June 2002

Science & Technology Review

National Nuclear Security Administration's
Lawrence Livermore National Laboratory

Designing Molecules to Fight Bioterrorism

Also in this issue:

- Adaptive Optics Bring the Cosmos into Sharper Focus
- Solving the Mystery of Comet X-Ray Emissions
- 50th Anniversary Highlight: The Enduring Contributions of Chemistry and Materials Science

Lawrence Livermore National Laboratory

Making History Making a Difference

1952-2002

About the Cover

Livermore bioscientists are designing synthetic molecules known as high-affinity ligands that bind strongly to the proteins of pathogens. These new molecules will be used to identify biowarfare agents and, when armed with a radionuclide, have potential applications for fighting cancer. On the cover, synthetic chemist Julie Perkins develops a two-pronged molecule that will bind securely to a specific toxin protein. In the background is a simulation of a *Clostridium* neurotoxin tetanus protein, one of the biowarfare agents that high-affinity ligands will be used to identify. The article reporting on this new approach to fighting bioterrorism and disease begins on p. 4.

Cover design: George Kitrinos

About the Review

Lawrence Livermore National Laboratory is operated by the University of California for the Department of Energy's National Nuclear Security Administration. At Livermore, we focus science and technology on assuring 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 10 times a year to communicate, to a broad audience, the Laboratory's scientific and technological accomplishments in fulfilling its primary missions. The publication's goal is to help readers understand these accomplishments and appreciate their value to the individual citizen, the nation, and the world.

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Science & Technology REVIEW

June 2002

Lawrence Livermore National Laboratory

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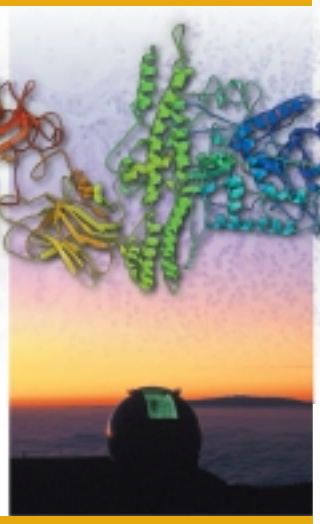

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Stroke treatment by wire

A springy plastic wire that changes shape at the flick of a switch could provide a safer treatment for strokes caused by blood clots. Developed by engineers at Livermore, the wire, made from shape-memory polymer, will allow surgeons to remove blood clots from the brain without using potentially dangerous clot-busting drugs.

The shape-changing wire is made from two types of polyurethane bundled into one. One type is harder than the other. Team member Duncan Maitland explains that the wire's main body is constructed from the softer material, with chunks of the harder material distributed though it.

The wire is first heated to allow both its hard and soft components to become malleable. The end of the wire is then twisted into a coil and cooled, fixing the shape of the coil into the polymer. Next, the wire is reheated but to a lower temperature than it was initially, so that only the softer part is deformed. The coil is pulled to straighten it and then cooled again to harden it. It becomes too rigid to spring back into the coiled shape. However, when heated again to 60°C, the plastic softens sufficiently for the end of the wire to spring back into a coil.

Maitland and his colleagues have tested their invention by conducting in vitro experiments using pig's blood. They fixed the wire to the end of an optical fiber and inserted both into a narrow catheter. They speared a clot with the wire, withdrew the catheter, and heated the wire with infrared light transmitted through the fiber. "The wire changed into a coil in a fraction of a second," says Maitland. It grips the clot from behind, and the clot is pulled out with the wire.

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New combustion method lowers power plant emissions

Livermore engineers have developed a unique combustion method that combines staged combustion with nitrogen-enriched air to lower power plant pollutant emissions.

The new technology, called staged combustion with nitrogen-enriched air (SCNEA), could help power plants comply with strict Environmental Protection Agency (EPA) requirements for decreasing power plant emissions. "As EPA requirements become tighter and tighter on emissions, most solutions become more difficult and more expensive to implement," says Larry Fischer, principal investigator for SCNEA. "With our technology, consumers will see cleaner air at a miniscule increase in their utility bills."

Before concerns about oxides of nitrogen (NO and NO_2, often called NO_x) and their relationship to photochemical smog and acid rain arose in the late 1980s, power plants typically burned fuel in boilers and furnaces with single-stage combustion using air as the oxidant. Today, NO_x emissions are regulated under provisions of the Clean Air Act and its amendments. Those regulations will become tougher by 2005, which means that the technologies used to lower NO_x emissions must be improved.

SCNEA lowers NO_x emissions with a combustion method that burns fuels in two or more stages. In the first stage, fuel is combusted with nitrogen-enriched air. The fuel remaining after the first stage is combusted in the remaining stage(s) with air or nitrogen-enriched air. This method substantially reduces NO_x emissions without significantly reducing power plant efficiency and is applicable to many types of combustion equipment and many types of fuels.

Livermore is working to form a consortium of representatives from the U.S. EPA, utility companies, boiler manufacturers, emission control equipment companies, and a company that produces nitrogen-enriched air to further develop SCNEA. The next stage is a small-scale pilot program.

Contact: Larry Fischer (925) 423-0159 (fischer3@llnl.gov).

Laser communication link completed

A Livermore team has completed a 28-kilometer, high-capacity laser communication link between the Laboratory and Mount Diablo. "This represents one of the longest terrestrial high-capacity air-optics links in existence," says Tony Ruggiero, principal investigator on the project to develop an optical wireless testbed for evaluating new laser communication technologies.

Laser communication consists of an optical system in which information is encoded on a laser beam and transmitted to a receiver telescope. Functionally similar to radiofrequency or microwave communications, lasers use the optical part of the electromagnetic spectrum. The laser communication beam is not visible or harmful in any way.

The initial Laboratory–Mount Diablo link transmitted data at a single-channel data rate of 2.5 gigabits per second—the equivalent to the transmission of 1,600 conventional T1 data lines, 400 TV channels, or 40,000 simultaneous phone calls.

The experiments are being conducted as part of the Secure Air-Optic Transport and Routing Network (SATRN) program, which is cosponsored by the Nonproliferation, Arms Control, and International Security Directorate and Laboratory Directed Research and Development to provide advanced technologies for long-range laser communications.

Proliferation detection, counterproliferation, arms control, counterterrorism, and warfighting all require the timely and secure communication of information in situations where fiber-optic cable is physically or economically impractical and data requirements exceed radiofrequency or microwave wireless capacity.

Ruggiero says that the next challenge for the SATRN team is transmitting data long distances for longer periods of time to establish a solid baseline for the availability, accessibility, and acceptability of the system's single-channel long-range link performance.

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Fighting Bioterrorism, Fighting Cancer

THE anthrax attack last fall spotlighted the need for fast, accurate, inexpensive methods to detect weapons of bioterrorism. Fortunately, long before this attack, Livermore was a leader in developing innovative methods and technologies for early detection of bioterrorism threats. Since the attack, the Laboratory has intensified its efforts in this area vital to national security. This month's issue of *S&TR* features Livermore's leading-edge biotechnology research with immediate applications for detecting the agents of bioterrorism and long-term possibilities for fighting disease, especially cancer.

Pathogens can be detected in two basic ways: look for their DNA, the genetic blueprint for the organism, or look for the protein building blocks that are generated from this genetic blueprint and make up the structure and machinery of the organism.

Lawrence Livermore is well known for its DNA detection capabilities. For the past decade, we have been developing both the technologies and science for fast, accurate detection and characterization of bioterrorism pathogens from their DNA. We have licensed a series of technologies to industry, most recently the Handheld Advanced Nucleic Acid Analyzer. Our DNA analysis capabilities were deployed at the 2002 Winter Olympics as the analysis core of the Bological Aerosol Sentry and Information System used for air-monitoring.

These DNA detection methods are highly sensitive and specific but require skilled personnel and sophisticated equipment to deploy them. As the article beginning on p. 4 reports, Livermore is also developing protein detection methods to identify pathogens. As with most protein recognition methods—home pregnancy tests, for example—our methods will be fast and easy to use. But they must also be more sensitive and specific than home pregnancy tests—more like DNA detection systems. Livermore's technique uses carefully designed antibodylike molecules, called high-affinity ligands, to identify pathogens. Our approach seeks to combine the best of both worlds—fast and easy to use as well as highly sensitive and specific.

In addition to applications in countering bioterrorism, this tool will also find widespread applications in the field of public health. Livermore researchers have already begun to develop a high-affinity ligand that will search out non-Hodgkin's lymphoma, a form of cancer. Cancer cells produce specific protein building blocks that properly designed high-affinity ligands can target. Arming the ligands with radionuclides to kill the cancer cells may result in an effective cancer treatment with minimal side effects.

Designing these high-affinity ligands draws on a spectrum of Livermore capabilities—bioscience research, high-performance computational modeling, synthesis of new molecules, and an array of molecular diagnostics such as nuclear magnetic resonance spectroscopy and mass spectroscopy. The ability to bring together these capabilities allows us to make advances that would be difficult or impossible anywhere other than at a national laboratory.

This high-affinity ligand technology has many other potential applications. At some time in the not-too-distant future, doctors, other public health workers, and food safety experts could use the same methodology to quickly detect proteins from pathogens such as streptococcus, salmonella, flu, foot and mouth disease, and *E. coli*. With faster detection will come more timely, effective intervention and treatment. The next generation of pathogen detectors—for fighting bioterrorism specifically and disease in general—will likely combine DNA and protein recognition for even greater speed and accuracy.

As part of the National Nuclear Security Administration's Chemical and Biological National Security Program, Livermore has for a decade been at the forefront of research to counter the effects of deadly weapons of biological terrorism. We are finding that almost every step forward in this research produces know-how that can benefit the everyday health of the general public. The specter of bioterrorism is frightening, and the world is never likely to be free of disease. Fortunately, we are finding better ways to fight both, and they often go hand in hand.

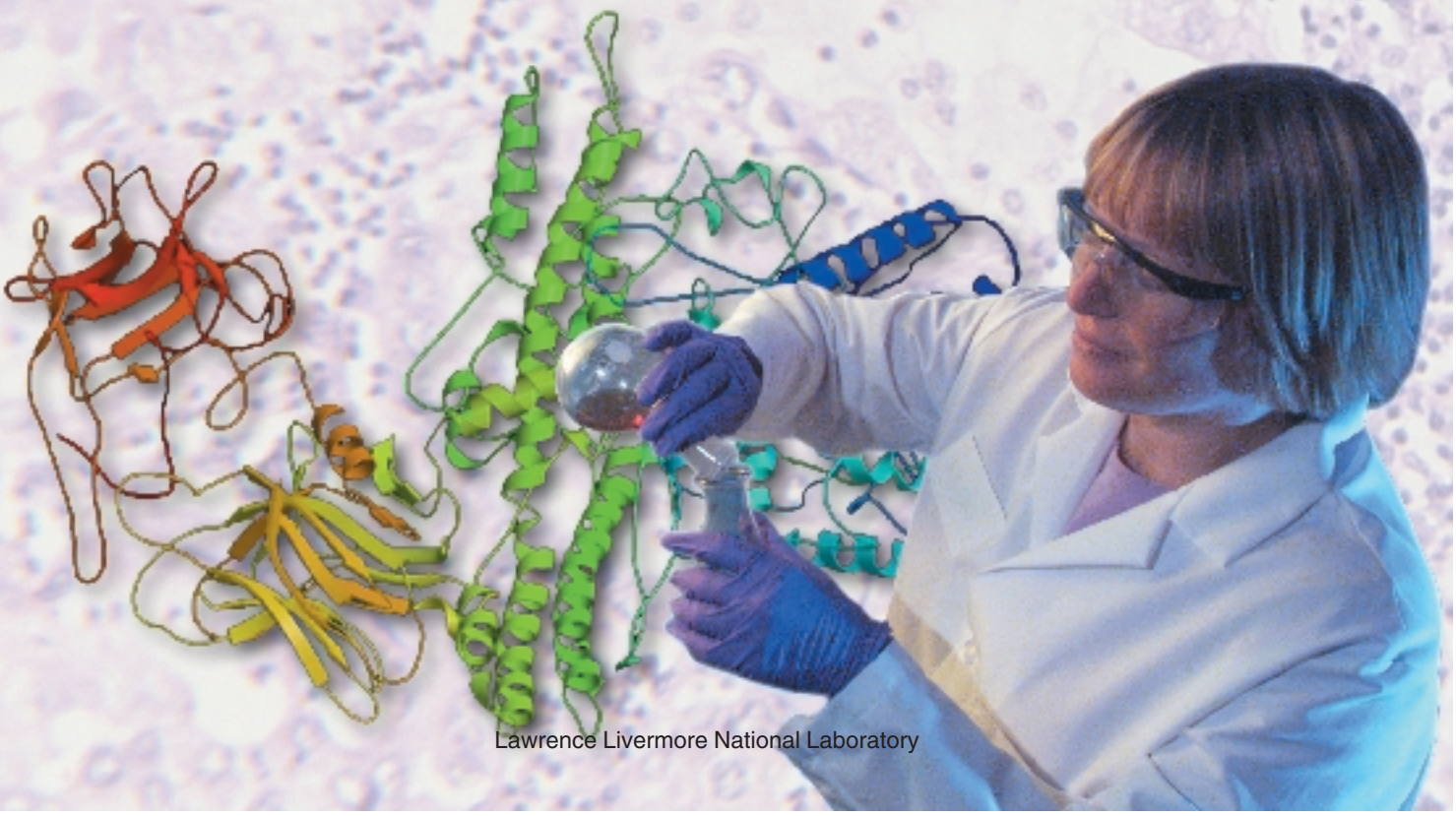
■ Bert Weinstein is acting associate director of Biology and Biotechnology Research Programs.

A Two-Pronged Attack on Bioterrorism

Livermore scientists are designing tiny synthetic molecules to detect biological warfare agents and fight cancer.

NEWLY designed molecules that bind to and capture biowarfare agents are on the drawing board at Livermore. The goal is for these molecules to quickly and efficiently detect such deadly pathogens as botulinum toxin, anthrax spores, or smallpox. Using synthetic chemistry, scientists produce these new molecules that bind to unique sites on the surface of the toxin or organism. Their two-pronged, or bidentate, structure is critical. When a small molecule binds to a protein, the attachment is usually weak, and the interaction between the two is short-lived. If, however, two or more small molecules that bind to the protein are linked together, their binding to the same protein may be thousands, even millions, of times stronger. By targeting specific proteins, the synthetic molecules will mimic some of the behavior in our immune system where antibodies recognize molecular foreign entities in our bodies and abnormalities such as cancer cells.

A single detector armed with many of these synthetic targeting molecules could simultaneously recognize an equal number of harmful biological agents that might be used in a terrorist attack. Assays using antibodies, known as immunoassays, are widely used to identify pathogens in the laboratory and form the basis for many biowarfare detection systems fielded to date.



However, only seven good antibodies are currently available for pathogen detection. Other detectors depend on recognizing the bioagent's DNA. "But some pathogens, such as viruses, require human exposure to only a small number of organisms to be acutely toxic," says Livermore biochemist Rod Balhorn. "With so little DNA present in each virus and given the rapid variation that occurs in the base sequences that make up the DNA, those pathogens are typically very difficult to detect."

Similarly designed targeting molecules could zero in on defective or overactive proteins in our bodies and poison them, just as our natural antibodies do. These antibodylike molecules can lock on to cancer cells or other pathogens and kill them—and only them. By targeting unique sites on other proteins that cause disease—for example, the proteases that cause inflammation in arthritis or enable HIV to function—the synthetic molecules would block the activity of the protein without entering its active site. The active site is a cavity on the surface of a protein that is used by the protein to perform its function. Similar active sites can be present in many proteins, both those that are essential to cell function and others that cause disease.

The pharmaceutical industry has already begun using this approach to develop drugs that function as intended without blocking the activity of healthy cells or proteins. Molecules that target unique sites on the surfaces of specific proteins may soon lead to a new generation of drugs that have minimal side effects.

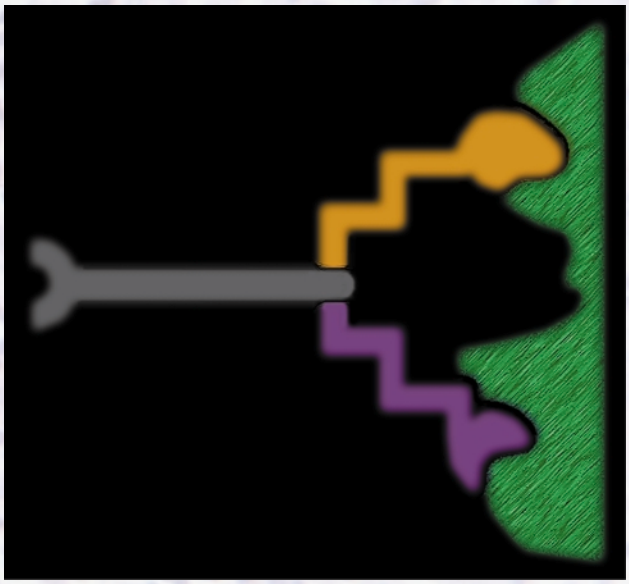
Balhorn is leading the program at Livermore to design synthetic molecules for bioagent detection and cancer treatment. He and a team of Livermore investigators are collaborating with scientists at Brookhaven and Sandia national laboratories and the University of California at Davis Cancer Center. Together, they are developing the methods needed to produce the first of these synthetic antibodylike molecules.

"Terminology is a little tricky," he notes. "It is tempting to call our new molecules 'synthetic antibodies.' But we are designing small molecules that function like antibodies, not large proteins that are synthetic versions of antibodies. So we use the term 'high-affinity ligands' to describe our molecules."

