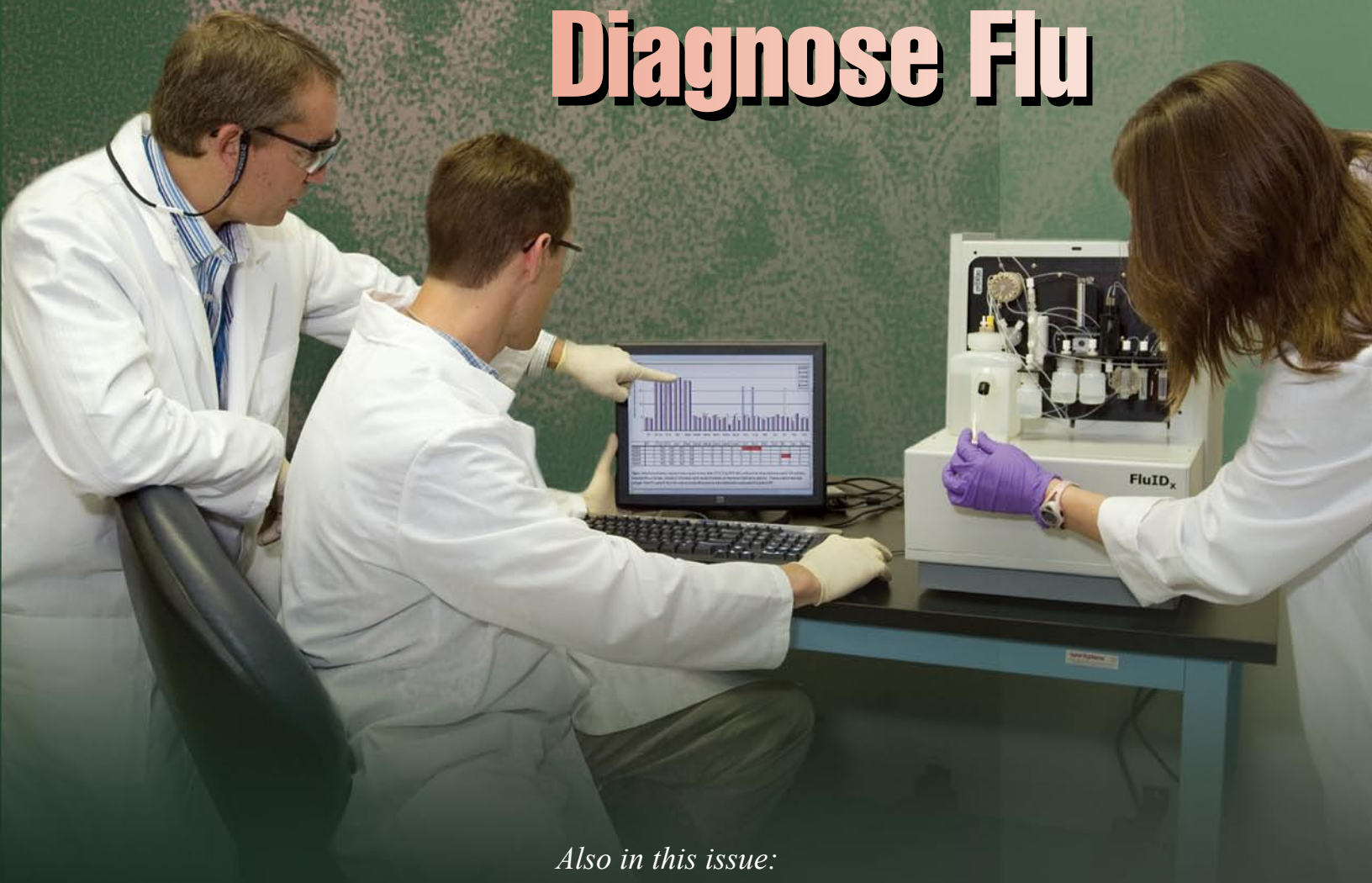
December 2006

Science & Technology REVIEW

National Nuclear Security Administration's
Lawrence Livermore National Laboratory

A Fast Test to Diagnose Flu



Also in this issue:

- **Emergency-Response Protocols for Airports**
- **Detecting Early-Stage Bone Disease**
- **Gamma Rays Probe Atomic-Scale Dynamics**

About the Cover

Seasonal influenza is a contagious respiratory illness caused by a virus that is easily passed from person to person. In the U.S. alone, more than 35,000 people die each year from flu and other respiratory viruses. Effective diagnoses of these viruses require time-consuming laboratory tests. The article beginning on p. 4 describes a new assay developed by Livermore scientists to diagnose respiratory viruses within two hours of taking a sample. Called $FluID_x$ (and pronounced "fluidics"), this device can diagnose five types of respiratory viruses, including influenza. $FluID_x$ can analyze samples at the point of patient care—in hospitals and clinics. On the cover, members of the Livermore team review data from a recent $FluID_x$ test. In the background is a micrograph of the 1918 influenza virus, which killed about 675,000 people in the U.S. (Micrograph reprinted courtesy of the Centers for Disease Control and Prevention.)

Cover design: Daniel Moore. Photographer: Nancy Rutter.

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 ensuring 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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Collaboration explores materials at extreme conditions

To better understand how high-strain-rate plasticity evolves, researchers from Lawrence Livermore and the University of Oxford are combining very large-scale molecular dynamics simulations with time-resolved data from laser experiments of shock-wave propagation through metals. A strong shock produces an unusual number of line defects, or dislocations, within a metal's crystalline lattice. Plastic deformation occurs when a high number of dislocations moves, changing the metal's mechanical properties such as its strength, ductility, and resistance to fracture and cracking.

The research team, which is led by Livermore scientist Eduardo Bringa, used atomistic molecular dynamics to simulate a strong shock wave in a metal with preexisting dislocation sources. The team studied the nucleation and motion of dislocations relaxing the large strain behind the shock front. An abrupt impact causes dislocations to multiply too rapidly, becoming entangled before they can move far enough to completely relax the uniaxial strain. When pressure increases gradually, fewer dislocations are generated. However, they are more effective at relieving the strain because they can move freely for a longer period.

Dislocation activity behind a shock wave has not been measured directly. However, Bringa's team has proposed that dynamic x-ray diffraction experiments, similar to those being conducted by Livermore physicist Hector Lorenzana and collaborators, could provide indirect information on such dislocation activity. The team's research, which is described in the October 1, 2006, issue of *Nature Materials*, will help scientists assess material properties and performance under extreme conditions, such as an automobile crash or an explosives detonation. Says Bringa, "Experiments and simulations make a powerful pair for exploring uncharted, even unimagined regimes of material dynamics."

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New method examines the function of cell membranes

A collaboration involving researchers from Lawrence Livermore, Stanford University, and the University of California (UC) at Davis has developed a method that can directly test for the existence of lipid rafts in cellular membranes. The cell membrane is composed primarily of a fluid bilayer of lipids. Previous research indicated that this lipid bilayer was a passive carrier for the proteins that perform the active work of the membrane.

The model being tested by the collaboration suggests that, instead, lipids are organizing the functional proteins of the cell membrane. "This is a very elegant hypothesis, under which the subtle affinities that certain lipids have for each other make the cell membrane self-organizing," says Livermore physicist Peter Weber.

