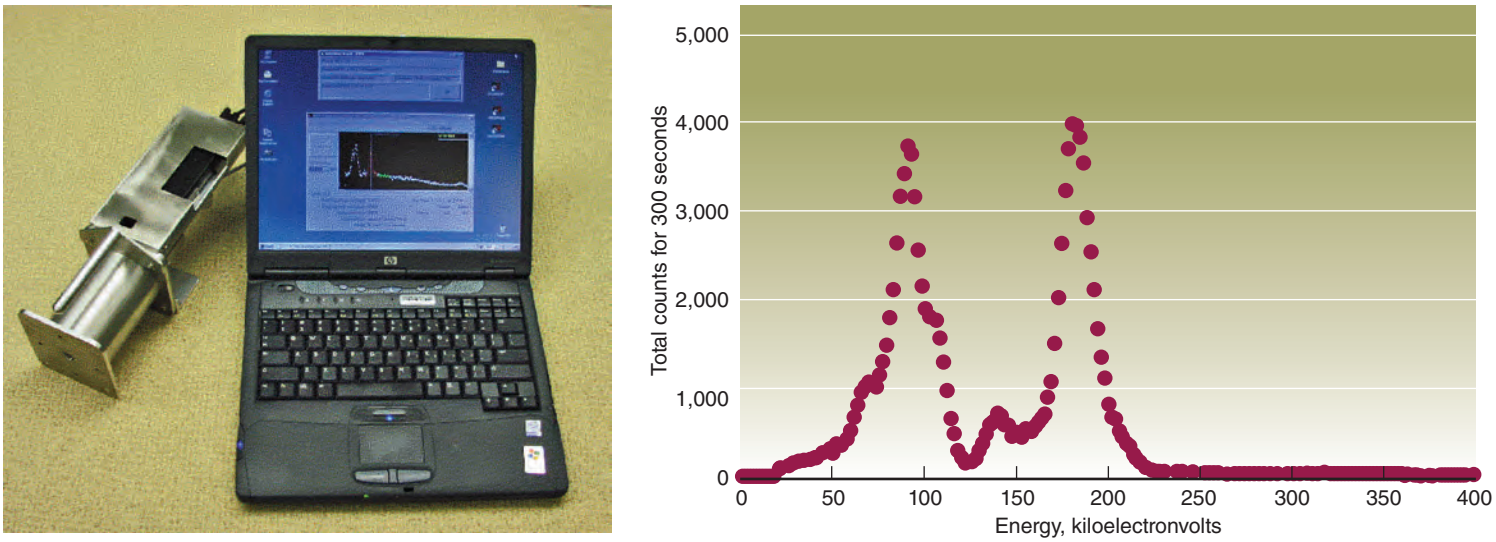
Developers of the NDA systems faced the unusual challenge that the equipment had to be low-tech for the program. "At the national laboratories, we're used to implementing the 'latest and greatest' technology," says Decman. "However, the systems developed for this program had to be simple, and they had to be reliable. The blend-down monitoring systems, which are deployed in Russian plants, need to operate continuously, with very limited access available to the U.S. monitors. The systems also had to be modular in design to accommodate maintenance and repairs in a timely manner."

An Eye on Health and Safety

The Laboratory provides H&S support to the HEU Transparency Program and to all U.S. monitors, including interpreters, who make the long trek to the heart of Russia. Since 1998, Livermore's Radoslav Radev has been the leader of the H&S efforts and has helped to develop a comprehensive H&S Plan, now in its 11th edition. "The plan has evolved as the conditions and regulations in Russia have changed," says Radev.

Included in the plan are the types of radiological and industrial exposures one could encounter from plant to plant, H&S training requirements, and administrative and engineering controls to mitigate potential hazards. The plan also provides information to help monitors acclimate to travel in Russia such as occupational safety signs that may be encountered and general tips on industrial H&S while working in Russian facilities. The H&S Plan is available to monitors 24/7 on the Web.

Livermore is also responsible for external and internal dosimetry service for all U.S. monitors. The Laboratory provides and analyzes thermoluminescent dosimeters that measure radiation doses from external sources. Radev notes that the dosimetry is complicated. "We have to take into account how extended airborne travel at high altitudes and multiple exposures from airport x-ray security screening affect the measurements," says Radev. "Also, some security personnel, particularly in



(left) The portable Livermore-developed nondestructive assay (NDA) system provides uranium enrichment measurements for the HEU Transparency Program. The low-cost, low-maintenance system is constructed of commercially available components. (right) The graph shows the spectrum of a 93-percent enriched U.S. uranium oxide standard, acquired with the portable NDA system. The count time was 300 seconds.

airports, are unfamiliar with the dosimeters carried by U.S. monitors. We've had cases in which the traveling dosimeters have been questioned, delayed, and even removed." Because monitors are not allowed to enter a nuclear facility without a dosimeter, emergency dosimeters are maintained at two locations in Russia. "We have to be prepared," says Radev. "Each trip is approved well in advance, and its duration and timing are fixed."