"Ligand" is a general term used to describe a small molecule that binds to proteins or other large molecules. The higher the affinity a ligand has for a specific protein, the more tightly it binds to it. Research by others has demonstrated that bidentate ligands have a vastly increased affinity for the target protein, anywhere from thousands to millions of times greater. Polyvalent ligands—molecules that bind to multiple sites on the surface of a protein—are observed in many biological interactions that require very tight binding. The seek-and-destroy antibodies of our immune system, which normally operate quite successfully, are one example.

"What we're doing is searching for two molecules that bind to two sites next to each other on the surface of a protein," says Balhorn. "Then our synthetic chemist joins them together using a third molecule, called a linker. The linker must be both flexible and robust, or the new molecule will fall apart. This new synthetic ligand will then behave pretty much like an antibody, binding tightly to the protein."

The new bidentate molecules, called high-affinity ligands (HALs), will have several advantages over naturally occurring antibodies. They can be totally inorganic (nonprotein) and can be synthesized in large quantities using methods to ensure that each batch is structurally and functionally identical. They will also be stable over a long period, making them excellent candidates for long-term deployment in detectors for agents of biological warfare.



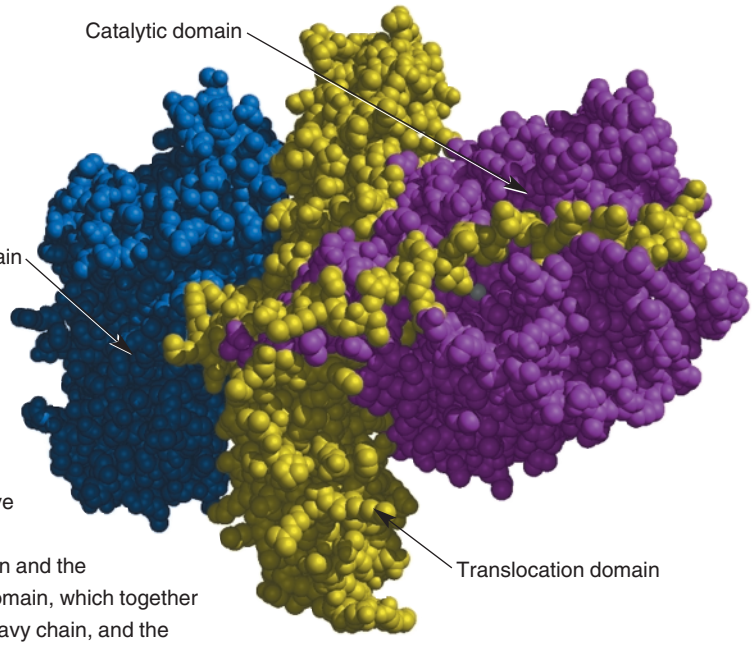
This schematic diagram shows how a linker molecule will connect molecules that bind to two sites on a protein. The goal is to develop a process for designing and producing high-affinity ligands for any structured surface. When two molecules are connected with a linker, they bind with up to a million times higher affinity than does each molecule alone.

The Toxic Targets

As bioagent detectors, HALs can be designed to target protein toxins produced by pathogens as well as any major protein component of pathogenic organisms. For the National Nuclear Security Administration's Chemical and Biological National Security Program, work is under way to develop HALs that bind to the *Clostridium* neurotoxins, which include botulinum and tetanus, the most toxic substances known. The *Clostridium* toxins attack the central nervous system and cause spastic paralysis in the case of tetanus and flaccid paralysis in the case of botulinum.

Balhorn's team is laying the groundwork for future development of HALs to target the *Staphylococcus* enterotoxins, which cause acute intestinal symptoms such as those associated with food poisoning, and ricin, a residue of castor bean processing that causes major intestinal or respiratory complications. The body's response to toxic quantities of either of these substances is swift and often fatal.

Work is also scheduled to begin in the near future on HALs that bind to proteins in the spores of *Bacillus anthracis* (anthrax) and in *Yersinia pestis* (plague). Once these HALs are completed, efforts will focus on the next highest priority agents: smallpox, *Francisella tularensis* (a plaguelike illness), and *Brucella melitensis* (an organism whose infections, often called Mediterranean fever, cause spontaneous abortions). Creating synthetic ligands even for proteins with a known structure is still a research project. Work began in 2000, and Balhorn estimates that high-affinity ligands for these eight bacterial toxins and threat organisms can be delivered in about 2005.



Clostridium neurotoxins have three parts: the targeting domain and the translocation domain, which together make up the heavy chain, and the catalytic domain, which makes up the light chain and is the toxic part of the molecule.

Got Structure?

If the structure of the target protein is known, the team uses that structure to develop a HAL. Work on these molecules is a logical progression from Livermore's protein structure and computational biology effort, with which Balhorn has been involved since its inception. (See *S&TR*, April 1999, pp. 4–9.) Using x-ray crystallography and nuclear magnetic resonance (NMR) spectroscopy, high-resolution structures for many proteins have been determined at laboratories around the world, including Livermore. These include several types of *Clostridium* toxins (botulinum and tetanus) and the *Staphylococcus* enterotoxins.

All toxins in the *Clostridium* family have three parts. The targeting (or binding) domain, which binds to receptor molecules on the nerve cell membrane, and the translocation domain, which makes a pore in the cell through which the toxin passes, together make up what is known as the heavy chain. The light chain, which contains the catalytic domain, is a protease that is injected into the nerve cell and disrupts its functioning.

For the *Clostridium* neurotoxins, the team is developing a HAL to bind to the targeting domain, that fragment of the protein that recognizes and binds to motor neurons. Of these neurotoxins, botulinum is considered a greater threat than tetanus, but tetanus is easier to work with. Fortunately, its targeting domain is sufficiently similar in structure to botulinum's that it serves as a model for botulinum.

In 1998, Livermore's x-ray crystallography group completed a high-resolution structure of the binding domain of the tetanus toxin. Researchers then computationally calculated the molecular surface of the protein to identify sites where binding is likely to occur. "We look

for pockets on the surface of the folded protein, places where another molecule would be able to fit tightly," says computational chemist Felice Lightstone. For the tetanus toxin, Lightstone found two appropriate sites adjacent to one another on the binding domain.

For a HAL to be effective, the sites designated for binding must be on a part of the toxin that is "conserved," meaning that these regions remain essentially identical across all strains of a toxin. When bioagents are being genetically engineered, areas such as these are difficult to modify without altering the toxicity of the agent. Ideally, a high-affinity ligand for tetanus toxin will be able to recognize engineered and other unknown or related *Clostridium* toxins.

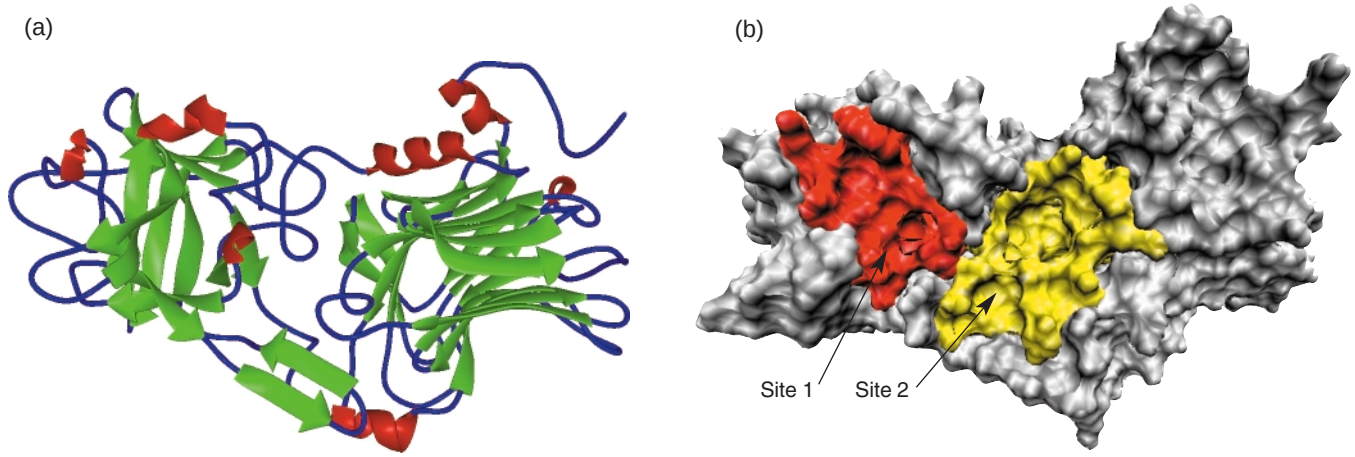
The next step involved selecting compounds that might fit into the two sites. All of the 300,000 compounds in the Available Chemicals Database, a listing of all commercially available compounds, were computationally inserted (docked) into each site. The potential fit and interactions were then assessed. The top 1,000 compounds were run again using a range of structures for each compound representing the different bond orientations and shapes, known as conformations, that each molecule is likely to adopt. In this manner, the top 100 compounds were identified. The calculations for each site took about 3 weeks on a Linux cluster of 40 dual-processor personal computers.

Sandia National Laboratories in Livermore has recently written new programs to expedite this time-consuming process. Each compound is tested in 10 different conformations to see which fits best into the rigid protein. This provides a more realistic test of binding, because many of these small molecules are not rigid and can adopt different conformations. "Computational docking projects typically have success rates of anywhere from 10 to 40 percent," says Lightstone. "Even before we started using our new version of this program, our success rate of identifying molecules that actually bind to the protein was in the 40- to 65-percent range. Now, the likelihood of getting a fit may be even greater."

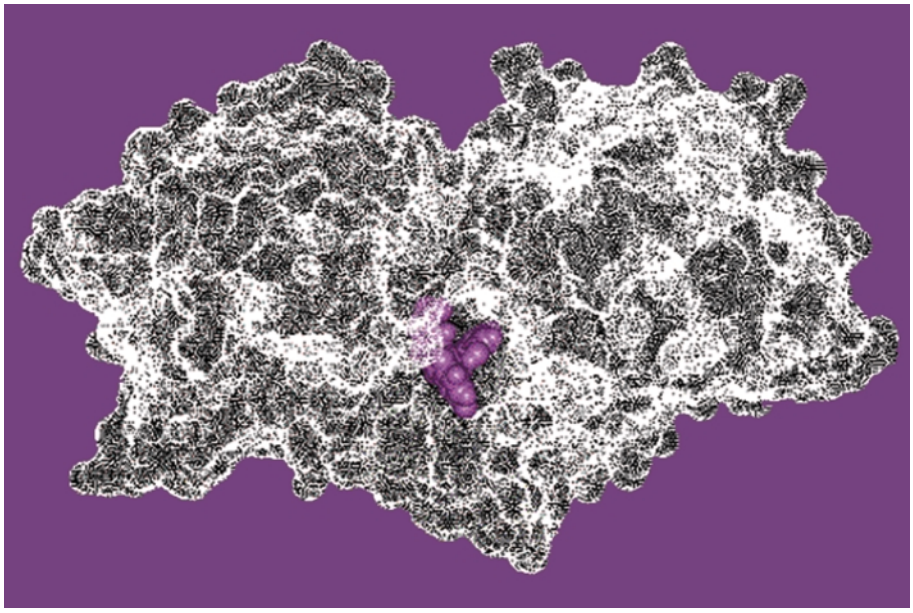
Into the Laboratory

Once possible ligands have been identified computationally, they must be tested in the laboratory to see whether binding actually occurs. Mass spectrometry (MS) and NMR spectroscopy are both effective for testing ligand–protein binding. NMR examines binding in the solution state, while MS looks at binding in the gas phase. MS typically requires much smaller samples, but it cannot handle certain compounds or chemical buffers. NMR can examine mixtures of compounds more easily and determine which combinations bind best in solution. Both techniques can identify where on the target protein binding is occurring.

The initial computational screening process to find new compounds that bind to tetanus neurotoxins resulted in 100 possible ligands that were predicted to bind to one of two sites (site 1 and site 2) on the tetanus neurotoxin's targeting domain. Experiments using electrospray ionization–mass spectrometry (ESI–MS) suggested that



(a) The x-ray crystal structure for the tetanus toxin showing how the amino acid chain is folded and (b) its calculated molecular surface showing sites 1 and 2, predicted binding sites for ligands.



The predicted structure of the tetanus–lavendustin A complex. Lavendustin A is shown in purple binding to site 2.

7 of the first 13 tested compounds bound to the toxin. With ESI–MS, ligand binding is confirmed when a new mass peak appears at the expected mass-to-charge ratio for the ligand–tetanus complex.

The antitumor drug doxorubicin was discovered to be the best fit at site 1. The binding of this ligand to site 1 was later confirmed by x-ray crystallography of doxorubicin–tetanus toxin and doxorubicin–botulinum toxin complexes. For site 2, the same MS method was used to screen 1 of 100 compounds, six of which were observed to bind. The figure above shows one of these ligands, lavendustin A, docked into site 2 in the predicted structure of the tetanus–lavendustin A complex.

The six ligands predicted to bind to site 2 were then screened for binding to the targeting domain using NMR. The six molecules were tested individually, as mixtures of different combinations of the compounds, and in the presence or absence of the known site 1 binder, doxorubicin.

When examined by NMR, small molecules exhibit weak, negative signals referred to as NOEs (nuclear Overhauser effects). Large molecules such as proteins exhibit strong, positive NOEs. When small molecules bind to proteins, the characteristics of the NOE for the large molecule are transferred to the small molecule. Thus, strong NOEs are detected for ligands that bind to the protein.

The NMR screening of mixtures containing the six predicted site 2 ligands confirmed that four bind to tetanus toxin in solution. Using a novel transfer NOE (trNOE) competition assay, researchers have determined that three of these ligands bind in the same site, presumably at site 2. The fourth ligand was determined to bind in a third site distinct from site 1 and site 2.

NMR experiments were also performed to evaluate how possible structural changes induced by the binding of one ligand in site 1 could influence the binding of the second ligand in another site. In these experiments, doxorubicin, which was added first, remained bound to site 1 throughout the additions of all six of the predicted site 2 ligands. The mixture containing doxorubicin and lavendustin A produced the strongest positive trNOE signal in the presence of the tetanus toxin. This experiment confirmed that both lavendustin A and doxorubicin bind simultaneously to the toxin, indicating that each must bind to a different site.

"Unfortunately, this assay cannot define the location of the binding site," says physical chemist Monique Cosman, leader of the NMR group at Livermore. "But since doxorubicin is known to bind to site 1, we know that lavendustin A must bind to a different site, which may be site 2.

By performing these trNOE binding experiments with pairs of molecules that were determined to compete for binding to the same site, Cosman developed a new NMR method for identifying the relative strength of binding of each ligand to a particular site on the protein. MP-biocytin, another molecule that binds to site 2, did so with a relatively lower affinity than lavendustin A. The affinity of the third ligand is similar to that of lavendustin A, but it was not studied further because it is too perishable.

Mass spectrometry was then used to verify where the molecules are binding. Chemist Sharon Shields developed a new method that combines MS with proteolysis, a process in which a protein is digested by enzymes. "This is unique," she notes. "Now we can study solution-phase biological processes using a gas-phase mass spectrometric method."

She first treated the targeting domain of tetanus toxin with proteases that make clips in the amino acid chain either alone or on the tetanus–

doxorubicin complex using various ratios of doxorubicin to the neurotoxin. Then she used matrix-assisted laser desorption ionization and ESI–MS to determine the pattern of enzymatic degradation that had occurred. In the tetanus–doxorubicin combinations, doxorubicin prevented the enzyme from digesting the protein at the binding site by limiting access to the amino acids located in that region.

The figure below shows a map of peptides (amino acid chains) produced by digesting the tetanus–doxorubicin complex compared to the tetanus toxin alone. In this experiment, Shields used the enzyme trypsin. The decreased abundance of peptides indicates the location where binding is occurring. That location contains amino acids 299–304, 351–376, and 394–434. Molecular docking calculations had predicted that doxorubicin would reside near amino acids 356, 358, 359, 407, 409, 419, 427, and 437. These predictions are a close match to MS results. Comparable locational experiments using other enzymes had similar results.

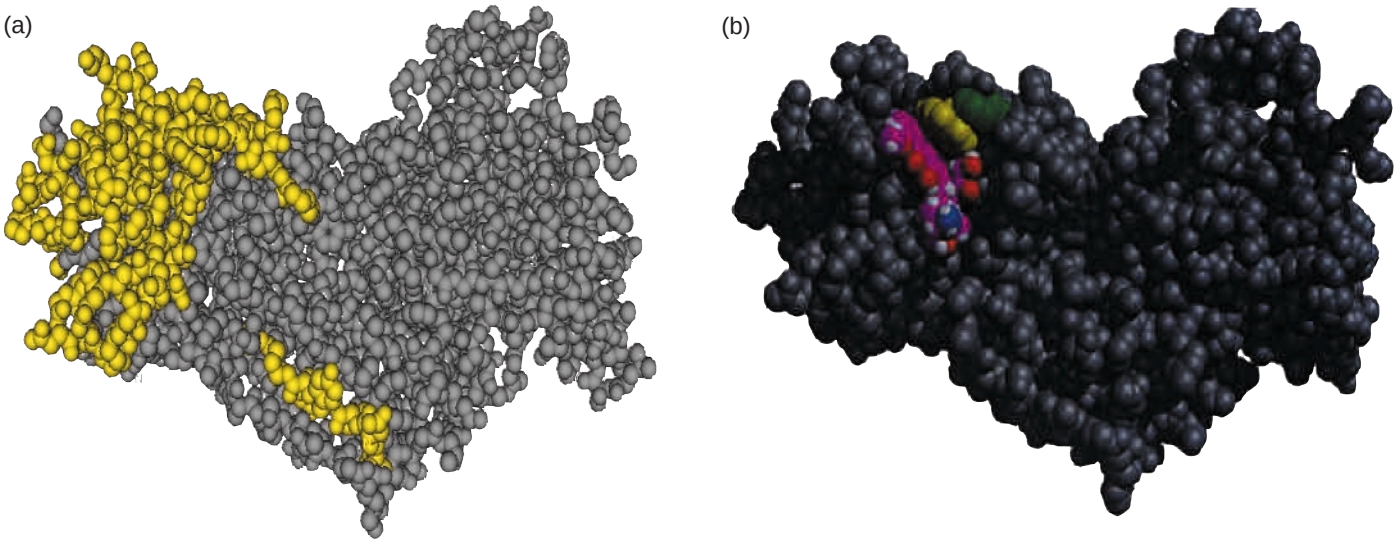
Shields also found that the presence of doxorubicin induces subtle changes in the tetanus toxin's three-dimensional structure, suggesting that the protein may envelope, or wrap around, doxorubicin when it binds. Further experiments are needed to confirm these results.