To develop the method, the research team formed model cell membranes on silicon chips, induced the formation of tiny lipid-raft-like gel domains, and freeze-dried the membranes. Then using NanoSIMS, the Laboratory's high-resolution secondary ion mass spectrometer, the scientists detected gel domains that measure about 100 nanometers laterally and 5 nanometers thick.

The team's work appears in the September 29, 2006, issue of *Science.* Results from this research could help scientists develop methods to short-circuit a virus attack on cells, to characterize structures within biological pathogens, and to increase the sensitivity and flexibility of biological sensors.

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Marine experiment tests detection capability

In August 2006, Livermore scientists participated with the Naval Postgraduate School (NPS) of Monterey in a series of experiments aimed at detecting, identifying, and interdicting nuclear materials in open waters. The experiments, which were conducted in San Francisco Bay, involved participants from several federal agencies, including the departments of Defense, Energy, and Homeland Security, as well as military representatives from several nations.

Marine-enforcement first responders face an enormous challenge attempting to screen cargo inside the endless stream of containers that enter a major facility such as the Port of Oakland. Many commercial products, including smoke detectors, radiant signs, and even bananas, emit radiation, and a shipment of such items can cause radiation detectors to alarm. A false-positive alarm slows commerce unnecessarily and increases product costs. Successful interdiction requires not only modern technology but also coordinated operations and effective communications among many agencies.

To test detection capabilities and agency preparedness, NPS conducted an exercise in which a vessel entering the Port of Oakland required inspection because it was emitting signs of ionizing radiation. For this exercise, the Alameda County Marine Enforcement Agency provided the operations center and the boarding vessel, and a boat operated by the Oakland Police Department played the target vessel. Coast Guard officers—or in some cases Laboratory researchers acting as Coast Guard officers—boarded the vessel to take readings with portable radiation detection instruments. Those readings were immediately relayed to scientific experts at other locations. Their results were radioed back to the boarding vessel for use by first responders on the scene.

"Experiments of this sort are iterative," says participant Bill Dunlop, a physicist in Livermore's National Security Office. "We find out what works well, what needs improvement, and what's unsuccessful. The next exercise will incorporate improvements from the lessons learned this time."

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Livermore's Biosecurity Research Directly Benefits Public Health

ONE major challenge in thwarting bioterrorism is that the relevant technologies and materials are inherently dual-use and have widespread legitimate application. Therefore, efforts to counter a bioterrorist threat must focus not on securing materials, as can be done for nuclear nonproliferation, but rather on rapid detection and characterization of disease agents and outbreaks.

Many of the pathogens of top concern for bioterrorism, such as those that cause anthrax and plague, occur naturally. The same is true for organisms that might be used in an agricultural terrorism attack. To counter these threats, researchers at Lawrence Livermore and other institutions are directing efforts at finding faster, easier, and cheaper methods to detect disease-causing organisms. They are also devising means of differentiating the truly deadly organisms from less harmful near-neighbors or those that present similar symptoms but cause different diseases.

Despite the attention and anxiety generated by the 2001 anthrax-laced letters, a far greater public health risk is posed by influenza. Every year brings a new flu season. In the U.S., more than 200,000 people are hospitalized annually for flu complications, and more than 35,000 die from flu—on par with the number of automobile-related deaths each year. And we know influenza has the potential for mass destruction. The flu pandemic of 1918–1919 killed some 675,000 people in the U.S. and between 20 and 40 million worldwide, more people than during all four years of the Black Death plague of 1347–1351.

Influenza is a zoonotic disease—that is, a disease caused by an infectious agent that can be transmitted between animals and humans. Indeed, many of the most devastating disease outbreaks in recent history were caused by viruses that originated in animals and made the jump to humans. For example, the virus that caused the 1918–1919 flu pandemic is thought to have an avian origin; the virus that causes AIDS (acquired immunodeficiency syndrome) has been traced to the simian immunodeficiency virus in chimpanzees and other primates in Africa; and the coronavirus that caused the 2003 outbreak of severe acute respiratory syndrome is believed to have jumped from civet cats in Asia.

The Centers for Disease Control and Prevention (CDC) has the mission to promote human health. Various CDC programs are aimed at detecting and identifying new diseases, investigating disease outbreaks, conducting research to enhance disease prevention and detection, and implementing strategies to prevent or mitigate disease. The U.S. Department of Agriculture (USDA) focuses on the nation's agricultural interests, including ensuring preharvest food safety and the security of the food chain. The Food and Drug Administration (FDA) is responsible for protecting public health by, among other things, ensuring the postharvest safety of the nation's food supply. Lawrence Livermore's work in rapid influenza detection is part of a growing effort in zoonotic disease that bridges the CDC, USDA, and FDA missions while directly supporting our national security program in bioterrorism countermeasures.

Laboratory scientists are developing new tools and technologies to strengthen the nation's ability to prevent, detect, respond to, and recover from a biological attack. As these capabilities are demonstrated and deployed with this mission in mind, they are simultaneously enhancing the nation's public health capabilities. The rapid influenza detection capability described in the article beginning on p. 4 is a prime example of this dual-benefit research. As we strive to ensure that the U.S. will never be the target of a deliberate bioterrorist attack, it is our sincere hope that the biodefense technologies we develop will find their principal application in benefiting human health.

■ Raymond J. Juzaitis is associate director for Nonproliferation, Homeland and International Security.

Diagnosing Flu

A new Livermore tool can quickly tell

PEOPLE with flulike symptoms who seek treatment at a medical clinic or hospital often must wait several hours before being examined, possibly exposing many people to an infectious virus. If a patient appears to need more than the routine fluids-and-rest prescription, effective diagnosis requires tests that must be sent to a laboratory. Hours or days may pass before results are available to the doctor, who in the meantime must make an educated guess about the patient's illness. The lengthy diagnostic process places a heavy burden on medical laboratories and can result in improper use of antibiotics or a costly hospital stay.

A faster testing method may soon be available. An assay developed by a team of Livermore scientists can diagnose influenza and other respiratory viruses in about two hours once a sample has been taken. Unlike other systems that operate this quickly, the new device, called FluID$_x$ (and pronounced "fluidics"), can differentiate five types of respiratory viruses, including influenza. FluID$_x$ can analyze samples at the point of patient care—in hospital emergency departments and clinics—allowing medical providers to quickly determine how best to treat a patient, saving time and potentially thousands of dollars per patient.

The FluID$_x$ project, which is led by Livermore chemist Mary McBride of the Physics and Advanced Technologies Directorate, received funding from the National Institute of Allergy and Infectious Diseases and the Laboratory Directed Research and Development (LDRD) Program. To test the system and make it as useful as possible, the team worked closely with the Emergency Department staff at the University of California (UC) at Davis Medical Center in Sacramento. Robert Derlet, M.D. and chief of the department, is enthusiastic about having FluID$_x$ available for testing.

"A dozen or more viruses cause symptoms in people that all look the same in the early stages," says Derlet. "With most viruses, people are sick for just a few days and then get better. But flu and other

In the background, a micrograph shows the morphologic features found in the 1918 influenza virus. (Photographer: Cynthia Goldsmith. Reprinted courtesy of the Centers for Disease Control and Prevention.)