At the conclusion of each trip, U.S. monitors provide a bioassay sample that is used by Livermore to determine any potential internal dose from uranium compounds that may have entered the body via ingestion, inhalation, or open wounds. Livermore's external and internal dosimetry procedures are DOE-lab accredited and meet federal requirements. The Laboratory provides each monitor with an annual dose report and provides HEU Transparency Program management with post-trip dose reports, quarterly bioassay reports, and annual health physics reports.

Winding Down

This year, the U.S.–Russian Highly Enriched Uranium Purchase Agreement and the accompanying HEU Transparency Program are winding down in an orderly fashion and on schedule. The oxidation process is now in its last phase. Most of the fluorination will be complete by the end of summer. In the fall, the final blend downs will take place, bringing the program to an end. Decman notes, "This enduring mission over the years has been a team effort of many national laboratories and an amazing collaborative effort. It's difficult to think of a similar program that has had this level of success over such a stretch of time."

Both sides can no doubt agree that the two-decade effort has been a great achievement. Although the blend-down and monitoring activities are ending, Rosatom and TENEX plan to continue making LEU at their facilities, selling it directly to U.S. utilities. In fact, TENEX already has signed contracts to provide fuel for reactors in the U.S., once the agreement is completed. The HEU Transparency Program deserves a portion of the accolades for the agreement's achievements. The efforts of Livermore and the other organizations involved served to assure both governments that the HEU did indeed come from dismantled weapons and the resultant LEU did indeed become reactor fuel. Thanks to the program, some of the world's most destructive weaponry was converted into the very electricity that powers our homes, schools, factories, and businesses.

—Ann Parker

Key Words: blend-down process, HEU Transparency Program, highly enriched uranium (HEU), low-enriched uranium (LEU), nondestructive assay (NDA), nuclear nonproliferation, U.S.–Russian Highly Enriched Uranium Purchase Agreement.

For further information contact Dan Decman (925) 422-3898 (decman1@llnl.gov).

The Joint Actinide Shock Physics Experimental Research (JASPER) Facility's two-stage gas gun produces temperatures and pressures high enough to study plutonium's properties at conditions important to stockpile stewardship.

The Shot Heard 'Round the Complex

PLUTONIUM is an enigmatic material, and it does not give up its secrets easily. A key component of nuclear weapons, plutonium undergoes physical changes during a nuclear event and also as part of its natural aging process. (See *S&TR,* December 2012, pp. 11–14; May 2007, pp. 12–20.) A thorough understanding of plutonium's properties, including its equation of state (EOS), underpins the National Nuclear Security Administration's Stockpile Stewardship Program and is a primary focus of research at Lawrence Livermore.

For many years, scientists conducted underground nuclear testing to assess weapons performance, including how materials such as plutonium behave under these conditions. In the absence of this experimental capability, scientists have turned to advanced supercomputers to simulate aspects of nuclear weapon performance in detail. However, these massive simulations require precise data on the properties of plutonium as input. Data derived from historic nuclear tests have been valuable but are limited and not physically reproducible.

Gas guns are a proven tool for studying material behavior under sudden high temperatures and pressures. They enable researchers to subject various materials to a broad range of conditions, and the data returned from these experiments can be extremely accurate. In 2003, the Laboratory began its first set of plutonium experiments on the two-stage gas gun at the Joint Actinide Shock Physics Experimental Research (JASPER) Facility located at the Nevada National Security Site. (See *S&TR,* June 2004, pp. 4–11.)

JASPER is a key scientific tool for investigating the physical properties of metals and actinides, specifically for studying plutonium at conditions relevant to the performance of nuclear weapons (see the movie at str.llnl.gov/content/pages/april-2013/images/jasper_facility.mov). The facility provides a much more cost-effective option for gathering data in comparison

to underground testing. On September 25, 2012, Livermore researchers fired the gas gun's 100th shot in an experiment that further improved their understanding of plutonium's properties and ushered in the next era of plutonium-based research.