Creating a New Molecule

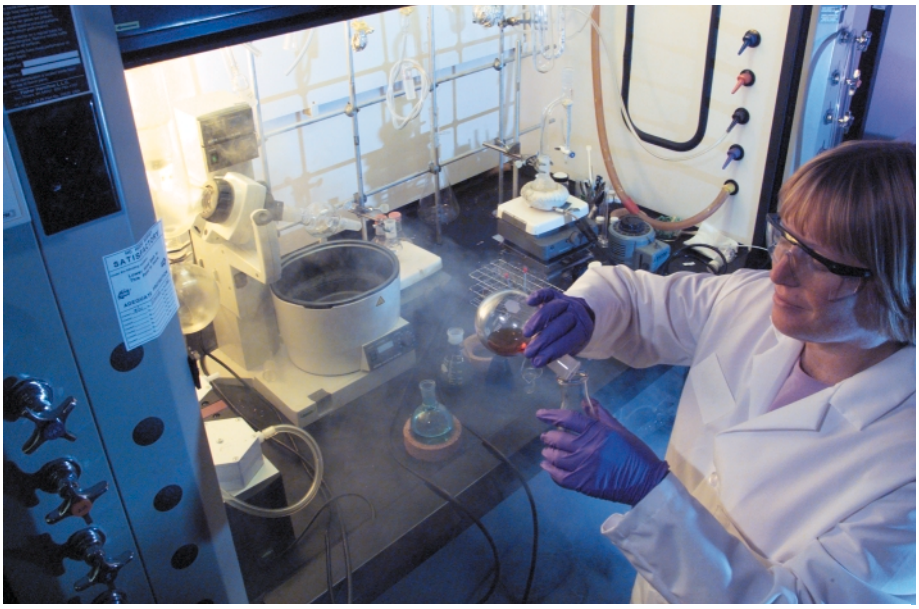
Synthetic chemist Julie Perkins has the job of linking the two molecules that bind to sites 1 and 2 to create a new HAL. This is the critical step. She is experimenting with linkers that will connect doxorubicin and MP-biocytin as well as doxorubicin and lavendustin A. "We know that each of these compounds binds individually to sites 1 and 2, but because they bind weakly, they can also float away," Perkins says. "When the compounds are linked together, they are much more likely to stay bound.

She is starting with the amino acid lysine as a linker. Lysine is an ideal building block because it has three distinct functional groups upon which she can perform synthetic chemistry experiments. Many derivatives of lysine are commercially available as well. The molecules that have been identified to bind into site 1 and site 2 can either be attached directly to lysine, resulting in their close proximity, or with a linker, which increases the distance between them. Increasing the distance between the two compounds with a flexible chain may also help increase the affinity of the ligand for the protein.

"To achieve maximum affinity of the ligand for the protein, we have to find the optimal length and rigidity of the linker," says Perkins, "and that can only be done experimentally." She is experimenting with a flexible glycol chain that can be attached to the lysine to increase the distance separating the two ligands.



(a) This map of peptides (amino acid chains) compares the doxorubicin–tetanus toxin complex to the tetanus toxin alone. Amino acids in yellow represent the peptides that showed a decreased abundance, which indicates that binding is occurring. (b) Computational docking studies predicted that binding would occur at the location shown. The two match quite well.



Synthetic chemist Julie Perkins works to link two molecules, each of which binds to two protein binding sites. The new molecule will bind more strongly and securely to a specific toxin protein than the individual molecules can.

Once she has synthesized each new compound containing the two linked ligands, conventional binding studies will identify the highest affinity and most selective ligand combinations. These studies will determine how tightly the HALs bind and confirm that they selectively bind only to *Clostridium* neurotoxins.

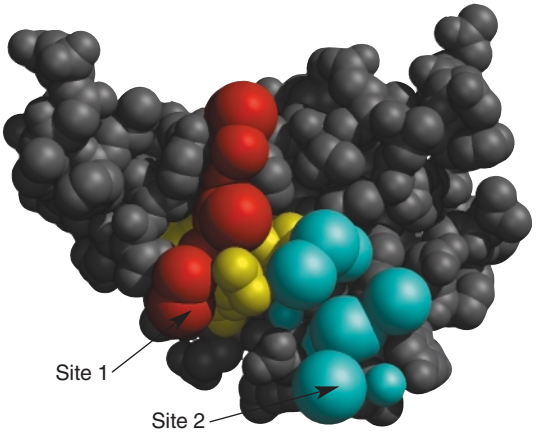
Targeting Cancer

For cancer therapy, the challenge is to synthesize molecules that bind with high affinity to each cancer cell without themselves generating an immune reaction from the body. Targeting molecules therefore must be smaller and more specific and have higher affinities than natural antibodies. They should also not be made of proteins, which elicit an immune response from the body.

The goal is to use these small, exceptionally high-affinity molecules to deliver a lethal radiation dose directly to a tumor. In this case, the HALs would be tagged with radioactive isotopes and introduced into the body. Research all over the world is focused on this new technique, known as isotopically enhanced molecular targeting.

To create new HALs for cancer treatment, Livermore is using the same process developed for producing HALs that bind to toxins and pathogens. The first project will be a HAL for a receptor protein found on the surface of non-Hodgkin's lymphoma, HLA-DR10. The crystal structures of four HLA-DR molecules are known, and unique binding sites on the HLA-DR10 protein have been identified using computer models of the protein generated by computational biochemists Adam Zemla and Daniel Barsky. Computational docking experiments are under way.

The HAL developed for binding HLA-DR10 and targeting human lymphomas will be designed to rapidly pass through the liver and kidney and thus minimize the systemic damage that can occur when antibodies carry radionuclides. "We are striving to convert the meaning of the word 'cancer' from 'fear, pain, suffering, and death' to 'just another treatable disease,'" says Balhorn.



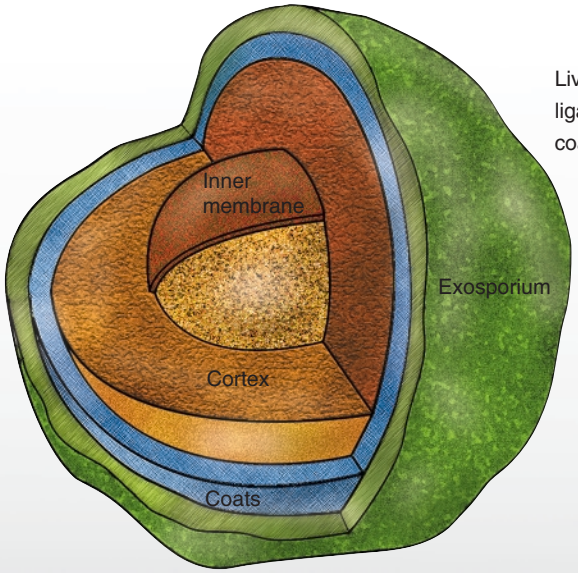
Sites 1 and 2 on the HLA-DR10 molecule (a protein receptor for non-Hodgkin's lymphoma) have been identified.

Targets of Unknown Structure

When a target protein's structure is not known, the team will use a different route to design and synthesize HALs. Computers cannot be used to predict the binding of molecules to

sites on these proteins. But NMR and MS processes that are being developed and fine-tuned now for identifying ligands that bind to known protein structures will identify ligands that bind to unknown structures.

Libraries of molecules will be experimentally screened for their ability to bind to the protein using a combination of Cosman's NMR technique and mass spectrometry methods being developed by chemist Lori Zeller. The molecules that bind will be segregated into sets that bind to different sites. Perkins will then synthesize all possible combinations of pairs of these small molecules using a series of different-size linkers. With Livermore's new Fourier transform ion cyclotron resonance mass spectrometer, mixtures of the HALs and protein can be quickly screened to identify the particular combination of ligands and linkers that produce HALs that bind to the protein. This approach should work well for creating detection reagents for pathogens. In collaboration with groups at Porton Down Defense Science and Technology Laboratory in England, Livermore researchers will design the first HAL for a protein with an unknown structure to bind to a protein on the coat of the anthrax spore.



Livermore will design a high-affinity ligand to bind to protein in the spore coat of *Bacillus anthracis* (anthrax).

Measuring Success

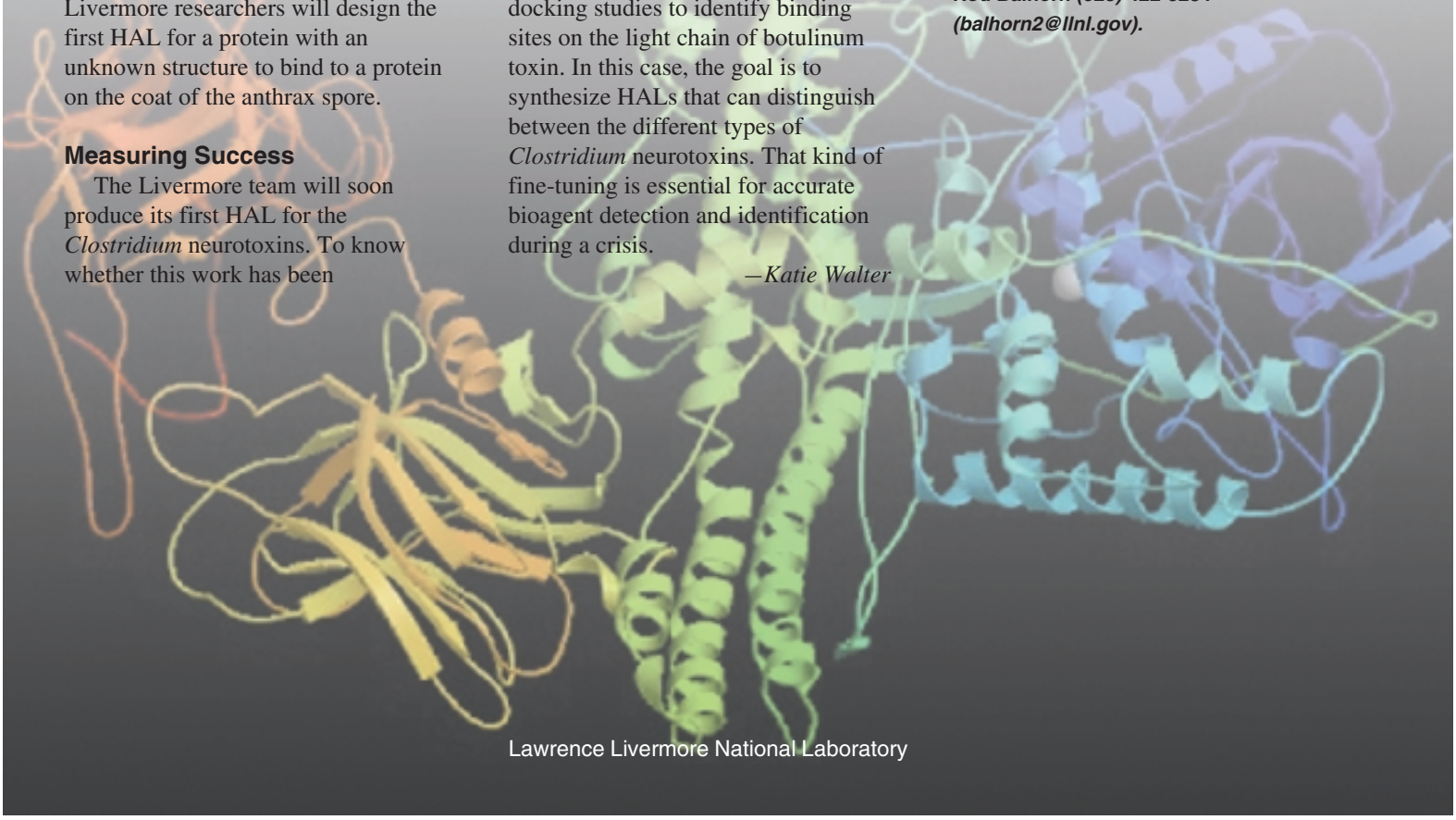
The Livermore team will soon produce its first HAL for the *Clostridium* neurotoxins. To know whether this work has been successful—whether the ligand works as designed in a bioagent detector—the team will send its results to the Department of Defense's Critical Reagent Program to be assessed for quality and specificity.

In the war against bioterrorism, the best defense begins with having the best possible data. Work has begun on docking studies to identify binding sites on the light chain of botulinum toxin. In this case, the goal is to synthesize HALs that can distinguish between the different types of *Clostridium* neurotoxins. That kind of fine-tuning is essential for accurate bioagent detection and identification during a crisis.

—Katie Walter

Key Words: antibodies, bioterrorism, botulinum toxin, cancer treatment, *Clostridium* neurotoxins, high-affinity ligands (HALs), mass spectrometry (MS), nuclear magnetic resonance (NMR), protein structure, synthetic chemistry, tetanus.

For further information contact Rod Balhorn (925) 422-6284 (balhorn2@llnl.gov).



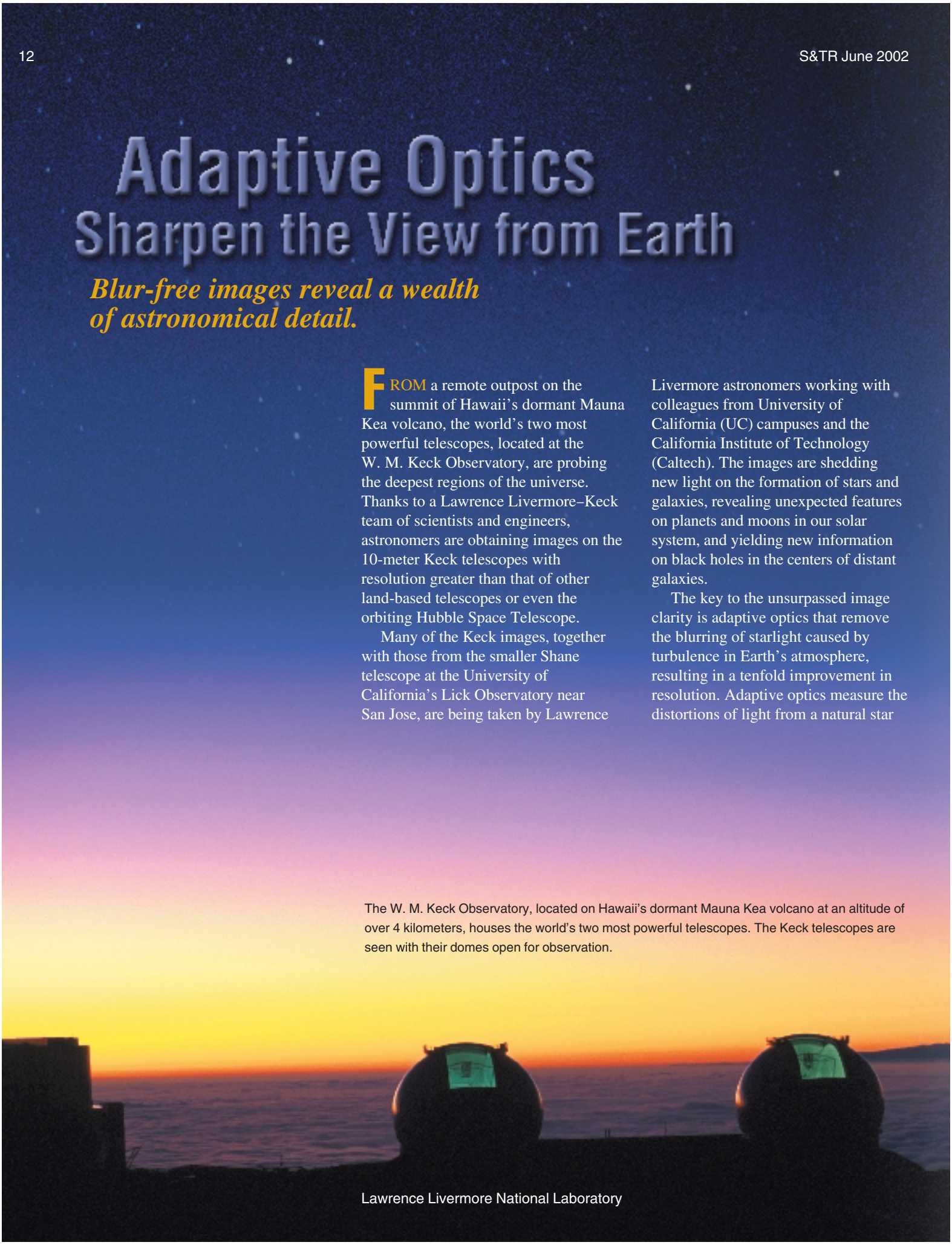
Adaptive Optics
Sharpen the View from Earth

Blur-free images reveal a wealth of astronomical detail.