Fast

which patients have influenza or another respiratory virus.

respiratory viruses can make some people really sick and even kill them. We need to be able to sort out the 'bad guys' so these viruses don't infect others."

From the Lab to the Clinic

Flu kills more than 35,000 people every year in the U.S. (See the box on p. 7.) The 2003 outbreak of severe acute respiratory syndrome and the ongoing concern about a possible bird flu pandemic illustrate the need for a fast, reliable test that can differentiate seasonal flu from a potentially pandemic influenza. Such a test should also discriminate influenza from pathogens that cause illnesses with flulike symptoms.

When a precise diagnosis is required to treat an adult patient with serious respiratory symptoms, sample cells are usually obtained with a nasal or throat swab and analyzed with one of several laboratory methods. The gold standard test is viral culturing, a highly sensitive method that can identify the specific strain of virus. However, viral culturing is a labor intensive process and requires 3 to 10 days to produce results, far too long for early intervention. Enzyme and optical immunoassays offer results in 30 minutes, but these methods are less sensitive than viral culturing so they can produce false positives or negatives. They also cannot distinguish the type of virus found.

Direct immunofluorescence antibody (DFA) staining is as sensitive as viral culturing. It also can detect multiple respiratory pathogens simultaneously by a process known as multiplexing. However, DFA staining requires expensive equipment, a skilled microscopist, and samples with enough target cells for testing. In addition, the results are ultimately subjective. Another method, called reverse transcriptase-polymerase chain reaction assay, offers sensitivity and specificity comparable to viral culturing and DFA staining. It also produces results in two hours and can rapidly test a large number of samples. The drawback with these tests, however, is that they must be performed in a laboratory. None of them can be used where they are needed most: in the clinic or emergency department where patients are being treated.

FluID$_x$ team members (from left) Jim Birch, Jack Regan, and Kristl Adams view results from a recent test. The system can diagnose influenza and other respiratory viruses in about two hours after a sample is taken.

Lawrence Livermore National Laboratory

FluID$_x$ team member Sonia Letant works on assay development.

Livermore's FluID$_x$ diagnostic system, with its instrumentation and multiplexed assays, is designed specifically for point-of-care diagnosis. The fast, easy-to-use system is based on the Autonomous Pathogen Detection System, a homeland security technology developed by Lawrence Livermore. This R&D 100 Award–winning technology constantly monitors the air to detect airborne bioterrorism agents, such as anthrax. (See *S&TR*, October 2004, pp. 4–5.)

FluID$_x$ is an integrated system designed to perform highly multiplexed polymerase chain reaction (PCR) nucleic-acid-based assays in real time. The FluID$_x$ system processes a sample, analyzes the data, reports the results, and decontaminates itself before another sample is taken. The device currently uses 16 assays—12 for individual nucleic-acid targets and 4 for internal controls. The assays can simultaneously detect influenza A and B, parainfluenza (Types 1 and 3), respiratory syncytial virus, and adenovirus (Groups B, C, and E).

Process for Assay Development

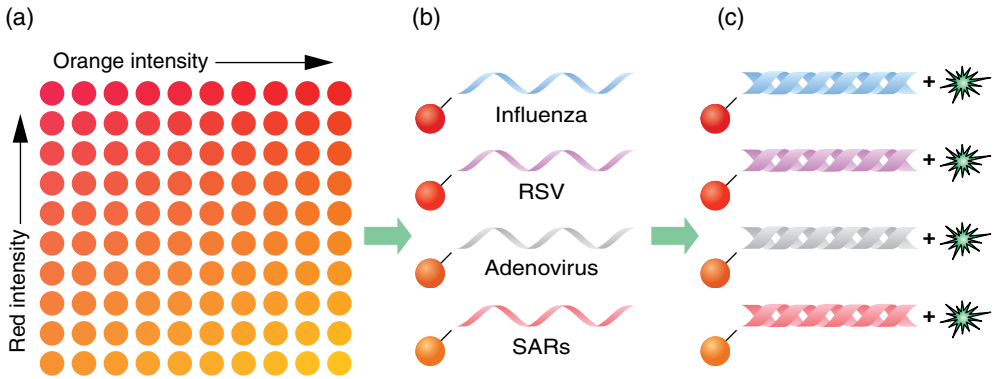
FluID$_x$ works so well because its nucleic-acid-based detection assays have been carefully vetted using a proven assay-development process. As a result, the assays produced are extraordinarily sensitive, specific, and robust.

The process begins with an analysis of all available genomic sequence information, which forms the basis for developing a signature—the region or set of regions on a chromosome that is unique to the target organism. Traditional approaches to developing DNA signatures start by identifying a gene that is considered vital to the target organism's virulence, host range, or other distinctive factor.

Livermore's bioinformatics team has developed a whole-genome comparative analysis software system called KPATH to improve the signature-mining process. (See *S&TR*, April 2004, pp. 4–9.) KPATH aligns multiple genomes of different strains of the target species and compares them to identify all the genomes that contain the target sequence. These genomes are then compared with Livermore's immense database of microbial organisms to establish that the organism-conserved target sequence does not occur in other sequenced microbial organisms. An algorithm subtracts any target sequence already listed in the microbial organism database. The resulting sequence is mined for potential signature candidates. Additional electronic screening catches nonexact matches that might produce false positives.

The signature-mining process then moves from the computer to the laboratory to further reduce the field of candidates. Potential nucleic-acid signatures are screened against more than 2,500 randomly selected nucleic-acid extracts from soils, microbes, bacteria, and other organisms that may be present in a sample when it is collected. Candidate signatures are also exposed to near-neighbor nucleic acids to reduce the potential for false results.

Signatures that pass the intensive background screening in real-time PCR are developed into assays in a format



(a) The FluID$_x$ system uses a liquid array of 100 beads, each with a unique spectral value. (b) Nucleic-acid probes capture beads that complement the target pathogens: influenza, respiratory syncytial virus (RSV), adenovirus, and severe acute respiratory syndrome (SARS). (c) Amplified nucleic acid is hybridized to fluorescently labeled beads and analyzed.

known as Taqman. At this stage, every parameter that might affect an assay's performance is optimized, and all assays are fully characterized against a standardized panel of targets and near-neighbors. The final results are captured in a certificate of analysis, providing a record of the assay's pedigree.

For the multiplexed liquid array format, individual signatures are added to the multiplexed PCR mix, with other panel signatures present. Signatures are tested several times to determine an assay's detection limit for each target and to control for reactivity among signatures.

FluID$_x$ at Work

The multiplexed nucleic-acid assays in FluID$_x$ use tiny polystyrene microbeads colored with unique ratios of red- and orange-emitting dyes. The result is an array of 100 beads that can be distinguished by their spectral values. The beads are coated with nucleic-acid probes whose sequences complement those of the five target pathogens. Flow-through PCR amplifies nucleic acids from the viruses, and the amplified DNA, or amplicons, are introduced to the beads. The amplicons hybridize to their complementary probes on the appropriate bead. Then the beads are illuminated with red laser light, which has a wavelength of 635 nanometers, to classify each bead. Next, illumination with 532-nanometer (green) laser light quantifies the assay at the bead's surface based on the strength of the fluorescence. Conducting the multiplexed assay requires several steps and significant PCR thermocycling times, resulting in the two-hour duration for a FluID$_x$ test.