A High-Powered Process

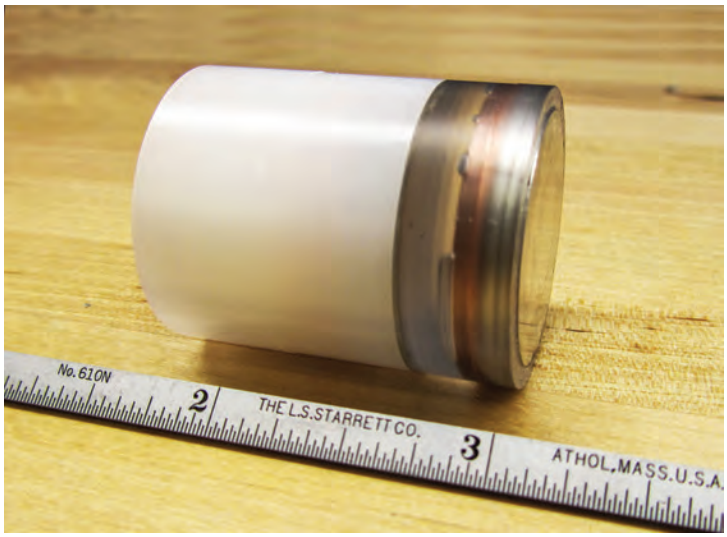
JASPER's 20-meter-long, two-stage gas gun uses a combination of gunpowder and a light gas, such as hydrogen, to fire projectiles at up to 8 kilometers per second into precisely engineered targets about the size of a quarter (see the movie at str.llnl.gov/content/pages/april-2013/images/shot.mov). The gunpowder propellant pushes a deformable piston down a gas-filled tube, and as the piston travels, it compresses the gas inside the tube to thousands of pounds per square inch. Once the gas reaches a certain temperature and pressure, a valve bursts, and the gas accelerates a projectile, or impactor, down another tube to the target.

Livermore physicist and JASPER chief scientist Neil Holmes says, "It is like slamming a bullet the size and weight of an ice cube into a target at 18,000 miles per hour [8,000 meters per second], 10 times faster than a bullet leaving a rifle." The impact of the projectile on the target drives the experiment. The event sends a one-dimensional shock wave through the target material, achieving pressures of millions of atmospheres and temperatures of thousands of kelvins. The entire experiment happens in 300-billionths of a second. Scientists use an array of sophisticated diagnostics connected to the gas gun and attached to each target to measure the material's response.

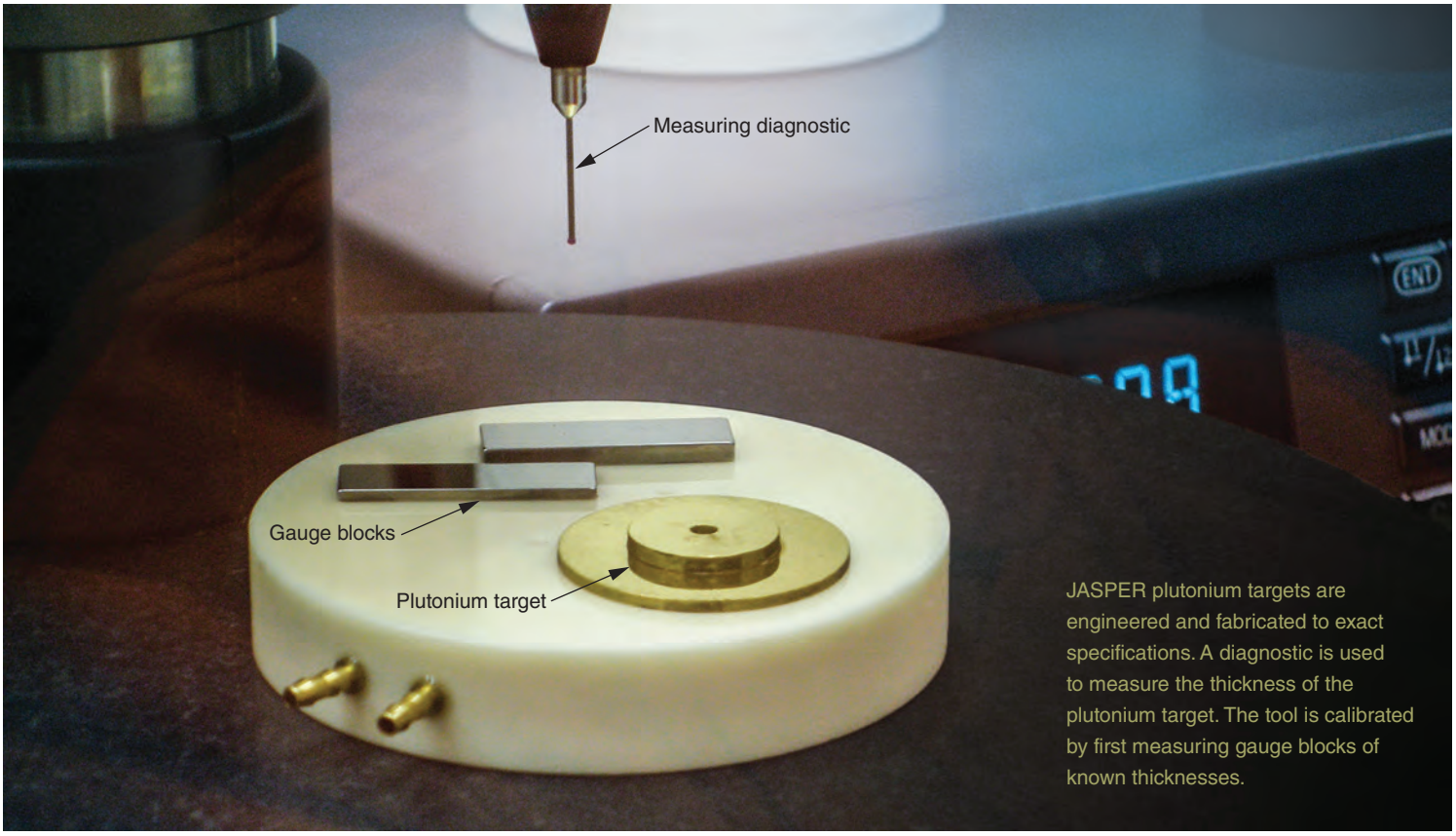
The primary goal of JASPER experiments is to measure plutonium's EOS. "EOS is the relationship between the pressure, density, and temperature of plutonium under a broad range of conditions," says Holmes. Plutonium is considered one of the most interesting of all the elements because of its remarkable properties and incredibly complex phase diagram. When the material is pressurized and heated, its crystalline structure changes at equilibrium—called a phase—causing it to act like a different metal at every turn. JASPER experiments enable scientists to observe and study known and unknown phase transformations based on experimental parameters. With every JASPER experiment, scientists try to identify a critical part of an unmapped region of plutonium's phase diagram.