FROM a remote outpost on the summit of Hawaii's dormant Mauna Kea volcano, the world's two most powerful telescopes, located at the W. M. Keck Observatory, are probing the deepest regions of the universe. Thanks to a Lawrence Livermore–Keck team of scientists and engineers, astronomers are obtaining images on the 10-meter Keck telescopes with resolution greater than that of other land-based telescopes or even the orbiting Hubble Space Telescope.

Many of the Keck images, together with those from the smaller Shane telescope at the University of California's Lick Observatory near San Jose, are being taken by Lawrence Livermore astronomers working with colleagues from University of California (UC) campuses and the California Institute of Technology (Caltech). The images are shedding new light on the formation of stars and galaxies, revealing unexpected features on planets and moons in our solar system, and yielding new information on black holes in the centers of distant galaxies.

The key to the unsurpassed image clarity is adaptive optics that remove the blurring of starlight caused by turbulence in Earth's atmosphere, resulting in a tenfold improvement in resolution. Adaptive optics measure the distortions of light from a natural star



The W. M. Keck Observatory, located on Hawaii's dormant Mauna Kea volcano at an altitude of over 4 kilometers, houses the world's two most powerful telescopes. The Keck telescopes are seen with their domes open for observation.

or one manufactured by a powerful laser, and then remove the distortions by reflecting the light off a deformable mirror that adjusts several hundred times per second to sharpen the image.

A Livermore-designed adaptive optics system was installed on Lick's 3-meter Shane telescope in 1994, and Livermore's sodium-layer laser guide star system was added in 1996. In September 1996, Lick obtained the first significant image improvement using adaptive optics with a laser guide star. Routine astronomical observation with the laser guide star began in August 2001, and the guide star was turned over to the observatory for operation in spring 2002.

Keck's adaptive optics system, for which Livermore scientists and engineers working with their Keck colleagues provided the wavefront control system, made its first observations in 1998 and began general use in late 1999. Its laser guide star, a Livermore–Keck project, was installed in fall 2001 and achieved "first light" on December 23, 2001. "We asked for an early present this year, and just before Christmas, we were given a virtual star that will dramatically increase the research capabilities of the world's largest telescope," announced Frederic Chaffee, director of the Keck Observatory. The laser guide star should be fully integrated with the adaptive optics system by autumn 2002, with the first astronomical observation following shortly thereafter.

Exceptionally Clear Images

Astronomers are reporting exceptional results from the adaptive optics systems installed at the two observatories. At Lick, roughly 50 percent of images are taken using adaptive optics, and about half of those images are made with the laser guide star. At Keck, reports Livermore laser scientist Deanna Pennington, "People are extremely pleased with the adaptive optics systems."

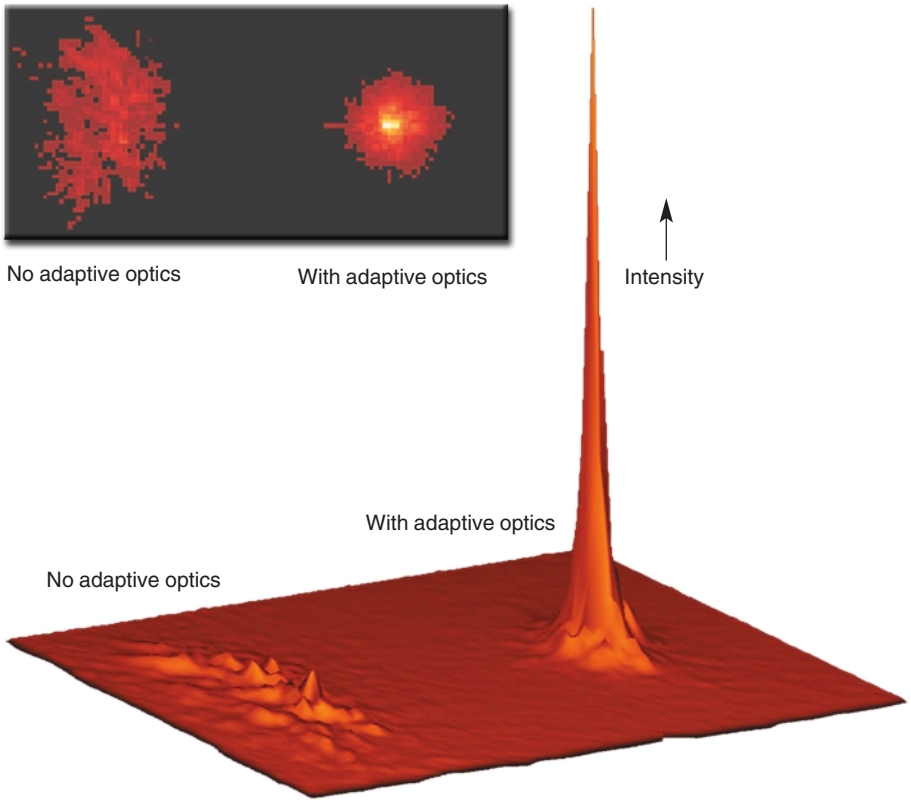
Pennington, who served as laser guide star project leader at both Lick and Keck, says astronomers are clamoring to use the Keck laser guide star because "It makes possible entirely new kinds of observations that astronomers simply couldn't access before."

Livermore astronomers have been among the first to use the adaptive optics systems. Most of them are part of the Livermore branch of the University of California's Institute of Geophysics and Planetary Physics. Since its establishment in 1983, the Livermore branch has been the focus of most astronomical activities at the Laboratory.

Livermore astrophysicists Claire Max, Bruce Macintosh, and Seran Gibbard have been observing objects within our solar system using both Lick and Keck adaptive optics. At Lick, they have been aided by Livermore's Don Gavel, lead engineer for the adaptive optics system. The Livermore efforts focused on observations of Io, Jupiter's largest moon; Titan, Saturn's largest moon; the planets Uranus and Neptune; and various asteroids.

Surprising Storms on Neptune

Astronomers using the Keck telescopes have obtained the best pictures yet of the planet Neptune, the eighth planet from the Sun. Thanks to adaptive optics, the images reveal a

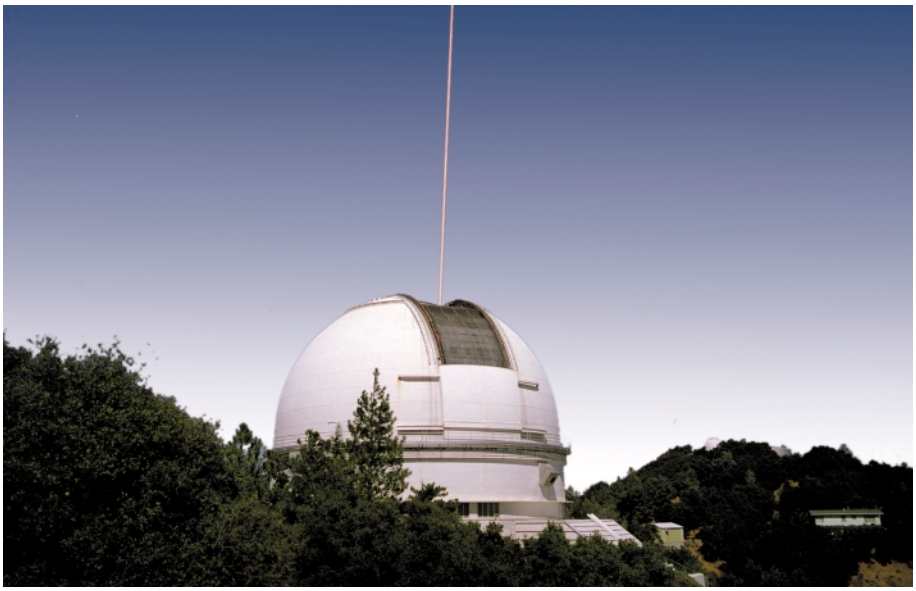


Adaptive optics sharply increase the resolution of images taken at the Lick Observatory near San Jose, California.

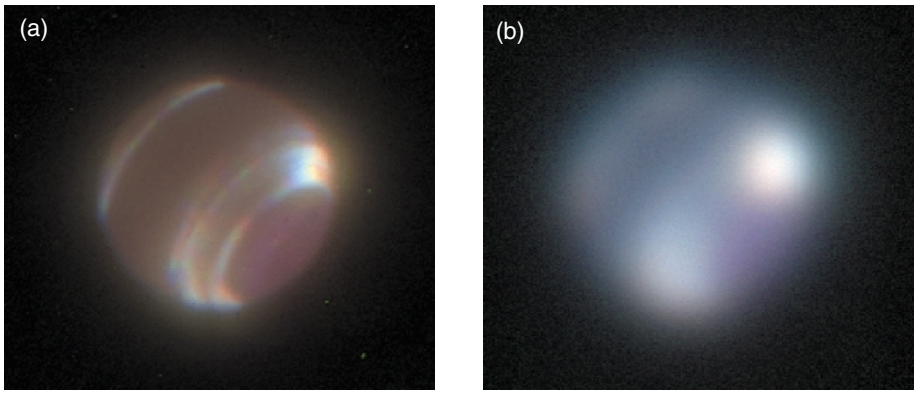
wealth of small-scale features in Neptune's atmosphere, including narrow, bright bands encircling the planet, similar to those observed on Jupiter. There appear to be waves within the bands and regions where the bands move apart and come together as if they are separated by a vortex.

The images suggest violent methane storms with wind speeds reaching more than 1,770 kilometers per hour. The imaging team, which has included astronomers from the UC campuses at Berkeley and Los Angeles (UCLA) and from Caltech, is working to understand what might be the source of the energy driving the extreme weather.

Working with UC Berkeley's Imke de Pater, the team has also captured near-infrared pictures of the planet Uranus, which mark the first ground-based detection of the faint rings around that planet. Also clearly visible is a layer of methane haze on Uranus's south polar cap, tiny cloud features at high northern latitudes, and, inside the planet's bright epsilon ring, three fainter rings.



Time-lapse photograph of the Lick Observatory and the laser guide star.



(a) Astronomers using Keck's adaptive optics have obtained the best pictures yet of the planet Neptune. The images show bands encircling the planet and what appear to be fast-moving storms of haze. (b) The same image without adaptive optics.

Keck images of Io have revealed many glowing volcanoes. Macintosh took the images in the infrared band to detect sources of heat on the moon. Other striking images, taken by Gavel, are of the asteroid Kalliope with its own moon. Gibbard has been using Keck to obtain images of Titan, the only solid body in the solar system besides Earth to have a substantial atmosphere (mostly nitrogen, with about 3 percent methane). Some astronomers believe that Titan's atmosphere may be similar to that of Earth's during our planet's early development. Methane haze in the upper atmosphere obscures Titan's surface features at visible wavelengths. However, in some narrow "transparency windows" in the near-infrared band, surface features can be seen through the haze.

Without adaptive optics, says Gibbard, "Titan looks like a fuzzy star." She has been analyzing a large series of images to assemble the first map of Titan's surface. "By taking many images over time, we can see which features do not change, and these belong to the surface," she says. The use of adaptive optics has replaced a process called speckle imaging, which involved taking hundreds of very fast exposures and assembling them. "Adaptive optics is much simpler," Gibbard says.

Imaging Stellar Nurseries

Macintosh and astronomers from UCLA are using adaptive optics on Lick and Keck to study the formation and evolution of planetary systems in the Trapezium (sword) region of the constellation of Orion. This region, the

closest large-scale star formation to our Sun, serves as a stellar nursery.

"One of the most fundamental questions in modern astronomy is the possibility of the existence of other solar systems like our own, those with potentially habitable planets," Macintosh says. He notes that although planetary systems have been detected through indirect methods, all are different from our solar system because they have massive, Jupiter-like planets occupying the inner part where Earth is located in our system. "It is unclear which type of system is more common in the universe," says Macintosh.

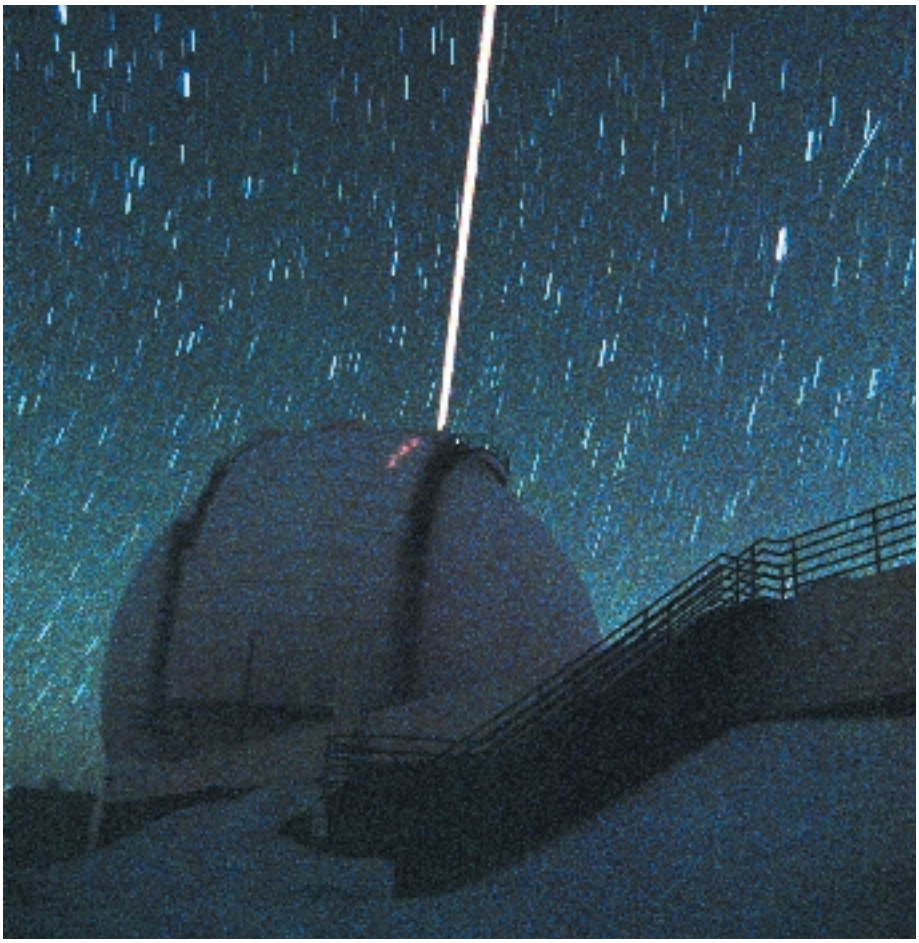
The astronomers first use Lick to scout for promising young stellar systems and then travel to Keck to obtain high-resolution images. Bright stars found in the constellation serve as handy natural guide stars for the adaptive optics system.

Macintosh says that large planets (about the size of Jupiter) that are 10 million years old or younger radiate significant near-infrared light. Keck's adaptive optics system can detect these planets even though they are a million times dimmer than the star they orbit. Macintosh has also imaged several of the Orion proplyds—protoplanetary disk envelopes surrounding young stars—that are being disrupted by intense radiation from nearby supermassive stars.

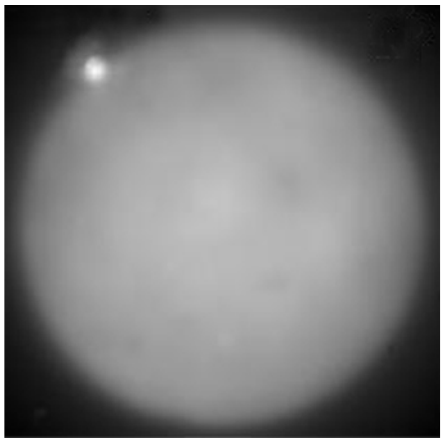
"Keck could be the first telescope to image a planet orbiting a star outside of our solar system," Macintosh says. He adds, "Keck's adaptive optics system represents the most significant advance in astronomical capabilities since the launch of the Hubble Space Telescope."

Jennifer Patience is studying the binary star systems that are found among the young stars in Orion's Trapezium. "We want to know how common it is for planets to form in binary systems," she says. Astronomers believe that the presence of a nearby companion star may disrupt circumstellar disks surrounding young stars (circumstellar disks provide the raw materials for planet formation). Working with astronomers from UC Berkeley and UCLA, she uses Keck and Lick adaptive optics systems to look at star systems in the near-infrared spectrum and to see through clouds of galactic dust and gas that mask images in visible light.

The team has imaged 150 stars in Orion with resolution never before attained. Keck's adaptive optics make it possible to resolve binaries with separations comparable to the distance



"First light" from the laser guide star on the Keck II telescope, December 23, 2001.



This image of Io, Jupiter's largest moon, reveals volcanic activity. (Image courtesy of Keck Observatory.)

Astronomy Benefits from Laser Advances

Since their invention, ground-based telescopes have suffered from blurred images caused by Earth's fast-moving and turbulent atmosphere. However, advances in optics and computer technology have made it possible to sharply reduce this blurring by the use of adaptive optics that correct atmospheric distortions and allow ground-based telescopes to reach their theoretical maximum resolution.

Adaptive optics systems have traditionally required the astronomer to find a bright star as a reference point of light. However, less than 1 percent of the sky contains stars sufficiently bright to be of use as a reference light. To extend the usefulness of adaptive optics, Livermore scientists developed a laser system that creates a virtual reference star high above Earth's surface to guide the adaptive optics system. The laser guide star is created by projecting light from a dye laser on a layer of sodium atoms that are in the atmosphere 90 to 100 kilometers above Earth.