Four control beads in every sample convey information about the system's status. For example, the instrument control bead verifies the optics of the green laser. This bead is coated with a probe that is unlikely to bind to other nucleic acids and with a dye that emits a constant fluorescence in all samples. A change in fluorescence on the control bead indicates a fluctuation in the green laser's performance. FluID$_x$ analyzes every sample in the context of all four controls, thereby minimizing the likelihood of instrument malfunction or false results.

Livermore was not the first institution to use coated microbeads as indicators. However, says McBride, "We have put them to excellent use, applying them in several biosensors." In the FluID$_x$ system, the beads' fluorescence signal above or below a threshold value indicates whether the assay is ruled positive or negative.

The FluID$_x$ sample preparation module and its detector are composed of commercially available parts with customized interfaces. The automated flow-through PCR unit, which was designed at Livermore, consists of a custom thermocycler with a copper heater mounted in line with the sample preparation unit. (See the figure on p. 8.) The software used in FluID$_x$ is similar to that developed for the Autonomous Pathogen Detection System, but its user-interface has been designed so that personnel can operate the system with minimal training. This version is easy to use, readily accommodates hardware changes, and enables communication with

What Is Flu?

Seasonal influenza, or the flu, is a contagious respiratory illness caused by viruses that spread in droplets from coughing and sneezing. Most adults may be able to infect others beginning one day before symptoms develop and up to five days after they become sick. Symptoms can include fever, headache, fatigue, cough, sore throat, runny nose, or muscle ache. Flu may cause only mild illness but also may lead to severe illness or even death.

Although seasonal flu is often thought of as a trivial illness, statistics tell a different story. Every year in the U.S., 5 to 20 percent of the population typically gets the flu. More than 200,000 people are hospitalized from flu complications, and about 36,000 people die from flu. Fortunately, most people have some immunity to seasonal influenza, and a vaccine is developed annually.

Common flu is usually caused by an influenza A virus. Avian, or bird, flu is a subtype of the influenza A virus that occurs naturally among birds. Different subtypes are caused by changes in certain proteins, such as hemagglutinin (HA) and neuraminidase (NA), on the surface of the influenza A virus and by the way the proteins combine. Some subtypes cause only mild symptoms. The bird flu subtype A/H5N1 is highly pathogenic, spreading rapidly among flocks of poultry. Its mortality rate can reach 90 to 100 percent, often within 48 hours.

Among humans, only three known influenza A subtypes are in circulation: A/H1N1, A/H1N2, and A/H3N2. The A/H5N1 bird flu variant is the most deadly of the few avian viruses to have crossed the species barrier to infect humans. Humans have no immunity to A/H5N1, and no vaccine is currently available. Since 2003, human A/H5N1 cases have been reported in Azerbaijan, Cambodia, China, Dijbouti, Egypt, Indonesia, Iraq, Thailand, Turkey, and Vietnam. More than half of the people infected with the A/H5N1 virus have died. To date, no human-to-human transmission of the disease has been sustained, but influenza viruses mutate rapidly. Health officials are concerned that A/H5N1 will evolve into a virus that can be transmitted from person to person.

Confusingly for physicians, other influenzalike illnesses start out looking almost exactly the same as common flu. Adenoviruses can affect not only the respiratory system but also the eyes, intestines, and urinary tract, most commonly in children. Parainfluenza and respiratory syncytial virus are common causes of lower respiratory tract disease in young children, and both can cause repeated infections throughout life. A tool such as FluID$_x$ will help physicians quickly determine the cause of a patient's flulike symptoms.

outside entities via an Ethernet connection or other medium.

Put to the Test

In tests of FluID$_x$, a technician at the UC Davis Medical Center collected more than 1,200 nasal swab samples from patients seeking treatment in the Emergency Department. As part of the federal requirements for research involving human subjects, study participants signed informed consent forms before samples were taken, and the testing protocol was approved by UC Davis physicians and the governing Institutional Review Board.

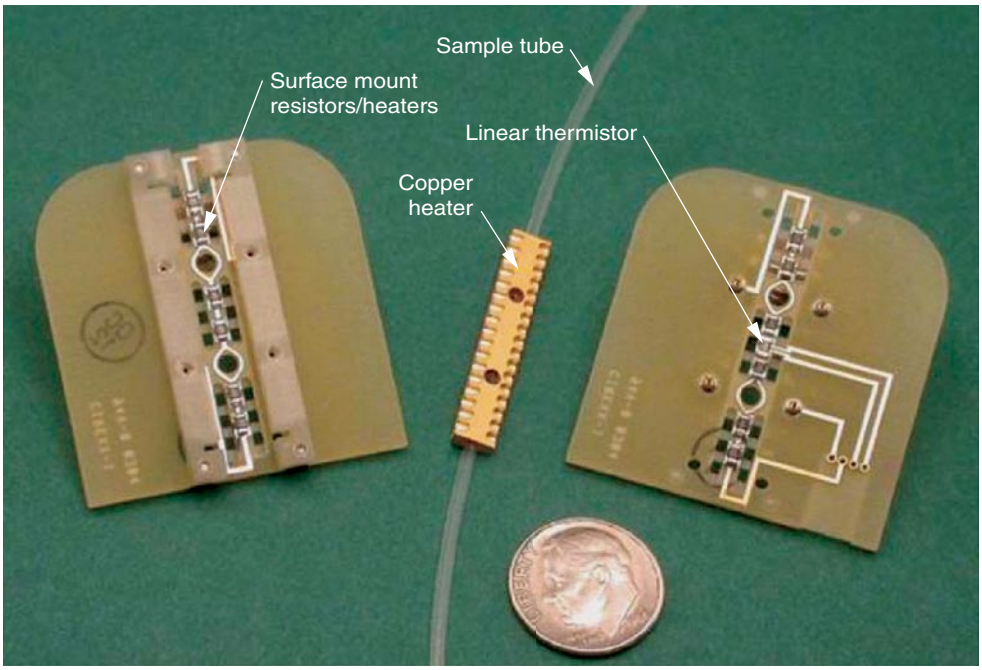
Nasal swabs were also collected from volunteers who showed no signs of illness. All samples were processed using viral culturing, DFA staining, and FluID$_x$. Sample comparisons revealed excellent results for FluID$_x$. In terms of sensitivity, the FluID$_x$ multiplexed assays were on par with the results from viral culturing. The system's specificity for identifying virus strains was significantly better than that obtained with DFA staining, which takes about the same time as FluID$_x$.

The Work Goes On

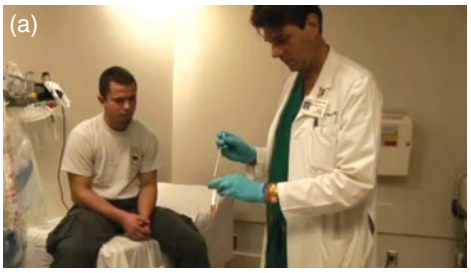
The Laboratory works closely with the Centers for Disease Control and Prevention (CDC), which provided a few assays for the FluID$_x$ panel. Livermore is part of the CDC Laboratory Response Network that would be activated in the event of a widespread flu pandemic. If the FluID$_x$ system can be made small enough to be taken into the field, it could be used by emergency responders. A field-portable unit would be invaluable if a flu pandemic were to occur.