The experimental conditions produced in a JASPER shot are exacting, and the results gathered are extremely precise. "JASPER provides accurate data that is beyond reproach," says Holmes. The needs of the Stockpile Stewardship Program demand measurements with an accuracy within 1 percent, and JASPER exceeds this requirement. "Each experiment includes a high level of rigor, analysis, and design to meet the expected goals of a shot," he adds. "Thus, each experiment must only be performed once to obtain the necessary data."

According to Randy Thomas, field manager for JASPER, the accuracy of data comes down to three main ingredients: the impactor, the target, and the diagnostics. "All three components have to be precisely fabricated and aligned to achieve such accuracy," says Thomas. Typically, experiments involve solid-metal impactors that produce a single-wave impulse. However, more recent experiments have benefited from a novel impactor developed in part by Holmes with other Livermore physicists several years ago. Called graded-density impactors (GDIs), these



(left) The graded-density impactor (GDI) combines up to 100 metallic layers of varying densities. This particular GDI comprises copper on the bottom, a combination of copper and magnesium in the middle, and magnesium on top. (right) The GDI is pressed into a plastic case to create the complete "bullet" (about 3.8 centimeters or 1.5 inches long) that travels down the gas gun. Only the metal plate at the top of the projectile impacts the target.



JASPER plutonium targets are engineered and fabricated to exact specifications. A diagnostic is used to measure the thickness of the plutonium target. The tool is calibrated by first measuring gauge blocks of known thicknesses.

multilayered "bullets" made of various materials allow researchers to carefully construct the pressure profile of experiments.

"The impactors are fabricated using materials with different densities, which allows us to vary the pressure pulse that moves through the target," says Thomas. GDIs help scientists achieve the exact temperature and pressure of the phase transitions rather than simply the relationship of pressure to density for a single, shocked state. (See *S&TR,* March 2007, pp. 23–25.) "GDIs have enabled us to take the science of studying plutonium to the next level," says Thomas. "We are investigating plutonium at pressures and densities previously inaccessible to experimentalists."

JASPER targets fuse engineering and artistry. "Our engineers combine innovative fabrication techniques and exceptional skill to manufacture high-quality targets within very precise specifications to meet the needs and goals of each test," says Holmes. Targets are fabricated with no more than a 2.5-micrometer deviation in height. Machining such flat surfaces is difficult, and plutonium is particularly hard to work with. Each target surface is polished by hand so that the components and bonding between them are within 1 micrometer of the target's specification. Technicians must perform these tasks inside a glovebox working through thick gloves. Finally, diagnostics are attached to the back of the target and are aligned to exact locations—also within a micrometer—to measure many types of data such as velocity and temperature. "It's this precision in our impactors, targets, diagnostics, and experimental design that makes us confident in the results," says Thomas.