The main components of an adaptive optics system using a laser guide star are a wavefront sensor camera equipped with a charge-coupled device detector, a control computer, a deformable mirror, a pulsed dye laser that is tuned to the atomic sodium resonance line at a wavelength of 589 nanometers, and a set of solid-state lasers to pump, or energize, the dye laser. The dye laser, similar to that pioneered at Livermore for its Atomic Vapor Laser Isotope Separation program, creates a glowing star of sodium atoms measuring less than 1 meter in diameter at an altitude of about 100 kilometers above Earth's surface. This artificial reference can be created as close to the astronomical target as desired so that the light from the laser star and the observed object pass through the same small part of the atmosphere.

At the telescope, wavefront sensors measure distortions due to atmospheric turbulence, using light from the guide star as a reference. The sensors relay this information to a computer, which in turn controls the movements of tiny actuators attached to the back of a deformable mirror. The mirror changes its shape hundreds of times per second to cancel out atmospheric distortion.

Near-infrared images obtained with the adaptive optics systems on the telescopes at the W. H. Keck Observatory in Hawaii are superior to images obtained with the Hubble Space Telescope because Hubble's light-gathering mirror is much smaller. (Adaptive optics will not, however, replace space-based observatories, many of which are designed to sample certain bands of electromagnetic radiation such as ultraviolet light that are blocked by Earth's atmosphere.)

Lick's dye laser projects light into the sky through a 30-centimeter refractive telescope that is mounted on the side of the main telescope. The laser was designed and built by Livermore's Herbert Friedman. The deformable mirror has 127 actuators to raise or lower a tiny part of the front surface by up to 4 micrometers.

The laser guide star at the Keck II telescope uses a 20-watt dye laser, the most powerful laser in use at a telescope. The laser light is projected onto the sky by a telescope with a 50-centimeter lens attached to the side of the 10-meter Keck II telescope. A 15-centimeter-diameter deformable mirror is adjusted continuously by 349 actuators.

Keck's laser guide star was built at Livermore and then reassembled at the observatory's headquarters in Waimea, Hawaii, which is slightly less than 1 kilometer above sea level. The observatory's telescopes are located at the summit of the Mauna Kea volcano, over 4 kilometers above sea level. Scientists observe on these telescopes remotely from the Waimea headquarters to avoid the risk of sickness from extended exposure to Mauna Kea's high altitude.

During the two-year temporary installation at headquarters, the Livermore team of Deanna Pennington, Curtis Brown, Pam Danforth, and Holger Jones made extensive improvements. "We installed a significant level of automation and diagnostics on the laser guide star system to make it more reliable and robust and permit it to be operated remotely from Waimea," says Pennington, laser scientist and systems engineer at both Lick and Keck. She notes that installing the adaptive optics system and laser guide star at Lick gave the Livermore team valuable experience in designing the larger system at Keck. The laser system was installed and activated on the telescope at the 122-kilometer summit over a 6-month period, culminating in the "first light" demonstration on December 23, 2001.

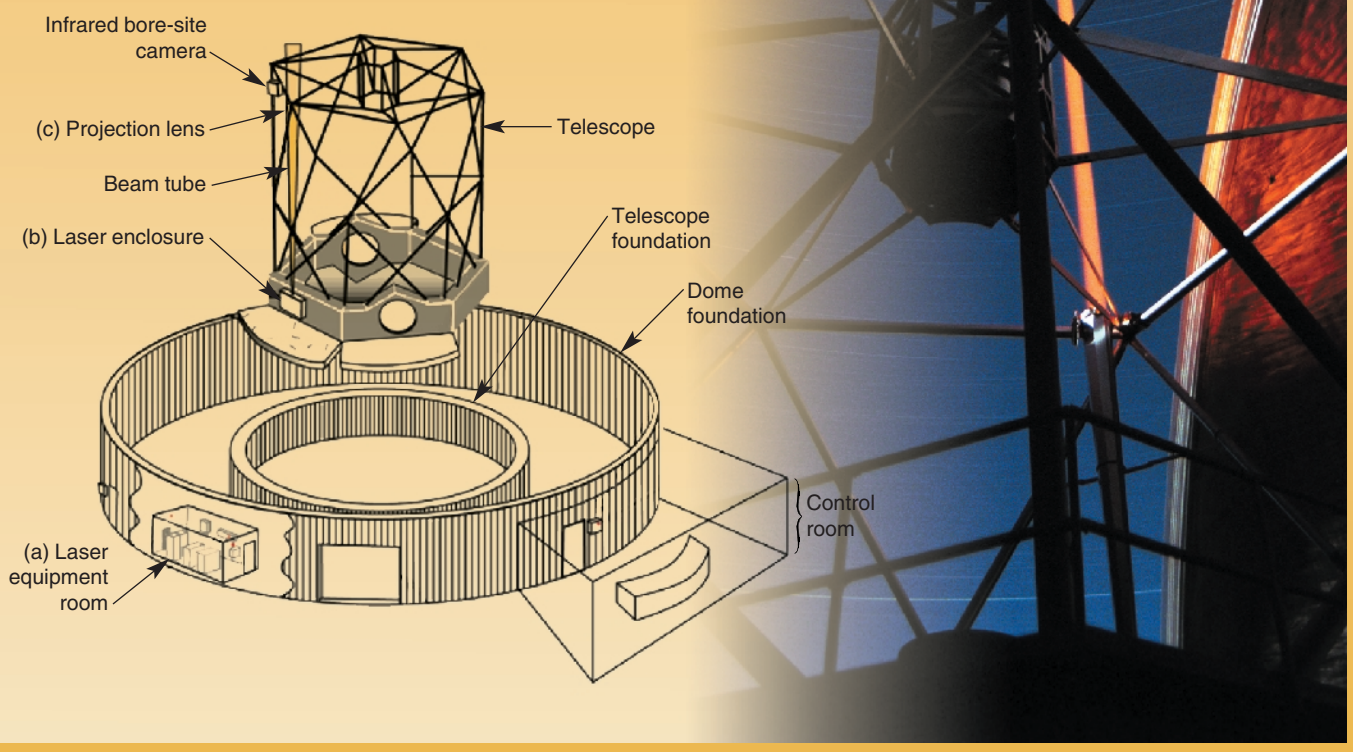
Keck's adaptive optics and laser guide star embody more than two decades of Livermore experience in adaptive optics technology. Adaptive optics systems with adjustable mirrors have been used on a succession of increasingly powerful lasers at Livermore, and they will be used on the National Nuclear Security Administration's National Ignition Facility (NIF), under construction at Livermore.

Claire Max and Friedman started Livermore's work on laser guide stars in the early 1990s. Feasibility tests conducted at Livermore in 1992 demonstrated the first laser guide star at usable power levels and determined the requirements for a telescope version.

Livermore scientists are working on the next generations of adaptive optics. About 20 Livermore employees belong to the Adaptive Optics program within the Physics and Advanced Technologies Directorate. One team is developing more reliable deformable mirrors based on microelectromechanical technology.

With funding from the Center for Adaptive Optics (see the box on p. 19) and the European Southern Observatory in Chile, Pennington will lead another group of Livermore scientists within the NIF Programs Directorate who are investigating fiber lasers to replace the current dye laser. Fiber lasers, widely used in the telecommunications industry, will be part of the NIF front end and will produce the laser beam before it is amplified. Pennington says that fiber lasers provide an "elegant solution" for generating 589-nanometer light because they are compact, efficient, and robust.

An overview of the layout within the dome of the Keck II telescope. (a) The laser equipment room on the dome floor houses the pulsed dye laser master oscillator, yttrium–aluminum–garnet pump lasers, and control systems. (b) The laser room on the elevation ring of the telescope houses an optics bench containing two stages of dye amplification, numerous diagnostics, and the bottom half of the projection telescope. (c) The 50-centimeter projection lens is located at the top end of the telescope.



between our Sun and Uranus, a distance that is less than the diameter of circumstellar disks. “We now have the capability of resolving most binary systems, including a range inaccessible to previous surveys,” Patience says. She notes that with the resolving power of Keck’s adaptive optics system, a person standing on Mauna Kea, located on the big island of Hawaii, could see objects as small as 1 centimeter tall on the island of Oahu, approximately 400 kilometers away.

Peering into Black Holes

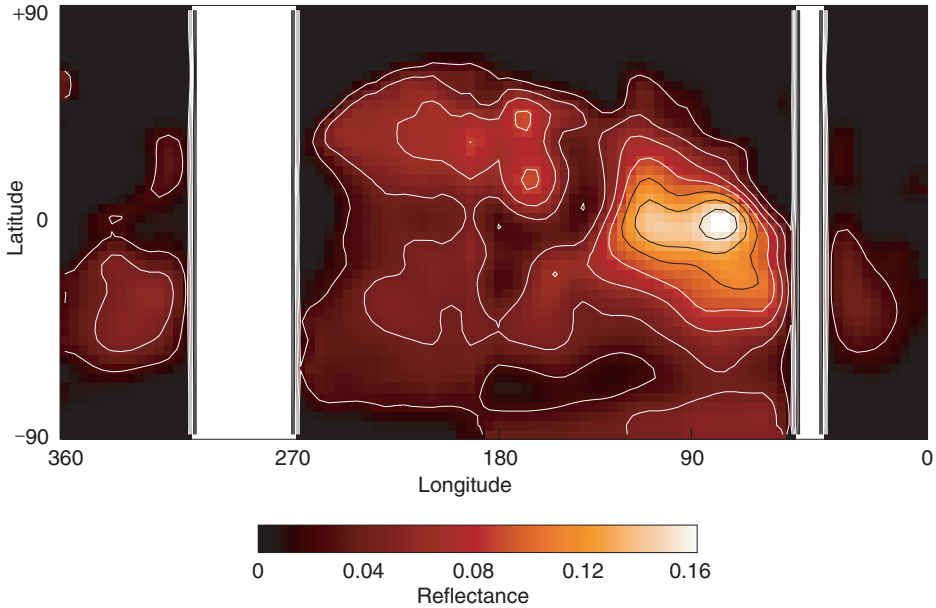
Max, her colleague Gaby Canalizo, and astronomers from UC Santa Barbara, are using adaptive optics on Lick and Keck telescopes and Lick’s laser guide star to observe nearby active galactic nuclei, which are small, extremely bright central regions in some galaxies. Very distant and bright active galactic nuclei are known as quasars. Active galactic nuclei are thought to contain black holes at their centers, which suck up stars, planets, and gas from the surrounding galaxy in a process called accretion. In some cases, the material is then shot out from the region surrounding the black hole at high speeds in outflows known as jets.

Max notes that for 30 years, Department of Energy laboratories have been doing pioneering work on the high-energy processes involved in black-hole formation and emission. However, only in the past few years has direct evidence for black holes begun to emerge—in the form of high-resolution observations that probe the active galactic nuclei close to the central black hole.

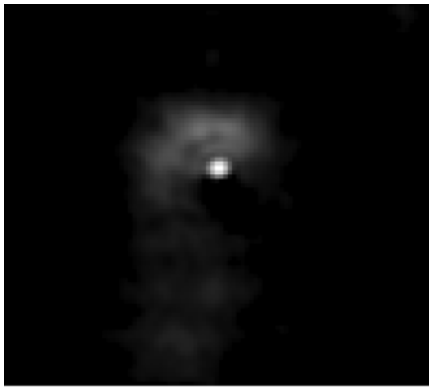
Max and Canalizo’s team is observing energy outflow from the process of accretion of matter into the most massive black holes in nearby galaxies. The images enable astronomers to explore the region nearby and the evolution of the central black holes. In the process, the astronomers have found double active galactic nuclei suggestive of galaxy mergers, which are believed to be a cause of black hole formation.

Looking to the Future

When the Keck laser guide star becomes available for viewing, Livermore scientists will be among the first to use it and thereby help to make laser guide stars a more accepted tool of astronomical research. Pennington notes that a National Academy of Sciences panel has identified laser guide stars as a key technology for advancing astronomy. Most experts say that the next generation of giant telescopes will not be feasible without adaptive optics systems equipped with laser guide stars.



The first map of the surface of Titan, Saturn’s largest moon, is being assembled with the help of adaptive optics. Colors denote reflectance, with 1.00 corresponding to the reflectance of a perfect mirror. Data from current observations are filling in the blank areas.



Keck adaptive optics image of a protoplanetary disk envelope surrounding a young star in the Trapezium region of the constellation Orion.

New Center Spreads the Word

Lawrence Livermore is a major partner in the Center for Adaptive Optics, which is headquartered at the University of California (UC) at Santa Cruz. The center, funded by the National Science Foundation, began operations in November 2001. The 27 partner institutions in the center also include several other UC campuses, the University of Chicago, the California Institute of Technology, the University of Rochester, the University of Houston, Indiana University, and 17 other partners.

The center's director is Jerry Nelson, professor of astronomy and astrophysics at UC Santa Cruz. Nelson designed the twin telescopes at the W. M. Keck Observatory in Hawaii. Livermore scientists Claire Max and Scot Olivier are associate directors, and Livermore scientists play important roles in center activities and sponsored research.

The center coordinates the efforts of researchers across the country involved in the growing field of adaptive optics for astronomical and vision science. The center also operates science education and outreach programs for scientists and college students.

"Our goal is to provide the sustained effort needed to bring adaptive optics from promise to widespread use by astronomers and vision researchers," says Max. She predicts that most large ground-based telescopes will have adaptive optics systems within the next few years. Relatively few astronomers, however, have experience with adaptive optics, let alone laser guide stars. "We want to inform the broader astronomical community about adaptive optics through conferences and workshops," she says.

Max points out that adaptive optics are also used in vision science to compensate for aberrations in the eye that affect vision and impede efforts to study the living retina. Adaptive optics has made it possible to obtain images of the living human retina with unprecedented resolution, enabling researchers to see individual light receptors. Adaptive optics may also provide normal eyes with supernormal vision. A team of Livermore researchers led by Olivier is developing a high-resolution liquid-crystal adaptive optics system for human vision correction that will be used at UC Davis to study the limits of human visual acuity.

However, as a telescope gets larger, the requirements for an adaptive optics system become increasingly rigorous. The proposed California Extremely Large Telescope (CELT), a collaboration between UC and Caltech, is designed to have a 30-meter-diameter mirror, three times the size of Keck's. CELT's adaptive optics system will probably require multiple laser guide stars with several mirrors working together to correct for different layers of atmospheric turbulence. Each mirror may require about 5,000 actuators.

Thanks to increasingly powerful telescopes, more capable adaptive optics systems, and advanced guide-star lasers, the heavens are sure to be revealing more of their secrets in the new millennium.

—Arnie Heller

Key Words: active galactic nuclei, adaptive optics, atomic vapor laser isotope separation, binary star, black hole, California Extremely Large Telescope (CELT), deformable mirror, dye laser, Hubble Space Telescope, laser guide star, Lick Observatory, W. M. Keck Observatory.

For further information contact Deanna Pennington (925) 423-9234 (pennington1@llnl.gov).

For online information on the W. M. Keck Observatory:
www2.keck.hawaii.edu:3636

For online information on the Lick Observatory:
www.ucolick.org/

For online information on the Center for Adaptive Optics:
cfao.ucolick.org/

Experiments Re-create X Rays from Comets

EARTH is continually showered by x rays traversing the universe from our Sun and other hot stellar objects. A major branch of astronomy is devoted to detecting and studying x rays from distant stars and galaxies, and Lawrence Livermore scientists have long studied the x rays that are produced from nuclear detonations.

However, it came as quite a surprise to scientists in 1996 when the Rosat X-Ray Satellite detected low-energy (less than 1 kiloelectronvolt) x rays streaming from the comet Hyakutake. X-ray emission is usually associated with hot plasmas from stars, nuclear reactions, and black holes, not from ice-cold objects such as comets. Since the original discovery, other x-ray satellites have established that several other comets traveling through our solar system emit x rays with fluxes, or intensities, as high as 10^{25} photons per second.

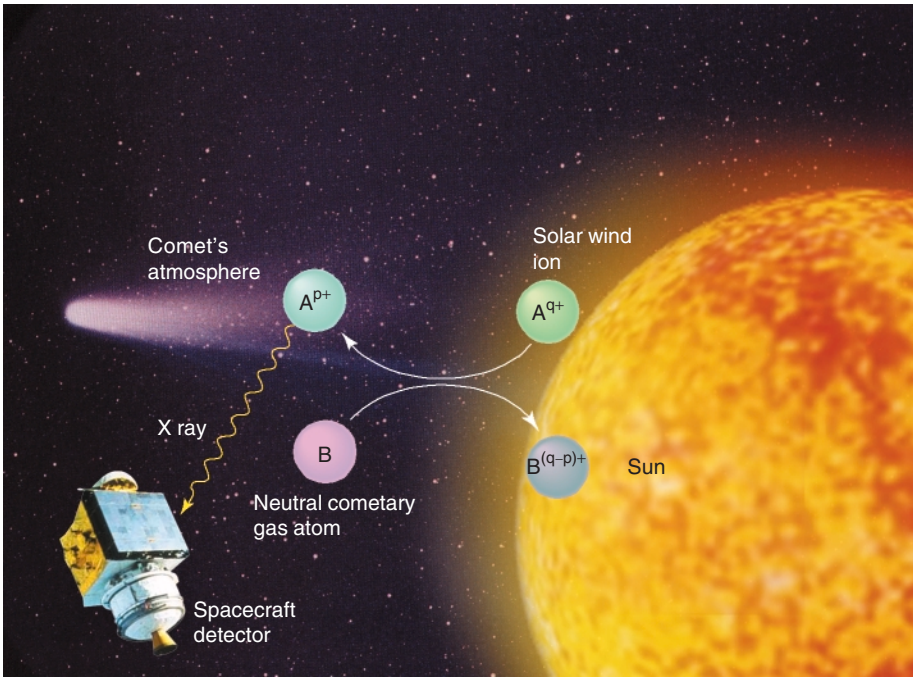
To help resolve the apparent contradiction, a national team of scientists headed by Lawrence Livermore physicist Peter Beiersdorfer is working on the laboratory production of low-energy x rays identical to those produced by comets traveling near the Sun. The team is using Livermore's electron beam ion trap (EBIT) to produce the x rays and an x-ray spectrometer (XRS) designed by the National Aeronautics and Space Administration (NASA) to detect them.