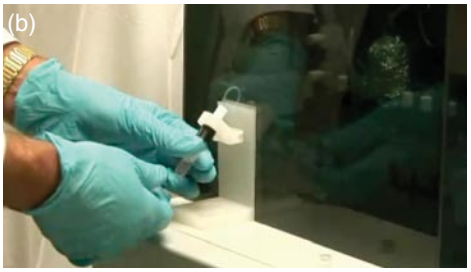
McBride and her team are developing additional assays that could be used to detect avian influenza (bird flu). Although the current panel can detect influenza A and B, it cannot differentiate normal seasonal flu from a potentially pandemic influenza. Influenza A is divided into subtypes based on the properties of two surface antigens, hemagglutinin (HA) and neuraminidase (NA). The HA antigen has 15 subtypes, and the NA has 9. Bird flu is subtype H5N1, while seasonal influenza is usually subtypes H1, H2, or H3.

The team used KPATH to identify and select most of the candidate signatures included in the FluID$_x$ respiratory panel. But KPATH could not identify nucleic-acid signatures in the required format for the HA gene, which is the basis for identifying the H subtypes of influenza A. Assays developed to operate in the Taqman PCR



Livermore's automated flow-through polymerase chain reaction thermocycler includes a circuit-board heater and a copper heater.





The FluID$_x$ device was tested in the Emergency Department of the University of California at Davis Medical Center. (a) Robert Derlet (right), M.D. and department chief, inserts a nasal swab sample collected from a volunteer into a vial and (b) places the vial in the FluID$_x$ device. (c) Less than two hours later, a screen read-out provides test results.

format handle one signature at a time. The HA gene, however, is highly divergent, so no single Taqman signature can capture all members of a subtype.

To identify the smallest number of signatures required to recognize all members of a target set, the team used the Livermore software Minimal Set Clustering. This software generates sets of Taqman signatures that it predicts can be used in combination to detect all of the genome target sequences. Both KPATH and Minimal Set Clustering ensure that the signatures are predicted not to cross-react with a sequenced nontarget organism.

In designing signatures for the influenza A subtype called H5, McBride's team obtained a target set of 217 H5 sequences from Genbank, which is part of the National Center for Biotechnology Information. Minimal Set Clustering showed that four Taqman signatures are needed to detect all members of this target set. The H5 subgroups also appear to cluster by lineage, indicating that the signatures may discriminate where a strain originated. The first and fourth signatures detect groups of North American sequences, and the second and third detect Eurasian sequences. This distinction is critical because, to date, all avian flu strains infecting humans have been of Eurasian lineage. Similar work revealed the minimal number of signatures needed to provide complete coverage for the other influenza A subtypes, H1, H2, H3, and H7.

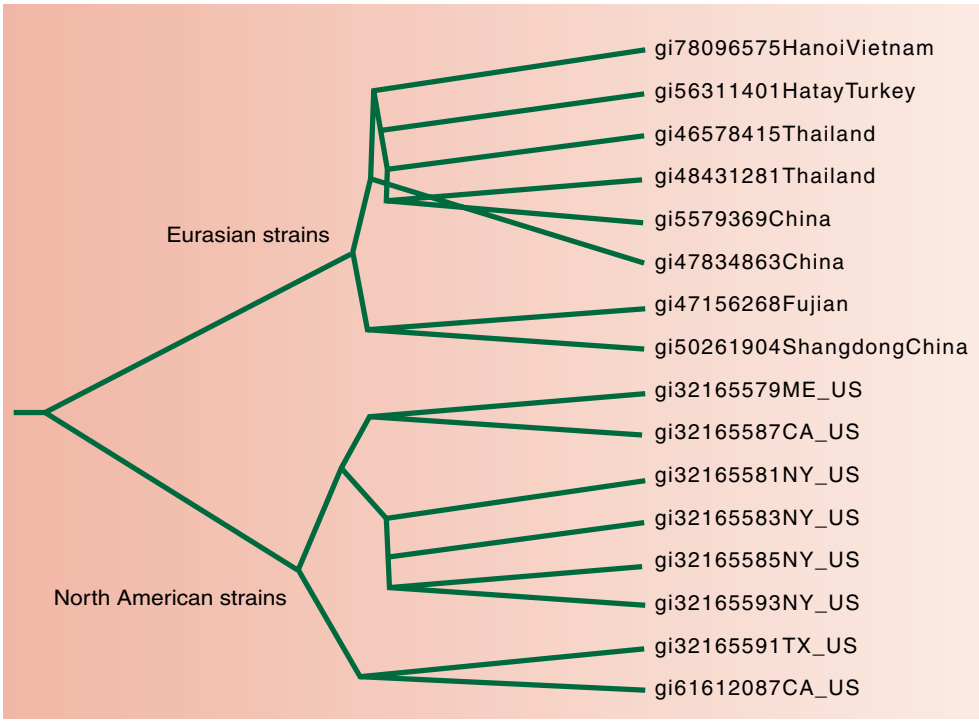
McBride and her team are also working with the CDC's Bioterrorism Rapid Response and Advanced Technology Laboratory, which will have lead responsibility for analyzing samples during a bioterror attack. Although the FluID$_x$ instrument is designed for use in hospitals and medical clinics, the technology can be adapted for any situation in which rapid biological assays are needed.

In October, the team submitted the FluID$_x$ system to the U.S. Food and Drug Administration to have it approved as a medical device. "Approval will likely take about a year," notes McBride. The Laboratory is already meeting with potential industrial partners who are interested in licensing the FluID$_x$ technology for commercial use.

In the meantime, the team continues to improve the assays and is working to automate a stand-alone device. The LDRD Program is supporting assay development to expand the FluID$_x$ panel. Device testing will continue at the Emergency Department of the UC Davis Medical Center until June 2007. If additional funding is awarded, the team will build several next-generation systems with 10 separate (parallel) PCR reaction chambers to enable asynchronous sample processing. Asynchronous processing will, in turn, allow sample throughput that is better aligned with the requirements of busy hospitals, especially during the influenza season or in the event of a pandemic influenza.

The flu season arrives every year without fail, bringing fever, coughing, and runny noses. Soon perhaps, FluID$_x$ will be a workhorse application, helping doctors decide how best to care for their patients.

—Katie Walter



Minimal Set Clustering software identifies the fewest number of signatures required to detect all members of a divergent target set. The branches on this phylogenetic tree show the four signatures needed to diagnose the relevant HA5 sequences of influenza A. The top two signatures target Eurasian strains, and the bottom two target North American strains.

Key Words: Autonomous Pathogen Detection System, FluID$_x$, influenza, KPATH, multiplex assays, point-of-care diagnosis, polymerase chain reaction (PCR), respiratory disease.

For further information contact Mary McBride (925) 423-2299 (mcbride2@llnl.gov).

An Action Plan to Reopen a Contaminated Airport

HOW would authorities respond if San Francisco International Airport (SFO) were to be contaminated with anthrax, and how long would it take to restore the airport to full usability? An intentional bioterrorist attack at the airport could endanger the health of hundreds of people. Long-term closure of this critical transportation hub during decontamination would have disastrous effects on the regional and national economy.