Peeking at the Answers

The 100th shot at JASPER was a milestone achievement for the Laboratory, its collaborators, and the Stockpile Stewardship Program. It was also the first of its kind in the nuclear weapons complex. When a shock wave passes through a plutonium target at JASPER, it accelerates the material and raises its temperature to the point that it becomes incandescent and emits light. During the 100th shot, researchers measured both the light emitted from the backside of the target and the velocity of the surface as the shock wave arrived. Previously, these measurements had not been made simultaneously. Together, they provide information about changes in plutonium's temperature and density under shock compression.

Measuring the light emitted from a shock-compressed target has been a significant challenge for the JASPER team, but one that was overcome through close collaboration with researchers from Los

Alamos National Laboratory and National Security Technologies, Inc. (managing contractor for the Nevada site). "We spent years working with our partners to design and fabricate targets, develop measurement techniques and instrumentation, conduct shots, analyze data, and deliver results," says Holmes. "These efforts are a model for how the laboratories can work together toward a common goal."

Results gleaned from JASPER experiments, such as those achieved in the 100th shot, are as Holmes describes, "like looking in the back of the book for the answer." Over the years, scientists have devised theories to explain how plutonium behaves under certain conditions. These theories have to be proven and often change when new data emerge. Having the answer, via experimental results, helps researchers work backward toward a better understanding of the problem, or in this case, the theory behind how the material behaves. With JASPER, scientists can effectively analyze errors, measure uncertainties, and build experiments that provide the framework for future analytical tools. "We need theoretical studies to develop really good experiments," says Holmes. "As we learn more, theories are improved and, in turn, so are experiments."

Theory and data are the essence of computational models for simulating weapons performance. "The JASPER gas gun produces data from dynamic shock experiments that for the first time are accurate enough to meet the needs of the Stockpile Stewardship Program," says Holmes. In addition to the shock-physics experiments at JASPER, ongoing subcritical experiments at the Nevada site and experiments conducted at the Laboratory's National Ignition Facility support stockpile stewardship initiatives, helping to ensure the safety, security, and reliability of the nation's nuclear deterrent.

New Paths of Exploration

Before experiments are run on JASPER, they are first put to the test at Livermore's High Explosives Applications Facility (HEAF) using surrogate materials. HEAF houses a two-stage, high-velocity gas gun similar to the one at JASPER. Researchers use the HEAF gun to demonstrate experimental methodologies and diagnostics prior to testing actinides and other hazardous materials at JASPER. For example, future x-ray diffraction experiments will first be conducted at HEAF. X-ray diffraction is a technique in which x rays generated from a pulsed-power capacitor are used to take a "flash photograph" of a material's crystal lattice structure as it undergoes phase transformations during an experiment. Holmes says, "We are pursuing methods for studying how a material's temperature, pressure, and phases change as a function of time. X-ray diffraction is one such method."

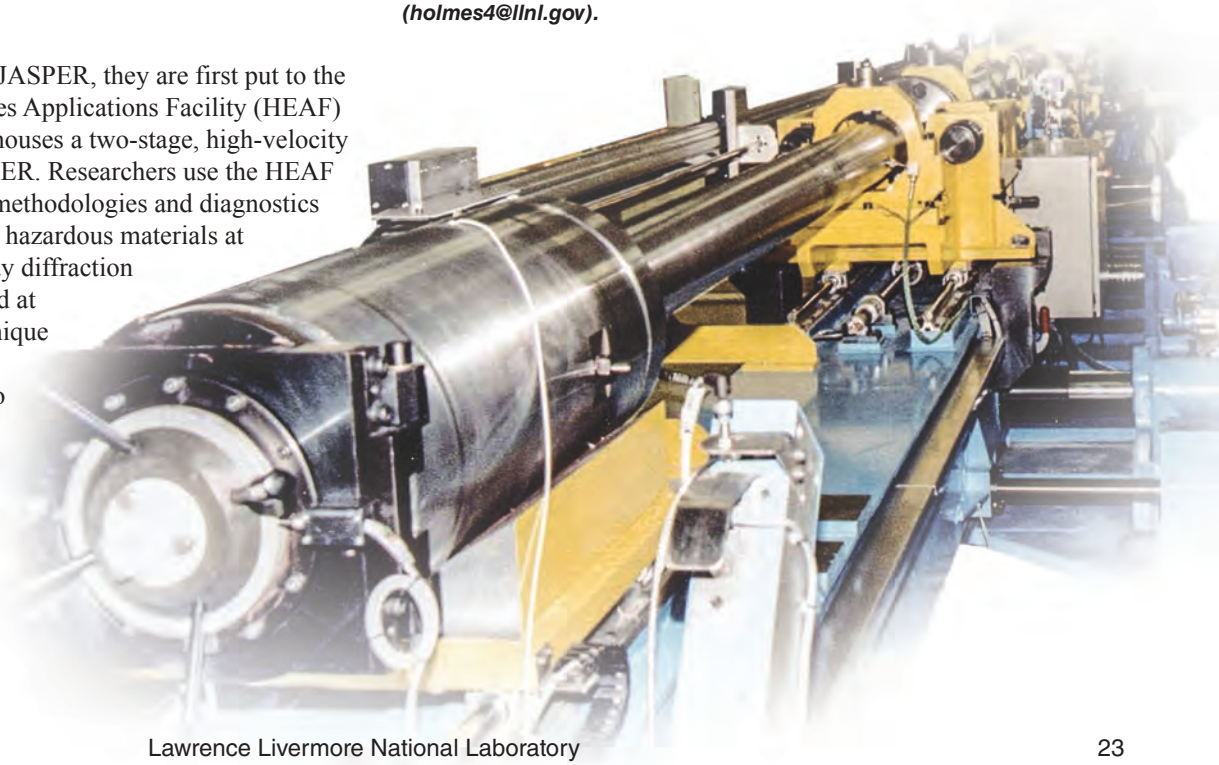
Another experimental technique for plutonium studies involves in situ temperature measurements. This technique is being used in diamond-anvil-cell (DAC) experiments by Livermore physicist Will Evans and his group. With DACs, researchers can study material behavior at constant temperature and pressures, and the devices have been invaluable for understanding the phase transition of materials deep inside planets. In another research study, Holmes and Livermore physicist Jeffrey Nguyen used Livermore's two-stage gas gun to discover the melting pressure of iron at conditions comparable to those in Earth's core. Their next goal is to measure temperature at the same conditions. "One of my greatest ambitions is to accurately measure the temperature at the center of Earth," says Holmes.