The research is providing much greater understanding about the x rays that are emitted by comets as they pass the Sun. The effort is also providing scientists with valuable information that will help them interpret data to be collected by a joint U.S.–Japan x-ray satellite mission scheduled for launch in 2005.

Primordial Chunks of Ice

Comets are odd-shaped chunks of ice (water and frozen gas) and dust a few kilometers to a few tens of kilometers in diameter. They are the oldest, most primordial objects in the solar system. X rays emanate from a comet's nebulous atmosphere called a coma, which can stretch tens of thousands of kilometers in front of or behind the comet. The coma is formed when the comet gets close enough to the Sun so that some of the ice is vaporized.

More than a dozen theoretical models were first proposed to explain why comets give off x rays. Some models predicted that comet x rays are reradiated x rays from the Sun. Other models were based on some kind of interaction between the molecules



The current explanation for comet x rays is called charge exchange. This process is believed to occur when heavy ions (A^{q+}) from the solar wind flowing from the Sun (right) collide with electrically neutral atoms and molecules (B) in the comet's atmosphere (left). During a collision, a heavy ion captures one or more electrons from a comet's atmospheric atom, ionizing it to $B^{(q-p)+}$. The solar wind ion, now A^{p+}, momentarily enters an excited state and kicks out an x ray as the electrons return to a low-energy state. The x ray can be detected by a spacecraft (lower left).

in the comet's thin atmosphere and ions or electrons from the Sun's solar wind, the stream of particles that blow off the Sun's corona at 400 kilometers per second.

The current leading explanation is called charge exchange. This process is believed to occur when solar wind forces heavy ions of carbon, nitrogen, oxygen, and other elements to collide with the electrically neutral atoms and molecules found in a comet's atmosphere. During a collision, a heavy ion from the solar wind captures an electron from a comet's atmospheric atom or molecule and momentarily enters an excited state. The ion immediately kicks out an x ray as the electron returns to a low-energy state.

"Very little experimental data are available on charge-exchange-induced x rays and what the spectrum emission lines look like," says Beiersdorfer. "The goal of our research is to re-create, in the laboratory, the same x-ray emissions that are produced when the solar wind and comets interact. In this way, we can better understand the nature of charge exchange and help other scientists interpret data taken by x-ray satellites."

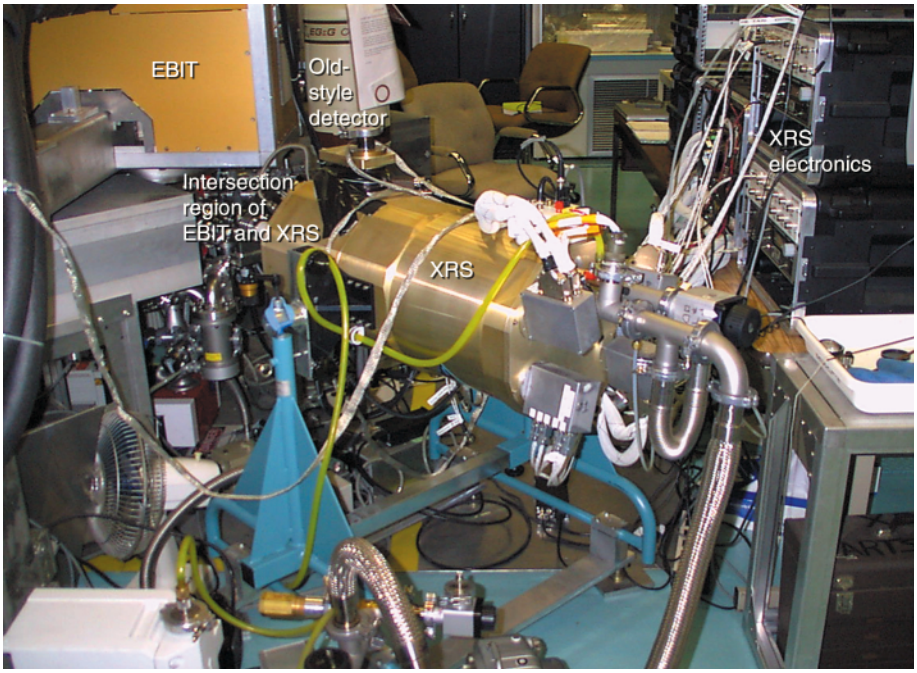
The research, supported by Laboratory Directed Research and Development funding and NASA, is a collaboration between scientists from Livermore, NASA's Goddard Space Flight Center, and Columbia University. The investigators include Daniel Thorn, Mark May, and Hui Chen from the Laboratory; Richard Kelley, Scott Porter, Caroline Stahle, Keith Gendreau, Gregory Brown, Andy Szymkowiak, and Kevin Boyce from Goddard; and Steven Kahn from Colombia. In addition, space researchers Casey Lisse from the University of Maryland and Bradford Wargelin from the Harvard Smithsonian Observatory are aiding the research effort.

The team is using Livermore's EBIT, which produces and traps highly charged ions by means of a high-current-density electron beam instead of traditional high-energy particle accelerators. The instrument was developed in 1985 by Laboratory physicists Mort Levine and Ross Marrs. Other electron beam ion traps, most of which are based on Livermore's design, are used at research centers in the U.S., Europe, and Japan.

EBIT's electron beam collides with selected ions to strip them of one or more electrons, depending on the beam's energy. The current version, named SuperEBIT, can produce an electron beam energy of up to 250 kiloelectronvolts, enough to make uranium (U^{92+}) ions. "SuperEBIT can produce virtually any ion, x ray, or visible photon desired," says Beiersdorfer.

New Generation of Spectrometer

The XRS was designed by NASA for Japan's Astro-E X-Ray Satellite, but a failed rocket launch in February 2000 means a wait of five years before its replacement, the Astro-E2 Satellite, can be placed in orbit. Fortunately, the Astro-E's engineering spare XRS was still available for laboratory x-ray astrophysics measurements. It was sent to Livermore after the failed launch



At Livermore's electron beam ion trap (EBIT) facility, scientists study the charge-exchange process and the effects of different ions and interaction gas molecules on the x-ray emission patterns recorded by the x-ray spectrometer (XRS) (front). The EBIT (in back) provides a source of ions to re-create solar wind particles. At the left is an old-style spectrometer. Also shown is the intersection of the XRS and EBIT.

of Astro-E. The Livermore–Goddard team adapted the instrument to fit on EBIT and uses it to study x-ray detection.

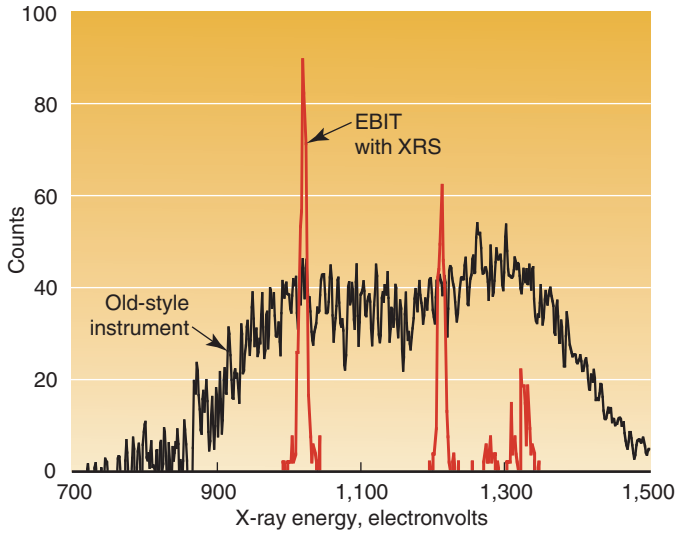
The XRS, a new generation of spectrometer, uses microcalorimeter detectors that are so sensitive they can detect the heat produced by the energy of an individual x-ray photon. To accomplish this, its microcalorimeter array is cooled to an extremely low temperature of –460°F (0.060 kelvin). (The absence of all heat, called absolute zero, is 0.0 kelvin, and has never been achieved.) The XRS has an energy detection range of 0.4 to 10 kiloelectronvolts with an energy resolution of 10 electronvolts, which allows scientists to see much finer detail in the x-ray spectrum.

At the Livermore EBIT facility, scientists study the details of the charge-exchange process and the effects of different ions and interaction gas molecules on the x-ray emission patterns recorded by the XRS. The EBIT facility provides a source of ions to re-create solar wind particles interacting with atoms and molecules in a comet's atmosphere. The XRS records the x-ray spectra, and diagnostic detectors characterize the experimental conditions. In effect, says Beiersdorfer, the EBIT facility has become a test stand for the Astro-E2 satellite, which will carry an enhanced XRS.

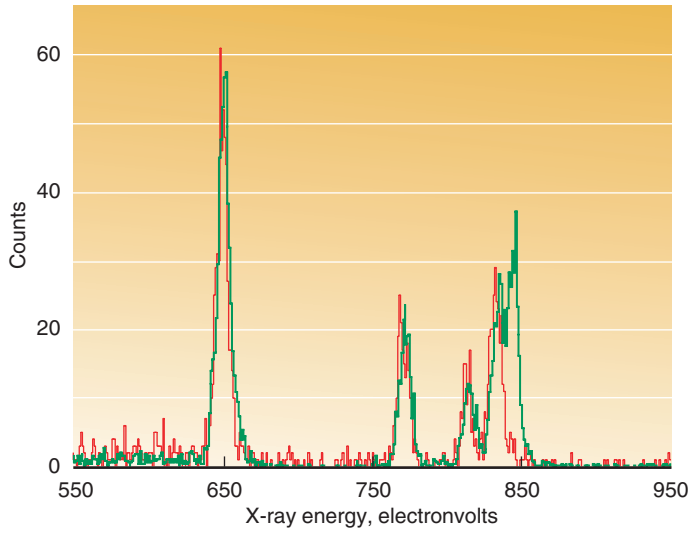
Experiments Mimic Space Interactions

The EBIT experiments begin with the production of several million ions of either carbon, oxygen, neon, magnesium, silicon, or iron. These ions are found in the solar wind and are believed to be involved in charge-exchange reactions with comets. The beam is then turned off, and the trap is operated in the so-called magnetic mode, in which the ions are confined by a magnetic field to a volume of about 2 cubic centimeters. At this density, the physics is the same as that found in the vicinity of a comet passing close by the Sun. (A greater density of ions would introduce completely different physics regimes.) Next, neutral molecules of water, methane, nitrogen, or carbon dioxide, all of which have been identified in comets' atmospheres, are injected into the trap.

For a few hours, the XRS records the x rays produced by charge-transfer collisions between the ions and the neutral molecules. The result is a catalog of emission lines that serve as tell-tale fingerprints of a particular ion's x-ray-producing collision. Beiersdorfer says that the experiments are validating the hypothesis that charge exchange is a viable mechanism for producing comet x rays, although the exact mechanics of the process are probably more complex than is known.



Data on charge-exchange-induced x-ray emissions supplied by electron beam ion trap (EBIT) experiments with the x-ray spectrometer (XRS) are enormously more detailed than data supplied by old-style detectors. This graph compares the data supplied by each instrument in registering x-ray emissions caused by charge-exchange reactions involving an ion of neon (Ne^{9+}).



Plots of x-ray emissions from an ion of oxygen (O^{7+}) caused by interactions of O^{8+} with methane (CH_4, the green trace) or with nitrogen (N_2, the red trace) reveal subtle changes in the x-ray emission lines when these different neutral gases collide with the heavy ions. The changes are found near 850 electronvolts.

The researchers discovered that the x-ray emission pattern changes with the kinetic energy of the ions. They found that the average x-ray energy emitted by the ions shifts to higher values as the kinetic energy of the ions is lowered. They also uncovered subtle changes in the x-ray emission lines when different neutral gases collide with the heavy ions. "The composition of the interaction gas is another important variable," says Beiersdorfer.

Comets as Probes

Beiersdorfer predicts that careful detection and measurement of x rays produced by the interaction between the solar wind and comets will one day provide a powerful means to monitor space "weather" inside the solar system without the need for spacecraft circling the Sun. In this way, he says, comets could be used as probes to measure the intensity, speed, and composition of the solar wind, its intermittent "quiet time," and the chemical composition of comet gases.

"Given that more than three bright comets with appreciable x-ray emissions enter the inner solar system each year, their x rays can provide a valuable diagnostic of the solar wind. This capability has opened up a whole new window to our solar system; it's a very rich field."

Some astronomers have conjectured that as the solar wind slows down throughout the heliosphere, it may generate weak x rays through charge-exchange reactions with natural gas streaming in from the interstellar medium (mostly hydrogen atoms). If this hypothesis is borne out by x-ray satellite data, astronomers will have to revise their assumption that the soft x-ray background that seems to permeate the universe may in fact be partly due to charge-exchange reactions from the solar wind.

Small Handbook on Comet X Rays

The result of the EBIT experiments will likely be a small handbook for scientists to guide their interpretation and understanding of the comet x-ray data sent back by Astro-E2, beginning in 2005. "The scientific community will be well prepared when Astro-E2 launches," says Beiersdorfer. In the meantime, NASA has committed a second, advanced XRS for the EBIT team's research.

As the EBIT experiments continue, other scientists are looking at the theoretical model of charge exchange. Atomic theorists Ronald Olson from the University of Missouri at Rolla; Jim Perez from Luther College in Decorah, Iowa; Charles Weatherford from Florida A&M University in Tallahassee; and Burke Ritchie from Livermore are aiding the research effort. Lawrence Livermore researchers have extensive experience in modeling short-wavelength radiation phenomena, and physicist Ritchie is using high-performance supercomputers to elucidate in greater detail charge-exchange reactions using the quantum theory of atomic collisions.

Clearly, primordial chunks of dirty ice still hold a few surprises for scientists.

—Arnie Heller

Key Words: charge exchange, comets, electron beam ion trap (EBIT), microcalorimeter, solar wind, x rays, x-ray spectrometer (XRS).

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Chemistry—50 Years of Exploring the Material World

OF the 70 or so people who came to work at the Livermore branch of the University of California Radiation Laboratory in September 1952, nearly a third were chemists, chemical engineers, and material scientists, hired to support the Laboratory's fledgling nuclear weapons program. These personnel had two immediate tasks. At the front end of a weapon's development, Livermore chemists had to be able to form parts out of unusual materials such as plutonium and uranium for nuclear test devices. Then after each device was tested, they had to be able to analyze the radioactive components of the leftover debris and gases to help determine the weapon's performance.

Livermore's chemists wasted no time setting up a processing laboratory in the only available room equipped with running water: the women's restroom of the bachelor officers' quarters of the former naval air station that was the home of the new "Rad Lab." By spring 1953, they had also put a laboratory in the former dispensary and set up a chemical fabrication capability in the assembly hall. The women's restroom and the assembly hall were merely temporary measures. The first permanent building at the Livermore site, completed in 1954, was built for the chemistry organization.

As the Laboratory grew and evolved, so did its chemistry organization. From studies of isotopes—particularly in the actinide group of elements—Livermore chemists built a first-class institute to study heavy elements and helped discover new elements. They developed high explosives that were safer but still delivered the power needed by weapons designers, and they tailored other special materials for specific applications. Chemists were the first at the Laboratory to use computers to automate laboratory processes. And their involvement with the computational world didn't stop there. With the explosion in computational abilities and sophisticated experimental capabilities of the past decade, chemists and material scientists are gaining a more complete and fundamental understanding of the behavior of materials as esoteric as aging plutonium and as common as the surface of water.

> *Nothing in life is to be feared. It is only to be understood.*
>
> *—Marie Curie, physicist and winner of the Nobel Prize for physics (1903) and chemistry (1911)*

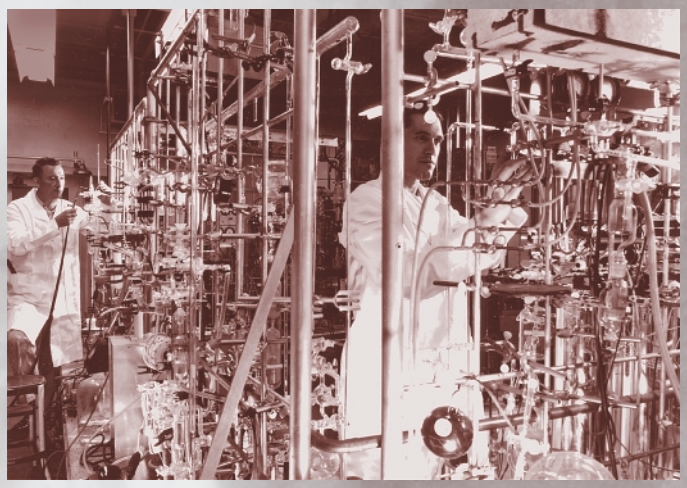
Of Yields, Isotopes, and Heavy Elements

In his preliminary plan for the Laboratory, Herb York, the young physicist whom Ernest O. Lawrence designated to get the Livermore project up and running, made specific note of the need for a radiochemistry group. Radiochemistry, a fairly new field in 1952, is the study of radioactive substances and is closely tied to nuclear chemistry, which is the study of the atomic nucleus, including fission and fusion reactions and their products. Radiochemical diagnostics were crucial to determining how well a device performed in a test. An exploding device produces large neutron fluxes. Those neutrons interact with the device materials, creating different isotopes and other elements. By determining the differences between the materials in the weapon before the explosion and those produced by the explosion, scientists can deduce what happened during the test.