Recall the events of late 2001 when letters containing anthrax spores contaminated office buildings and postal facilities in Florida, New York City, Washington, DC, and other locations. Although some buildings were back in full operation in less than a month, others took many months to reopen, and one Department of State facility was closed for three years.

With that experience in mind, the Department of Homeland Security (DHS) funded a project to minimize the time a major transportation facility would be closed following a biological attack. Lawrence Livermore and Sandia national laboratories led the project, in partnership with SFO, to develop response and restoration protocols for such events. The group's work culminated in January 2006 when 120 officials from local, state, and federal agencies participated in a two-day demonstration at SFO's old international terminal to test the new procedures.

Returning the international terminal and a boarding area at SFO to full operation from a large-scale terrorist incident may have taken up to two years based on other biorestoration activities and the decontamination and restoration methods that were available in 2001. Using the protocols developed by the Livermore–Sandia team reduces that time by at least 50 percent. In fact, the team estimates that the time required would actually be less than six months, depending on the level of planning in place prior to an attack.

In January 2006, an interagency group of emergency responders tested the response and restoration protocols developed by Lawrence Livermore and Sandia national laboratories in a two-day demonstration at San Francisco International Airport.

Planning and Preparedness Are Key

To develop the protocols, team members worked with the public agencies that would respond to an attack at SFO or would help decontaminate the facilities. Participants included officials from SFO and other major airports, the U.S. Environmental Protection Agency (EPA), California EPA, Centers for Disease Control and Prevention (CDC), U.S. Postal Service, Department of Defense, Federal Bureau of Investigation, and National Institute for Occupational Safety and Health (NIOSH). The interagency group developed a list of activities that would be central to crisis and consequence management following a bioterrorist attack. (See the table on p. 11.)

The group then identified several areas for improvement. Perhaps most important was preincident planning and preparedness. Livermore scientist Ellen Raber notes that, before this project started, little realistic planning had been done for responding to a deliberate act of bioterrorism against a public transportation facility. However, having a restoration plan vetted and facility personnel trained substantially reduces the overall time for a restoration operation. "Planning and preparedness are keys to success, not only for the specific facility but for all public agencies that might be involved," says Raber, who leads the Response and Recovery Program in Livermore's Nonproliferation, Homeland and International Security Directorate.

Environmental scientist Tina Carlsen, who works in the Laboratory's Environmental Restoration Division, helped the team develop a generic biological restoration plan for major airports. The plan includes templates for characterizing and removing the contamination and obtaining clearance to reopen the airport. It recommends actions for emergency responders, methods for sampling and analysis, and handling procedures for decontaminated waste. The restoration plan also evaluates the decontamination methods available, including liquid, gel, and gaseous reagents. Special emphasis is given to chlorine dioxide and vaporous hydrogen peroxide, the methods that were used to clean up anthrax-contaminated facilities in 2001. The plan pulls all of this work into a framework that decision makers can use in the event of bioterrorism.

After review by CDC, regional EPA offices, NIOSH, and other agencies, the *Biological Restoration Plan for Major Airports* was submitted to DHS and EPA. These two organizations will issue the report in 2006 as a DHS–EPA guidance document that airports can use to plan recovery activities following a bioterrorist attack. The document also offers guidance on developing incident- and facility-specific restoration plans. SFO now has such a plan for an anthrax attack, thanks to its partnership in this project.

The Livermore team is working with Los Angeles International Airport to develop a site-specific data supplement to this plan. Workshops are also being held with major East Coast airports to begin transferring elements of the project to more users.

Making a Clean Sweep

A fast, accurate sampling and analysis process is essential to shorten the time line for restoration. Surfaces and the air must be tested to determine the extent of contamination and to ensure that the facility has been decontaminated. A large building such as an airport terminal has enormous air-handling systems that would likely become contaminated by a cloud of aerosolized bioagent. The moving air in heating and cooling systems can re-aerosolize a bioagent, remobilizing it to contaminate yet more surfaces and air. Thus, a fast response is essential to limit the spread of a bioagent.

Current methods for identifying a biological agent and determining whether it is viable (alive) involve culturing a sample—a process that can take several days. To reduce the turnaround time, Sandia scientists focused on improving sampling methods and efficiency, while Livermore's task was to speed up the analysis process.

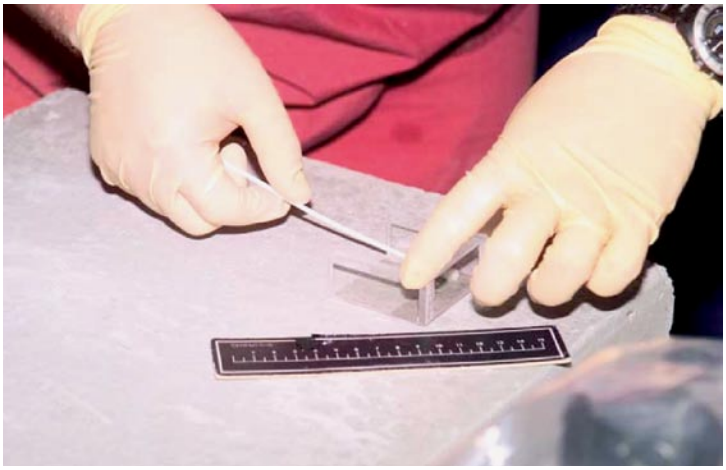
Crisis Management		Consequence Management			
Response Activities		Restoration Activities			Recovery Activities
Notification	First Response	Characterization	Remediation/ Cleanup	Clearance	Reoccupancy
Receive and assess information Identify suspect release sites Relay key information and potential risk to appropriate agencies	HAZMAT and emergency actions Forensic investigation Public health actions Screening sampling Determine agent type, concentration, and viability Risk communication	Detailed characterization of biological agent Characterization of affected site Site containment Continue risk communication Characterization/ environmental sampling and analysis Initial risk assessment Clearance goals	Decontamination strategy Remediation action plan Worker health and safety Site preparation Source reduction Waste disposal Decontamination of sites and/or items Decontamination verification	Clearance sampling and analysis Clearance decision	Renovation Longer-term environmental and public health monitoring Reoccupation decision

The Livermore–Sandia project identified a set of activities for restoring a contaminated facility following a bioterrorist attack.

The Livermore researchers expanded high-throughput sample analysis assays that use polymerase chain reaction (PCR). This system, called rapid viability PCR (RV-PCR), can analyze hundreds to thousands of samples per day, compared with at most 30 samples a day for the standard culturing process. RV-PCR is based on CDC–NIOSH protocols and uses commercially available automation techniques. For *Bacillus anthracis* (the causative agent for anthrax), it reduces the time to determine viability from several days to between 10 and 16 hours. The team has demonstrated similar reductions in detection time in proof-of-concept tests for *Yersinia pestis* (plague), *Brucella* (a bacteria), and *Francisella tularensis* (tularemia).

In the January demonstration, the RV-PCR data were tracked using the Building Restoration Operations Optimization Model (BROOM) developed by Sandia. BROOM software is useful for many phases of an indoor decontamination operation: planning, data collection, data management, and data analysis. The system can store thousands of facility drawings, which can be downloaded during sampling, and its barcode system eliminates manual data entry. A Web-based relational database offers remote, secure access to sampling procedures, collected data, floor plans, ventilation drawings, and other information. In addition, the software's statistical algorithms can estimate the total contamination using a limited sample set.