Over the next five years, Holmes and the JASPER team will continue their pursuit of plutonium's properties and move through the material's phase diagram to explore those areas where theory is not completely sound. Holmes says, "We are embarking on a new exploration of plutonium, one that will confirm what we know and one that may also serve up surprises." It appears the mysterious plutonium still has some secrets to reveal.

—Caryn Meissner

Key Words: 100th shot, actinide, diamond anvil cell (DAC), equation of state (EOS), gas gun, graded-density impactor (GDI), High Explosives Applications Facility (HEAF), Joint Actinide Shock Physics Experimental Research (JASPER) Facility, phase diagram, plutonium, Stockpile Stewardship Program.

For further information contact Neil Holmes (925) 422-7213 (holmes4@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.

Patents

Compound Transparent Ceramics and Methods of Preparation Thereof

Joel P. Hollingsworth, Joshua D. Kuntz, Thomas F. Soules, Richard L. Landingham
U.S. Patent 8,329,090 B2
December 11, 2012
In one method of preparing a composite transparent ceramic preform, a suspension of oxide particles is first formed in a solvent that includes a dispersant but does not include a gelling agent. The suspension is added to a shaped mold, and the mixture is uniformly cured until stable. A second suspension of oxide particles is formed in a second solvent that includes a second dispersant but does not include a gelling agent. This suspension is added to the stable first suspension in a second shaped mold, and the mixture is uniformly cured until stable. Other methods of preparing a composite transparent ceramic preform are also described.

Systems for Increasing the Sensitivity of Gamma-Ray Imagers

Lucian Mihailescu, Kai M. Vetter, Daniel H. Chivers
U.S. Patent 8,330,114 B2
December 11, 2012
These systems increase the imaging resolution and granularity of double-sided, segmented semiconductor detectors. The detectors are used as either Compton cameras or position-sensitive radiation detectors in imaging systems such as single-photon emission computed tomography and positron emission tomography. They are also used in coded apertures, multipinhole imagers, and other spatial or temporal modulated imagers.

Hybrid Fiber-Rod Laser

Raymond J. Beach, Jay W. Dawson, Michael J. Messerly, Christopher P. J. Barty
U.S. Patent 8,334,420 B2
December 18, 2012
Single or near-single transverse-mode waveguide definition is produced using a homogeneous medium to transport both the pump excitation light and the generated laser light. When the pump deposition and resulting thermal power generation in the waveguide device are properly configured, a thermal focusing power is established that supports perturbation-stable guided wave propagation of an appropriately configured single or near-single transverse-mode laser beam or pulse.