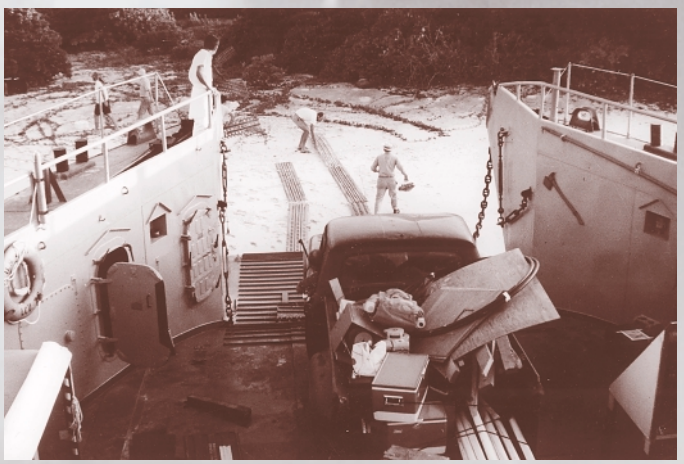
Obtaining those results was a long, extremely complex process, and not without its hazards. (See the box on p. 27.) Livermore conducted nuclear experiments for nearly four decades, at first in the atmosphere and later underground. Throughout that time, radiochemists examined fission products, heavy elements, products resulting from neutron capture, products from other neutron interactions, and short-lived gases. Their results—when combined with results from nonchemical diagnostics (such as those described in *S&TR*, April 2002, pp. 22–24)—gave weapon designers a picture of how well the device worked.

For example, to determine the fusion yield of a device, chemists would add detectors—small quantities of specific elements, such as yttrium—to various parts of a device as it was being made. Radiochemist David Nethaway, who started his Laboratory career during the early days of atmospheric testing, explains, "Certain reactions between neutrons and detector materials such as yttrium only occur when the neutron energies are above a particular threshold." For instance, the reaction that converts an atom of yttrium-89 to an atom of yttrium-88 plus two neutrons only occurs when a neutron with an energy greater than 12 megaelectronvolts (MeV) smashes into the yttrium-89 atom. "By measuring the amount of yttrium-88 in debris samples recovered from the test, we could determine the fluence of 14-MeV neutrons, and from that we infer a fusion yield," says Nethaway. (See *S&TR*, May 2002, pp. 16–21.)

Over time, Livermore's radiochemical expertise was applied to other projects as well. In the early 1970s, radiochemists performed radiological surveys of Enewetak Atoll in the Pacific Ocean to prepare for the islanders' return after the atmospheric tests of the 1950s. The initial focus was on elements of particular use to nuclear weapons research and testing, including the set of elements known as actinides. This work led to the establishment of the University of California's Glenn T. Seaborg Institute for Transactinium Science at Livermore in 1991. Since the Laboratory's early days, Livermore chemists have also been involved in searches for new elements to add to the periodic table. This work includes detailed studies of debris from the Hutch Event, a 1969 underground test specifically designed to produce superheavy



A 1957 photo of Livermore's chemists setting up equipment in a gas analysis laboratory. Rare gases such as krypton and xenon were regularly analyzed as part of the chemical diagnostics for nuclear weapon tests.



In the mid-1950s, inhabitants of Enewetak Atoll in the South Pacific relocated when the U.S. began conducting atmospheric nuclear tests nearby. When the islanders were preparing to reinhabit Enewetak, Livermore led a research force, members of which are pictured here, drawn from 19 federal and scientific organizations to perform a radiological survey of the soils, plants, and marine environment of the islands.

elements, and culminates with the recent synthesis of elements 114 and 116. (See *S&TR*, January/February 2002, pp. 16–23.)

After a decade of underground testing at the Nevada Test Site, Livermore's radiochemists began studying the movement in groundwater of radioactive elements from those tests. Using both radioactive and stable isotope tracers, these scientists investigated groundwater sources, ages, travel times, and flow paths. Having proved their usefulness at the Nevada Test Site, isotope tracer methodologies have since been applied to other water resource projects, including one for the Orange County Water District in southern California. (See *S&TR*, November 1997, pp. 12–17.)

Today, radiochemists and nuclear chemists are also contributing their skills in radiation detection, gamma-ray spectrometry, and mass spectrometry to programs aimed at preventing nuclear proliferation. For example, sophisticated codes originally developed to analyze the complex gamma-ray emissions from nuclear explosion debris now form the standard for analyzing samples collected by the International Atomic Energy Agency (IAEA) and other international organizations. Nuclear chemists are also developing gamma-ray imaging technology that can be applied to a range of counterterrorism applications.

Developing Safe Explosives, New Polymers, and More

In the division assigned to develop and design thermonuclear weapons and testing devices, York also sketched in spots for chemists and metallurgists, noting, "[C]ertain unusual mixtures of materials are very frequently needed . . . and are normally unobtainable outside." Over the years, Livermore's material specialists have dealt with nearly every element in the periodic table. Sometimes they created new materials, and sometimes they synthesized existing materials in unusual or exotic ways or combinations.

At the start, new materials development was strictly related to nuclear weapons and mostly involved unusual alloys (including a corrosion-resistant "stainless" uranium) and plastics. About those earliest days, chemical engineer Barney Rubin recalled, " A major activity was becoming expert in making plastic parts or fabricating components out of weird exotic materials that used plastics as binding agents. We also got heavily into metallurgy. We weren't material scientists in the sense that they are known now. We were sort of kludging things together as best we could—sometimes by intuition and black art, sometimes by science, and sometimes by a combination of the two."

In the area of high explosives (HE), Livermore started pretty much from scratch. The chemists turned for assistance to the centers for HE expertise —Los Alamos and certain Department of Defense laboratories. Livermore's chemists worked closely with weapon designers to develop an HE program that made sense for the design effort, eventually creating the LX series of explosives for Livermore's weapons.

"We had a general goal of trying to get more bang per unit volume," says Gus Dorough, an early leader of the chemistry organization. "It was a point that clearly interested the nuclear

A collaboration with Lawrence Berkeley researchers resulted in the discovery of element 106 in 1974. A separate collaboration (pictured above) with the Joint Institute for Nuclear Research in Dubna, Russia, that began in 1989 led to the discovery of several new isotopes in the early 1990s and in the recent synthesis of superheavy elements 114 and 116.

Fran Foltz examines crystals of the insensitive high explosive triamino-trinitrobenzene (TATB) under the microscope. The background shows TATB crystals at high magnification.

designers, and it turned out to be a very sophisticated and subtle subject. It's not just a matter of more potential energy per unit volume; it's a matter, for instance, of how that energy is released, what kind of chemical detonation products are formed, and the equations of state of those products. Just developing a good technique to measure energy release so we could screen new compounds was no simple matter."

Several empirical tests for measuring HE energy and sensitivity were developed, including the Susan Test (named after Dorough's daughter), which measured safety properties of explosives under simulated accident conditions. Livermore also developed insensitive HE that met the designers' requirements while significantly improving the safety and survivability of munitions, weapons, and personnel. One such, triamino-trinitrobenzene (TATB), is nearly invulnerable to significant energy release in plane crashes, fires, and explosions or to deliberate attack with a small firearm. (See *S&TR*, November 1996, pp. 21–23.)

Polymers—substances made of giant molecules formed by the union of simple molecules—have long been of interest to the Laboratory. In the 1980s, a low-density lightweight polymer called aerogel, first invented in the 1930s, caught the attention of Livermore chemists who went on to create superlight silica aerogels and organic aerogels for the Strategic Defense Initiative. (See *Energy & Technology Review*, November 1994, pp. 16–17.)

Since then, Livermore has developed and improved aerogels for national security applications and synthesized electrically conductive inorganic aerogels for use as supercapacitors and as a water purifier for extracting harmful contaminants from industrial waste or for desalinating seawater. Recently, chemist Glenn Fox led a desalinating project to bring atomic-level control to the design and synthesis of organic aerogels. (See *S&TR*, June 2000, pp. 23–25.) A team headed by chemist Randy Simpson created aerogellike energetic materials with structures that can

Samples from the Sky—Radiochemistry in the Era of Atmospheric Tests

The atmospheric tests of nuclear weapon devices presented unique challenges in data gathering for radiochemists. Right after an atmospheric test, much of the material—radioactive particulates and gases—resides in the signature mushroom cloud. The objective of researchers was to get representative samples of this cloud for analysis.

In an interview conducted nearly 20 years ago, the late Harry Hicks, one of the early radiochemists at Livermore, described what was involved in collecting and processing the samples. The first step was to look at the expected yield of an upcoming test to estimate the size of the cloud and its altitude. "Then you look at the mix of fission and fusion," said Hicks. "The fission products tell you what the radiation level is in the cloud. What you want to do is to send the aircraft in to get your samples, but you don't want to overexpose the crews."

A plane with a Laboratory chemist would be in the air before shot time. After the shot went off, the chemist would observe the cloud and its formation. "If you saw a wisp of cloud or a likely spot," said Hicks, "you'd go over and find out whether it was radioactive or not by flying through to see if you wanted to sample the thing." If the cloud appeared promising, an Air Force sample plane would fly in and obtain a sample. Particulates were captured on large filter papers mounted in pods on each wingtip. Short-lived gases were drawn through the filter, compressed, and stored in 30-centimeter spheres.

Radioactive elements decay constantly, so time was of the essence. Planes landed immediately after obtaining samples, and the samples were removed, packaged, and rushed back to Livermore by courier plane. The samples from Pacific tests normally came in at seven or eight o'clock at night, and the chemical analysis—which took place inside gloveboxes in a building without air-conditioning—began. First, a chemist dissolved the filter papers, a nasty business involving beakers, hot plates, red fuming nitric acid, and hot perchloric acid. Once the papers were dissolved, each desired chemical element had to be completely separated out and completely cleaned of other materials. "Our procedures were relatively new," noted Hicks, "and they weren't exactly reliable, so we would do everything in quadruplicate, hoping we got three, or two, to agree. It just took a long time to be able to say, 'I'm sure that there's nothing but that element there.'"

As the shots got larger, the test clouds got larger and higher, so planes could only sample the tail end of the cloud. In the early 1960s, Livermore researchers had the unique idea of using rockets to determine how representative such samples were. "With remotely controlled rockets, we were able to get samples from higher up and earlier than we could with planes flown by pilots," says retired Livermore chemist John Kury. Results from the rocket tests showed that plane samples—taken later and lower—were indeed representative of the clouds. "At the time, this project made a real difference in our understanding of the radiochemistry needed to analyze device performance," notes Kury, "and it made a real difference for years after, by validating the samples done in earlier tests."

Chemist Harry Hicks ready to board an Air Force RB-57 sampling plane.

be engineered at the nanometer scale. (See *S&TR*, October 1999, pp. 19–21.)

Aerogels aside, polymers have long been used by Livermore's material scientists to create smooth, spherical thin-walled shells or coatings for targets used in laser fusion experiments. (See *S&TR,* June 1997, pp. 22–24.) Another organic polymer, Mercaptoplex, was originally developed at Livermore for use in processing nuclear fuel rods. Mercaptoplex has found another application in removing toxic mercury from industrial waste streams and public water supplies. (See *S&TR*, November 1999, pp. 17–19.)

A piece of extremely lightweight aerogel poised on soap bubbles. Aerogels have the highest internal surface area per gram of material of any known material and also exhibit the best electrical, thermal, and sound insulation properties of any known solid.

Multilayers—exceedingly thin alternating layers of materials—are another example of the Laboratory taking an existing material, developing it further, and expanding its applications. First demonstrated more than 50 years ago, multilayers offer extraordinary strength, hardness, heat-resistance, and unexpected new properties. In 1987, chemist Troy Barbee led a team that designed and synthesized multilayer optics for the soft x-ray and extreme ultraviolet regions of the spectrum. Telescopes with these multilayer x-ray optics were used to capture high-resolution, wide-field x-ray images of the Sun. (See *S&TR*, December 1997, pp. 12–19, and December 1999, pp. 11–13.) Multilayer optics are also used in electron microprobes, scanning electron microscopes, and particle beamlines in accelerators. Multilayer optics are crucial to the current collaboration among Livermore, other Department of Energy laboratories, and private industry to develop extreme ultraviolet lithography for manufacturing the next generation of microcomputer chips. (See *S&TR*, November 1999, pp. 4–9.)

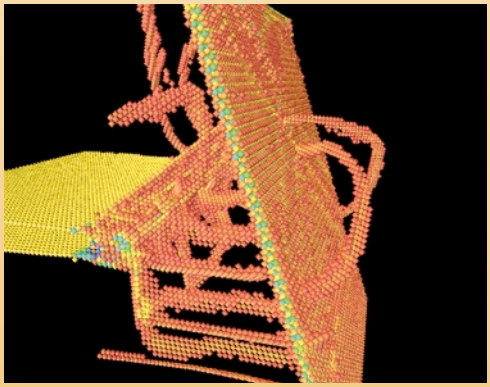
Tools of the Chemistry Trade

The tools of Livermore's chemists and material scientists extend beyond the typical array of glassware and general chemistry apparatus to include nuclear radiation counting instruments, accelerators, vapor deposition equipment, a variety of microscopes and mass spectrometers, and, of course, computers.

Chemists were the first at the Laboratory to integrate computers with laboratory equipment using a PDP-7 in the gas-analysis laboratory in 1965. By 1971, the computer was simultaneously controlling an assortment of experimental equipment including a vacuum-fusion device, a mass spectrometer, an emission spectrograph plate reader, and an automatic sampling atomic absorption system.

As computers evolved, so did the chemistry organization's applications of them. In the mid-1970s, chemistry designed the first completely computerized triple-quadrupole mass spectrometer, a marvel of its time. The system allowed chemists to detect and measure less than 1 nanogram of a sample and was used to analyze trace sulfur compounds in processing oil shale and to investigate the thermal decomposition kinetics of high explosives.

Today, massively parallel computers are a mainstay of efforts to understand material properties and behaviors. For instance, computer simulations of energetic material properties led theoretical chemist Riad Manaa to propose a novel energetic material consisting of a nitrogen analog of the familiar carbon buckyball. (See *S&TR*, June 2001, pp. 22–23.) Chemists are also supporting efforts to model chemical warfare agents by developing kinetic models for surrogate and actual agent chemicals, which could then be used in atmospheric dispersion and other accident and terrorist scenarios. As part of this effort, chemists recently developed the first detailed kinetic model for the agent sarin and modeled comparisons of the chemistry of sarin and its surrogates.



Kinetic model for the agent sarin.

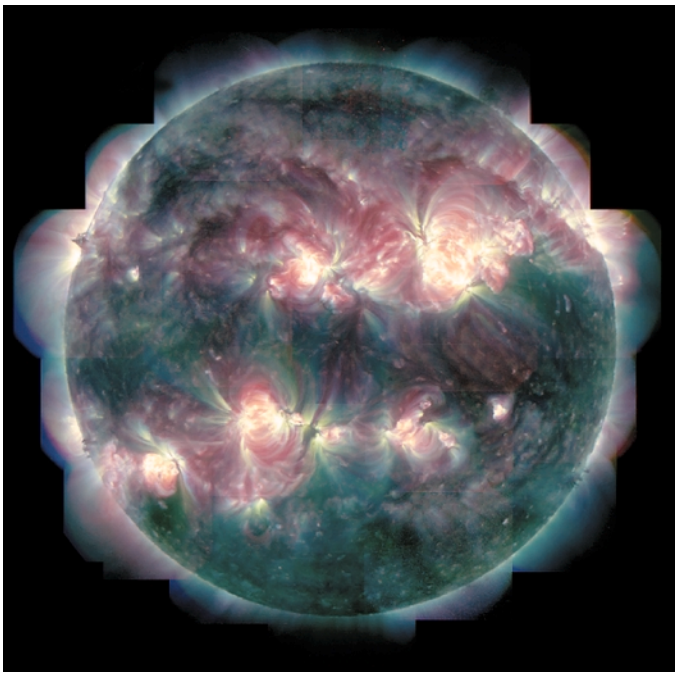
Delving into Material Behavior and Properties

"Exploratory, basic scientific research is key to the Laboratory's success in fulfilling its missions," explains Hal Graboske, associate director for Chemistry and Materials Science (C&MS). "In all of our work, we are pushing the frontiers of science and often must know the basics before we can proceed with the more complex." To meet the Laboratory's programmatic needs, Livermore's chemists and material specialists have often returned to the basics, investigating the behaviors and properties of elements and various materials in ever-increasing detail and at more encompassing scales.

Nuclear weapons include highly reactive metals—plutonium and uranium—as well as organic compounds that degrade over time from exposure to radiation, high temperatures, and accumulated gases. In the past, scientists at Livermore studied how various materials aged and interacted under stockpile conditions to guide the selection and use of the best available materials for new weapons. They developed accelerated aging tests, subjecting small samples of candidate materials to elevated temperatures for a day to several months. These tests measured gas evolution, weight loss, and chemical reactions with contacting materials. Materials that passed this screening were assembled into configurations that modeled the material interfaces in the weapon design and tested at temperatures appropriate to service conditions for months or even years.