To help authorities determine how clean a facility must be before it can be reopened, the National Research Council (NRC) of the National Academies, with oversight by Livermore, prepared a framework for evaluating decontamination efforts. In 2005, NRC published this framework in *Reopening Public Facilities after a Biological Attack*, which recommends risk assessment actions, public health safeguards, sampling procedures, and decontamination standards. No universal standard is offered for determining when a building would be safe to reenter because the type of pathogen and the amount disseminated affect cleanup operations. The report, therefore, includes questions about pathogen characteristics—such as how far it has spread, whether it is transmissible between humans, and how long it will survive to pose a threat—to help decision makers determine the appropriate response.



Swipe samples collected from surfaces are analyzed following a biological dispersal to determine the extent of contamination. Tests are repeated following cleanup activities to verify the effectiveness of decontamination.

Past cleanup efforts, such as those for the 2001 anthrax attacks and the EPA's Superfund Program, offered vital lessons learned. For instance, federal officials determined that response and remediation activities following the 2001 attacks were hindered because procedures or regulations prevented law-enforcement and public health agencies from sharing the data collected at contaminated sites. The NRC report encourages building owners and managers to plan responses to bioterrorism and advocates full transparency in sharing health information so that decision makers can better evaluate the risks involved in a recommended action.

Open and Shut Cases

A new DHS assignment for Livermore is to develop protocols for responding to and cleaning up a large outdoor area contaminated by a bioagent. Researchers already know that sunlight will naturally degrade many biological pathogens. Also, when some bioagent particles hit soil, they stay there, so re-aerosolization is less of a problem. Still, planning for such an attack is new territory. Says Raber, "At this point, no one has experience with wide-area urban decontamination."

The Laboratory is also developing a site-specific biological restoration plan for Grand Central Station in New York City, where Livermore's Autonomous Pathogen Detection System has been tested. (See *S&TR*, October 2004, pp. 4–5.) A major subway station offers yet another set of challenges because it is part of a web of tunnels, staircases, and large semi-contained areas. "We look forward to continuing our involvement with major transportation facilities," says Carlsen. "They are a key to our nation's economic vitality and the well-being of our citizens."

—Katie Walter

Key Words: airport, bioterrorism, decontamination, emergency response and recovery, rapid viability polymerase chain reaction (RV-PCR), subway, transportation facilities.

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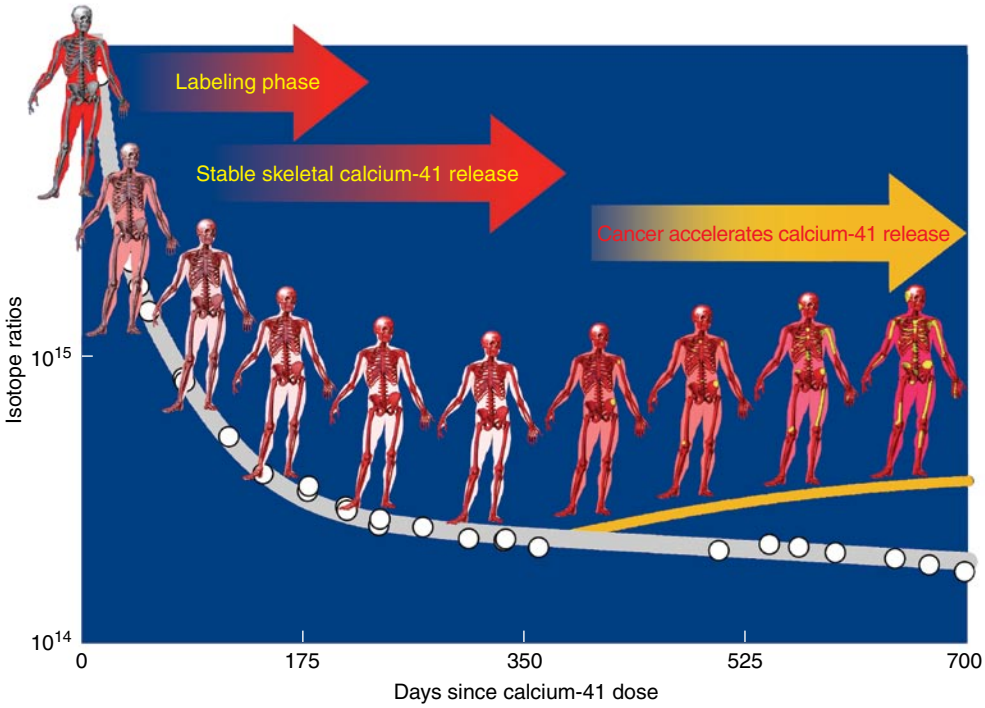
Early Detection of Bone Disease

THE American Cancer Society estimates that more than 230,000 new cases of prostate cancer and 212,000 of breast cancer will be diagnosed in the U.S. in 2006. In at least 80 percent of the cases that result in death, tumors will have spread to bone and significantly damaged the skeleton. This damage often causes uncontrollable pain and usually goes undetected until it is too late to treat effectively. Bone cancer spreads quickly because the skeleton is a nutrient-rich environment for the malignant cells. As tumor cells multiply, they also send signals to the body that trigger a rapid increase in bone destruction.

Medical researchers know that skeletal disease correlates with the bone turnover rate. The skeleton is a dynamic system composed of protein and calcium minerals. At any one time, about 10 percent of the system is in the process of being formed or destroyed. In adult humans, the skeleton is completely replaced once every 10 to 15 years. Early detection of the increased bone destruction that occurs in the initial stages of cancer metastasis could help physicians design methods to prolong a patient's life or even arrest disease progression.



Accelerator mass spectrometry (AMS) can measure a calcium-41 tracer in blood or urine to track small changes in skeletal calcium. After the tracer mixes with the body's calcium, the calcium levels stabilize, providing a baseline. Tracer concentration can then be measured over time. A sudden increase in the amount of calcium-41 released from bone (yellow line) signals the onset and progression of bone disease.

Conventional diagnostic methods are not sensitive enough to detect early-stage bone cancer. For example, measurements of the bone turnover "markers" found in blood or urine samples normally fluctuate by 20 to 30 percent, making small changes impossible to detect. Medical imaging methods can be sensitive to bone abnormalities. However, these diagnostics cannot be used for routine screening because the equipment is expensive to operate, the tests expose patients to radiation, and interpreting the results is a time-consuming process requiring highly skilled personnel.

A team of Livermore scientists, with funding from the Laboratory Directed Research and Development Program and the National Institutes of Health (NIH), has developed a technique that improves the diagnostic capabilities for bone disease. The technique uses accelerator mass spectrometry (AMS) with calcium-41 as an isotopic tracer to measure small changes in the rate of skeletal bone turnover. With this technique, physicians could monitor a patient's calcium level over his or her lifetime and detect metastatic cancer in the early stages, when treatment would be more effective. The AMS technique could also be used to diagnose other health problems involving calcium loss, such as osteoporosis and kidney failure.