Radial Reflection Diffraction Tomography

Sean K. Lehman
U.S. Patent 8,335,555 B2
December 18, 2012
A wave-based tomographic imaging method and apparatus are used for nondestructive evaluation. The apparatus includes one or more oriented transmitting and receiving elements that rotate radially outward. At successive angular locations at a fixed radius, a predetermined transmitting element can launch a primary field, and one or more predetermined receiving elements can collect the backscattered field in a "pitch and catch" operation. A Hilbert space inverse wave algorithm can construct images of the received scattered energy waves using operating modes chosen for a particular application. Applications include improved intravascular imaging, borehole tomography, and nondestructive evaluation of parts with existing access holes.

Transparent Ceramics and Methods of Preparation Thereof

Joel P. Hollingsworth, Joshua D. Kuntz, Zachary M. Seeley, Thomas F. Soules
U.S. Patent 8,338,322 B2
December 25, 2012
In one method of preparing a transparent ceramic preform, a suspension of oxide particles is formed in a solvent. The suspension includes a dispersant but does not include a gelling agent. The suspension is uniformly cured to form a preform of gelled suspension. In another method, a mixture is created of inorganic particles—a solvent and a dispersant—that have a mean diameter of less than about 2,000 nanometers. A gelling agent is not added. The mixture is agitated, added to a mold, and cured.

Awards

Laboratory scientist **Regina Soufli**, a member of NASA's Solar Dynamics Observatory (SDO) Science Investigation Team, recently received a **Group Achievement Award** from **NASA**. Soufli's team included Livermore's **Jeff Robinson**, **Eberhard Spiller**, **Sherry Baker**, and **Jay Ayers** as well as collaborators from Lawrence Berkeley National Laboratory and other institutions. Launched in 2010, SDO is NASA's most advanced solar mission to date. Soufli led a team in the design, development, fabrication, and calibration of the multilayer mirrors aboard the SDO imaging telescopes. The multilayer mirrors act as reflective lenses and are responsible for capturing the images and movies of the Sun produced by SDO at seven extreme ultraviolet (EUV) wavelengths. By imaging the Sun at specific EUV emission lines from the solar plasma, the telescopes record solar activity in exquisite spatial, spectral, and temporal resolution for the purpose of studying the Sun's extremely complex and dynamic magnetic field, its plasma, and related phenomena.

The **American Physical Society** (APS) has selected **Andris Dimits**, a physicist in the Fusion Energy Sciences Program, as a 2012 **Fellow**. Dimits was cited in the plasma physics category for "important insights and contributions to the theory and simulation of kinetic turbulent transport in magnetized plasmas, including the effects of self-consistent turbulence-induced velocity shear and Coulomb collisions." He joined the Laboratory in 1990 and has worked on theory and simulation of magnetized fusion plasmas, hydrodynamic instability and turbulence, and high-energy-density physics.

APS fellowships are awarded after extensive review and are considered a distinct honor because the evaluation process relies on nomination and recommendation by one's professional peers. Election to APS fellowship is limited to no more than one-half of one percent of the society's membership for a given year.

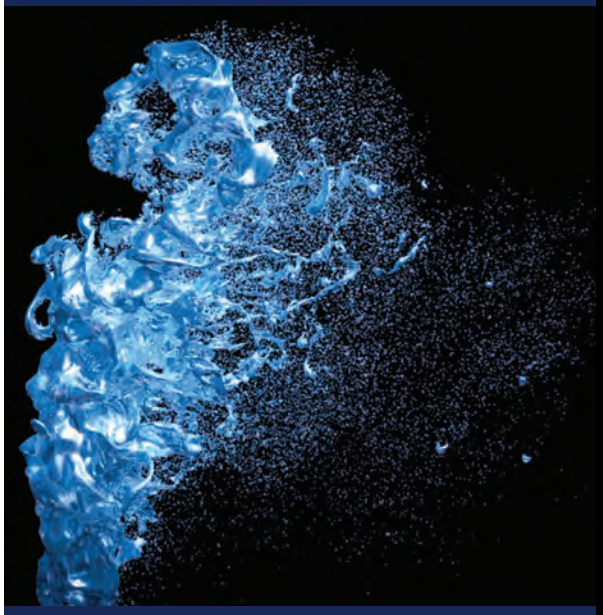
Abstract

A Faster and Cheaper Method to Detect Agents of Disease

The Lawrence Livermore Microbial Detection Array (LLMDA) system combines innovative bioinformatics with a tiny device called a microarray to rapidly identify any microbe whose genetic code has been sequenced. About 360,000 probes—short stretches of DNA or RNA—are arrayed in a microscopic square grid on a 2.5- by 7.5-centimeter glass slide. When a fluorescently labeled sample of fluid containing the genetic material of microbes comes into contact with the array's probes, only the squares with DNA or RNA unique to a particular organism are activated. The activated squares produce a fluorescent pattern, from which species present in the sample are identified. In this way, multiple pathogens are detected simultaneously. LLMDA is being used to identify viruses and bacteria that are correlated with high cancer risk, vaccine safety, and defense against a bioterrorist attack. If widely adopted, LLMDA could enable professionals in medicine, pharmaceuticals, law enforcement, product and food safety, human and animal health, the military, and global disease surveillance to detect within 24 hours any virus or bacteria that has been sequenced and included among the array's probes.