With the advent of stockpile stewardship in the 1990s, material scientists looked for ways of predicting the lifetime of key weapon materials and developing "age-aware" material models for use in codes that predict the lifetime of the overall weapon system. (See *S&TR*, September 1999, pp. 4–11.) For example, metallurgist Adam Schwartz is part of a team conducting experiments to measure the structural, electrical, and chemical properties of plutonium and its alloys and determine how these materials change over time. (See *S&TR*, March 2001, pp. 23–25.) "Plutonium is a complex and perplexing element," notes Schwartz. "For instance, it has seven temperature-dependent solid phases—more than any other element in the periodic table. Each phase has a different density and volume and its own characteristics." Instruments such as the transmission electron microscope image the microstructure, allowing researchers like Schwartz to see not just the surface, but the internal structure of the material at the atomic scale, providing the measurements needed for Livermore's material models.

It's not just exotic materials such as plutonium that get the close scrutiny. Water, for instance, was the subject of a recent collaboration between Lawrence Livermore and Lawrence Berkeley chemists. (See *S&TR*, November 2001, pp. 20–23.) Any system involving liquid water—hemoglobin in blood, proteins in water—is affected by the way that hydrogen bonds to the oxygen atoms. The researchers developed a technique using synchrotron radiation to determine for the first time the distance of bonds between hydrogen atoms and oxygen atoms at the surface of liquid water.



The Sun's corona seen with x-ray optics designed at Livermore.

The properties and behaviors of materials are also greatly affected by the processes they undergo—whether the process is welding metals or growing crystals. Livermore metallurgist John Elmer has researched details of the welding process since the early 1990s. Dependable welds are important for maintaining the performance and safety of nuclear weapons and play a key role in the long-term storage of nuclear wastes. Recent experiments using x-ray synchrotron radiation have revealed second-by-second changes in a metal's microstructure during welding, providing the first real-time look at the welding process. (See *S&TR*, November 2001, pp. 4–11.)

In the mid-1980s, C&MS researchers began to investigate ways to rapidly grow the crystals used for optical switching and frequency conversion on high-power laser systems. (See *Energy & Technology Review*, November 1994, pp. 3–5.) With the advent of the powerful atomic force microscope in the 1990s, Livermore researchers began to clarify on the

nanometer scale the growth mechanisms and three-dimensional structures of widely different solution-based crystals. (See *S&TR*, November 1996, pp. 12–20.)

In the past, advances in materials were accomplished by extensive laboratory testing combined with a healthy dose of guesswork, a time-consuming and often costly approach. As experimental tools such as microscopes have become increasingly powerful, so have the computers used to model and predict material behavior. At Lawrence Livermore, home to some of the most powerful massively parallel computers in existence, C&MS researchers are linking computer simulations to laboratory experiments. (See the box on p. 28.) Codes are now so sophisticated that Livermore researchers are beginning to predict what scientists will see when imaging materials through electron microscopes.

Chemistry's Future Grows with the Laboratory

It's been a long journey for Livermore's chemistry organization from the women's restroom in the old barracks to today's highly sophisticated state-of-the-art laboratories and equipment, from analyzing radiochemical diagnostics for weapon tests to simulating the behavior of materials at the atomic level using supercomputers.

"For the past half-century, our goals have been to provide the right people for the Laboratory's programs and a research environment that fosters growth," says Graboske. "The people have always risen to the challenge, meeting the changing needs and seizing emerging opportunities over the decades." From continued support of the weapons program to dealing with the nation's recent threat of terrorism, the Laboratory's chemistry and materials science experts remain at the cutting edge of scientific discovery.

—Ann Parker

Key Words: actinides, aerogels, atmospheric tests, chemistry, computer simulation, crystal growth, high explosives, isotopes, materials aging, material science, metallurgy, multilayers, multiscale modeling, plutonium, polymers, radiochemistry, radiochemical sampling, welding.
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For more information about the Chemistry and Materials Science Directorate:

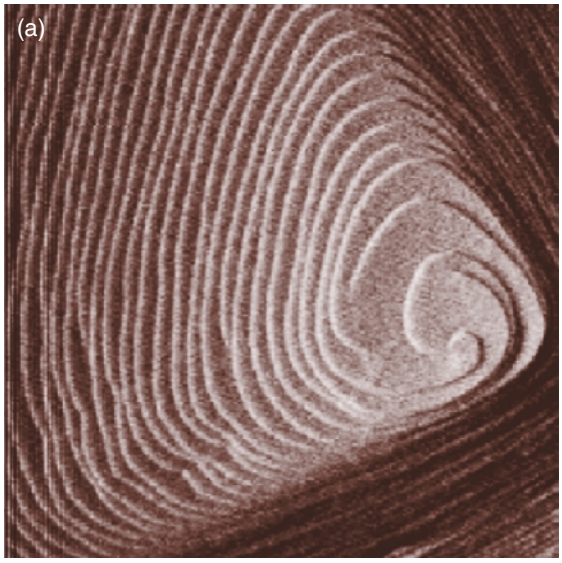
www-cms.llnl.gov/

For more about the history of the chemistry organization at Livermore:

www-cms.llnl.gov/50_year_anniversary/

For further information about the Laboratory's 50th anniversary celebrations:

www.llnl.gov/50th_anniv/



(a) An 8- by 8-micrometer scanned image of the face of a potassium dihydrogen phosphate (KDP) crystal. The morphology and dynamics of crystal growth are relevant to the National Ignition Facility (NIF) as well as to projects that study biomaterials. (b) An example of a large KDP crystal grown for the NIF laser.

Patents and Awards

Each month in this space we report on the patents issued to and/or the 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

Miniature X-Ray Source

James E. Trebes, Gary F. Stone, Perry M. Bell, Ronald B. Robinson, Victor I. Chornenky
U.S. Patent 6,353,658 B1
March 5, 2002
A miniature x-ray source capable of producing a broad spectrum x-ray emission over a wide range of x-ray energies. The miniature x-ray source comprises a compact vacuum tube assembly containing a cathode, an anode, a high-voltage feedthrough for delivering high voltage to the anode, a getter for maintaining high vacuum, a connection for an initial vacuum pumpdown and crimpoff, and a high-voltage connection for attaching a compact high-voltage cable to the high-voltage feedthrough. At least a portion of the vacuum tube wall is highly x-ray transparent and made, for example, of boron nitride. The compact size and potential for remote operation allow the x-ray source, for example, to be placed adjacent to a material sample undergoing analysis or for medical applications in proximity to the region to be treated.

Sputtering Process and Apparatus for Coating Powders

Daniel M. Makowiecki, John A. Kerns, Craig S. Alford, Mark A. McKernan
U.S. Patent 6,355,146 B1
March 12, 2002
A process and apparatus for coating small particles and fibers. The process involves agitation by vibrating or tumbling the particles or fibers to promote coating uniformly, removing adsorbed gases and static charges from the particles or fibers by an initial plasma cleaning, and coating the particles or fibers with one or more coatings. The first coating is an adhesion coating, and subsequent coatings are deposited in situ to prevent contamination at layer interfaces. The first coating is of an adhesion-forming element (tungsten, zirconium, rhenium, chromium, titanium) and is 100 to 10,000 nanometers thick. The second, or final, coating is multiple elements (copper or silver, for example, for brazing processes, or other desired materials). It is 0.1 to 10 micrometers thick and defines the new surface-related properties of the particles. An essential feature of the coating process is the capability to deposit the coating in situ without interruption to prevent the formation of a contaminated interface that could adversely affect the coating adhesion. The process may include screening of the material to be coated and either continuous or intermittent vibration to prevent agglomeration of the material to be coated.

System and Method for 100% Moisture and Basis Weight Measurement of Moving Paper

Jose E. Hernandez, Jackson C. Koo
U.S. Patent 6,355,931 B1
March 12, 2002
A system for characterizing a set of properties for a moving substance. The system includes a first near-infrared linear array, a second near-infrared linear array, a first filter transparent to a first absorption wavelength emitted by the moving substance and juxtaposed between the substance and the first array, a second filter blocking the first absorption wavelength emitted by the moving substance and juxtaposed between the substance and the second array, and a computational device for characterizing the resulting data from the arrays. The method includes the steps of filtering out a first absorption wavelength emitted by a substance, monitoring the first absorption wavelength with a first near-infrared linear array, blocking the first wavelength from reaching a second near-infrared linear array, and characterizing data from the arrays into information on a property of the substance.

Colloidal Spray Method for Low Cost Thin Coating Deposition

Ai-Quoc Pham, Robert S. Glass, Tae H. Lee
U.S. Patent 6,358,567 B2
March 19, 2002
A dense or porous coating of material is deposited onto a substrate by forcing a colloidal suspension through an ultrasonic nebulizer and spraying a fine mist of particles in a carrier medium onto a sufficiently heated substrate. The spraying rate is essentially matched to the evaporation rate of the carrier liquid from the substrate to produce a coating that is uniformly distributed over the surface of the substrate. Following deposition to a sufficient coating thickness, a single sintering step may be used to produce a dense ceramic coating. This method allows coatings ranging in thickness from about one to several hundred micrometers. Also, because the method uses a plurality of compounds in the colloidal suspension, coatings of mixed composition can be obtained. Because the method uses a plurality of solutions, separate pumps, a single or multiple ultrasonic nebulizers, and varying individual pumping rates and/or concentrations of the solutions, a coating of mixed and discontinuously graded (stepped) or continuously graded layers may be obtained. This method is particularly useful for depositing dense ceramic coatings on porous substrates for improving electrode performance in high-power-density solid-oxide fuel cells and on gas turbine blades, sensors, and steam electrolyzers. The invention has general use in preparation of systems requiring durable and chemically resistant coatings and for coatings having other specific chemical or physical properties.

Chimeric Proteins for Detection and Quantitation of DNA Mutations, DNA Sequence Variations, DNA Damage and DNA Mismatches

Sandra L. McCutchen-Maloney
U.S. Patent 6,365,355, B1
April 2, 2002
Chimeric proteins having both DNA mutation binding activity and nuclease activity are synthesized by recombinant technology. The proteins are of the general formula A-L-B and B-L-A, where A is a peptide having DNA mutation binding activity, L is a linker, and B is a peptide having nuclease activity. The chimeric proteins are useful for detection and identification of DNA sequence variations, such as DNA mutations (including DNA damage and mismatches) by binding to a mutation and cutting the DNA once the mutation is detected.

Tiltmeter Leveling Mechanism

Steven L. Hunter, Carl O. Boro, Alvis Farris
U.S. Patent 6,370,784
April 16, 2002
A tiltmeter device having a pair of orthogonally disposed tilt sensors that can be leveled within an inner housing containing the sensors. An outer housing can be rotated to level at least one sensor of the pair while the inner housing can be rotated to level the other sensor. The sensors are typically rotated up to ±100 degrees. The device is effective for measuring tilts of wells at various angles of inclination and can be used to level a platform containing a third sensor.

Ultrashort Pulse Laser Deposition of Thin Films

Michael D. Perry, Paul S. Banks, Brent C. Stuart
U.S. Patent 6,372,103 B1
April 16, 2002
Short-pulsed laser deposition is a viable technique for producing high-quality films with properties close to those of crystalline diamond. The plasma generated using femtosecond lasers is composed of single-atom ions with no clusters producing films with high diamond-to-graphite content. Using a high-average-power femtosecond laser system, this invention dramatically increases deposition rates up to 25 micrometers per hour (which exceeds the rate of many chemical vapor deposition processes) and produces particulate-free films. In the present invention, deposition rate is a function of laser wavelength, laser fluence, laser spot size, and target–substrate separation. The relevant laser parameters ensure particulate-free growth, and characterizations of the films grown are made using several diagnostic techniques, including electron-energy-loss spectroscopy and Raman spectroscopy.

Plates for Vacuum Thermal Fusion

James C. Davidson, Joseph W. Balch
U.S. Patent 6,372,328 B1
April 16, 2002
A process for effectively bonding plates or substrates of arbitrary size or shape. The plates or substrates can be glass, plastic, or alloy with a moderate melting point and a gradual softening point curve. The process incorporates vacuum pull-down techniques to ensure uniform surface contact during the bonding process. The essence of the process involves the application of an active vacuum source to evacuate interstices between the substrates while providing a positive force to hold the parts to be bonded in contact. This process allows the temperature of the bonding process to be increased to ensure that the softening point has been reached; it also permits small void areas to be filled and come in contact with the opposing plate or substrate. The process is most effective when at least one of the two plates or substrates contains channels or grooves that can be used to apply vacuum between the plates or substrates during the thermal bonding cycle. Also, providing a vacuum groove or channel near the perimeter of the plates or substrates is beneficial to ensure bonding of the perimeter of the plates or substrates and to reduce the unbonded regions inside the interior region of the plates or substrates.

Awards

Claire Max, founding director of Livermore's Institute of Geophysics and Planetary Physics (IGPP), has been name a **fellow** of the **American Academy of Arts and Sciences**.

Founded during the American Revolution by John Adams, James Bowdoin, John Hancock, and other early U.S. leaders, the academy is today an international society with the dual function of electing to membership individuals of exceptional achievement, drawn from science, scholarship, business, public affairs, and the arts, and of conducting projects and studies responsive to the needs and problems of society.

Max was selected in the physics division of the academy. She joined Livermore as a physicist in 1974, founded IGPP in 1983, and became director of University Relations in 1995. She now serves as associate director for the National Science Foundation's Center for Adaptive Optics at the University of California at Santa Cruz, in which Livermore plays a significant role. She is also a professor of astronomy at UC Santa Cruz.

Max's most recent work focuses on the use of adaptive optics on the telescopes at the W. M. Keck Observatory in Hawaii. (See the article beginning on p. 12.)

Edward Teller is the only other academy member from the Laboratory. Others selected as fellows in 2002 include Senator Edward Kennedy of Massachusetts and Academy Award–winning actress Anjelica Houston.

Abstracts

A Two-Pronged Attack on Bioterrorism

New synthetic molecules known as high-affinity ligands that bind to and capture biowarfare agents are being designed at Livermore. With a bidentate (two-pronged) structure, their binding strength will be thousands to millions of times stronger than molecules that join at just one place. The first such ligand is being designed for a *Clostridium* neurotoxin tetanus protein, using its structure as a starting point. Using computational techniques, researchers have located two adjacent binding sites on the tetanus targeting domain and also identified numerous compounds that would fit into the sites. Laboratory experiments using nuclear magnetic resonance spectroscopy and mass spectrometry narrowed the choices of molecular compounds by determining which compounds actually bound to the two sites. The two best choices will be joined by a third linker molecule to create a ligand to bind tightly to the tetanus toxin. Similarly designed molecules can also be used to target proteins that cause disease and block their activity. Armed with the radionuclide used in radiation therapy, such molecules could make excellent cancer-fighting tools. Work has begun on a high-affinity ligand for a surface receptor for non-Hodgkin's lymphoma.

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Adaptive Optics Sharpen the View from Earth

Astronomers are reporting exceptional results from the adaptive optics systems installed at the W. M. Keck Observatory in Hawaii and the University of California Lick Observatory near San Jose. The images are shedding new light on the formation of stars and galaxies, revealing unexpected features on planets and moons in our solar system, and yielding new information on black holes residing in the centers of distant galaxies. Adaptive optics measure the distortions of light from a natural star or one manufactured by a powerful laser, and then remove the distortions by reflecting the light off a deformable mirror that adjusts several hundred times per second to sharpen the image. Livermore researchers have been among the leaders in designing and using adaptive optics systems on astronomical telescopes. Livermore also has been the leader in designing laser guide stars to allow adaptive optics to be used over more of the sky. The next generation of telescopes almost certainly will require laser guide stars and adaptive optics systems.

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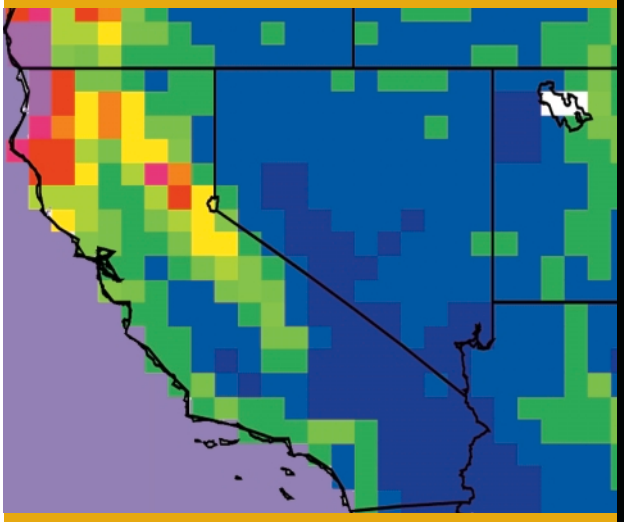
Simulations Explore the Causes and Effects of Climate Change



Livermore climate scientists are using supercomputers to clarify some issues in the global warming debate.

Also in July/August

- ***Experiments guide development of codes for predicting metal failure.***
- ***Statistical tool provides more meaningful data interpretation.***
- ***50th Anniversary Highlight: The Nonproliferation, Arms Control, and International Security Directorate had its beginnings in work to understand and counter the nuclear threat. Today, the directorate's responsibilities must also encompass technology and intelligence in biological and chemical terrorism.***

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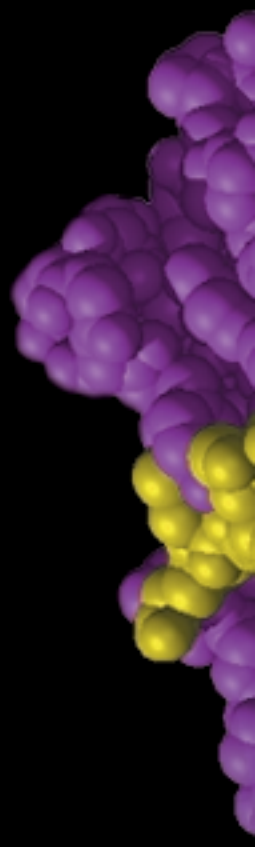

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