U.S. Government Printing Office: 2013/670-075-50022

Energy Innovation through Advanced Computing



A pilot project teams Livermore and industry scientists to demonstrate how supercomputing can energize technology development.

Also in June

• A team of experts from Livermore travels to Iraq to train members of the Iraqi government in securing their critical energy infrastructure.

• Computer scientists engage in friendly competition to develop, test, and present new software during the Laboratory's "ShipIt" events.

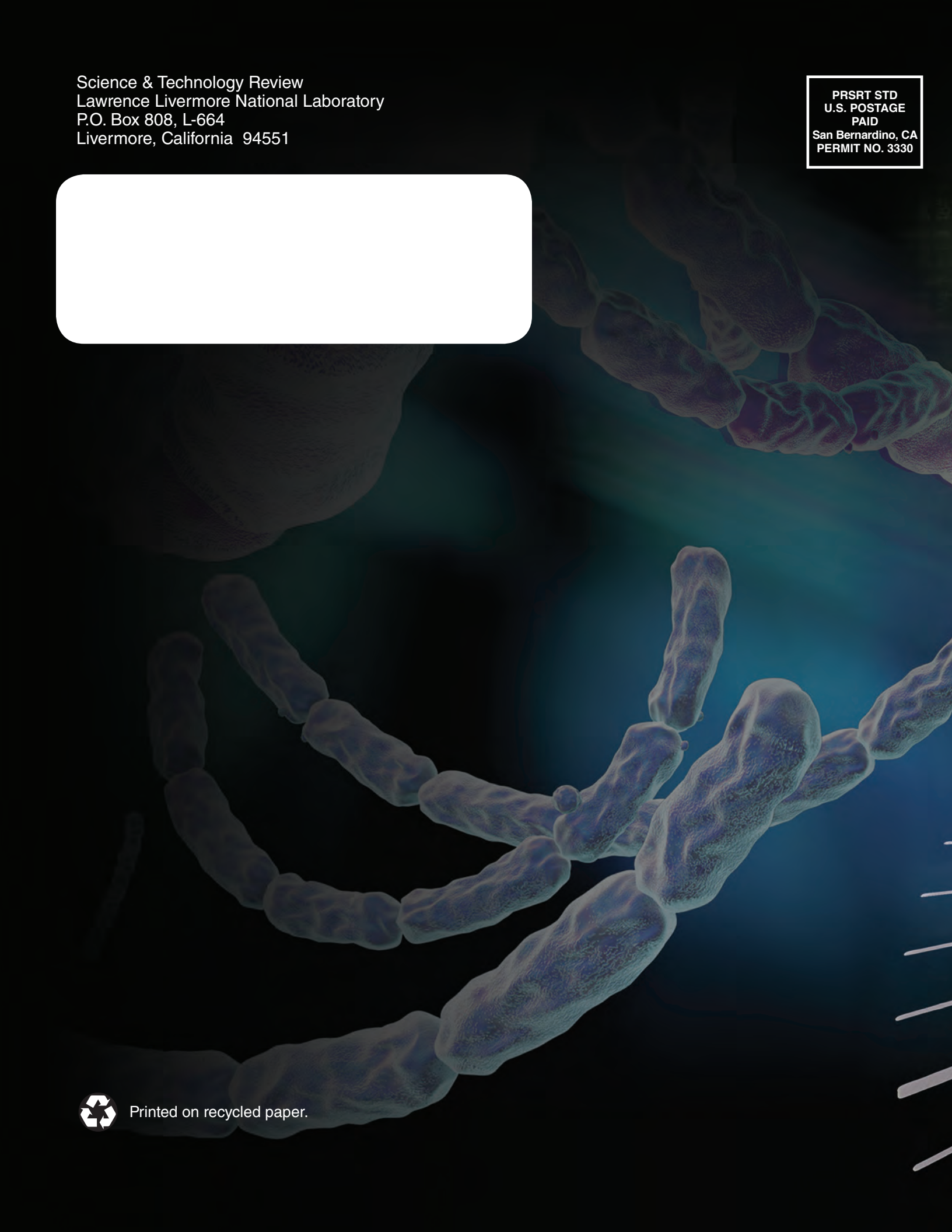
• Livermore meets the challenge of maintaining its certification as a laboratory for the Organisation for the Prohibition of Chemical Weapons.

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



Printed on recycled paper.