High Precision with a Tiny Tracer

The Livermore team chose calcium-41 as the tracer isotope because only a small dose is needed for the diagnostic. Calcium-41 is extremely rare in nature, so its signal is clearly distinguished from those of other calcium isotopes that occur naturally in the body. In addition, calcium-41 has a long half-life (104,000 years) and decays by a low-energy process to potassium-41, a naturally occurring and stable isotope. "The dose to be given is less than one-fiftieth of the radiation a person would receive from a single x-ray bone-density test, but

this small amount of calcium-41 is enough to track the skeletal calcium loss over a person's lifetime," says team leader Darren Hillegonds, a chemist in the Laboratory's Center for Accelerator Mass Spectrometry (CAMS).

The amount of calcium-41 used in this research is so low that conventional mass spectrometry cannot separate it from other elements. AMS, however, is about a million times more sensitive than the conventional technique, so it can measure nanogram quantities of isotopes.

Livermore has used AMS to analyze isotopes for many research areas, including environmental and earth sciences, energy, materials analysis, and archaeological radiocarbon dating. In the early 1990s, the Laboratory pioneered the use of AMS for biomedical applications. In 1999, NIH designated CAMS as its National Research Resource for biomedical AMS. (See *S&TR*, November 1997, pp. 4–11; July/August 2000, pp. 12–19.)

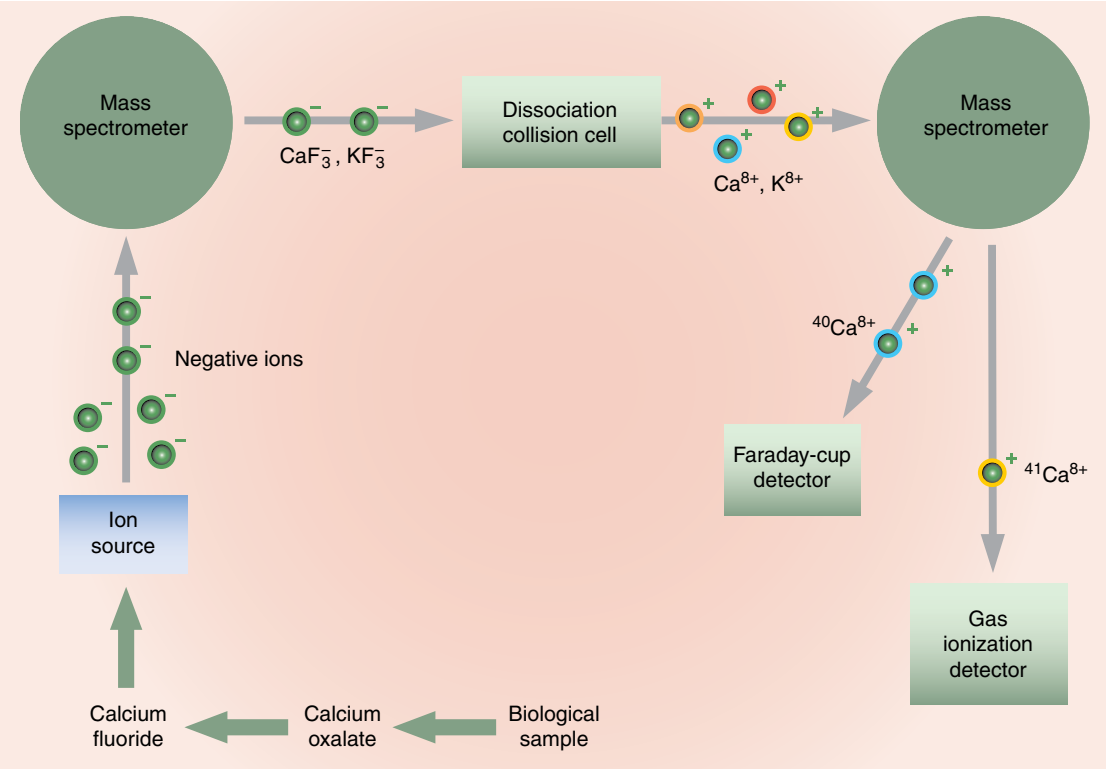
The Livermore team is working with collaborators from the University of California (UC) at San Diego and the UC Davis Cancer Center, which sees more than 250 new breast cancer and 150 new prostate cancer patients each year. CAMS director John Knezovich says, "The calcium-41 work represents an exciting intersection of nuclear physics and health research. AMS enables scientists to begin to answer questions in biomedical research that cannot be studied anywhere else."

Detects Small Changes over a Lifetime

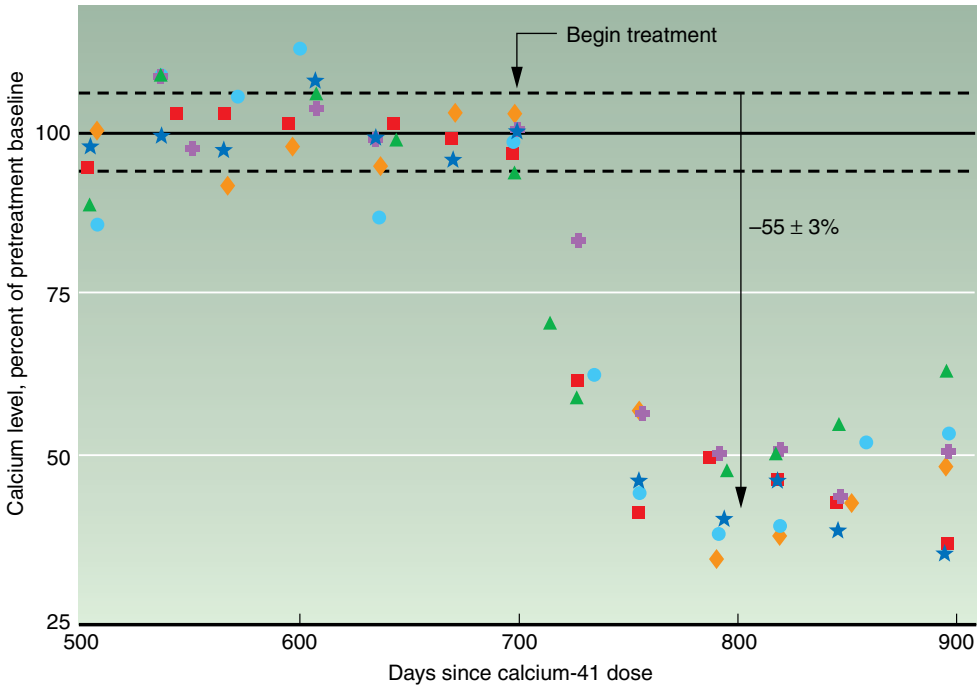
Hillegonds's team used UC Berkeley's Madonna software to develop a kinetic model of human calcium homeostasis. The model predicts how the levels of calcium-41 in urine will change during the first few hours after a dose is administered until many years later. The modeling results also helped validate the methods designed to administer a calcium-41 tracer to a patient and track changes in urine.

"Doctors would administer the tracer isotope to patients when they were diagnosed with breast or prostate cancer," says Hillegonds. "Within hours, the tracer would mix with the calcium in bodily fluids and tissues, and within months, it would be incorporated into the skeleton. The patient's calcium level could be monitored by testing urine samples several times a year. As bone breaks down, tiny amounts of calcium-41 atoms become markers in the urine and can be counted by AMS." If bone disease occurs, the calcium-41 level in a patient's urine would rise dramatically.

The Livermore researchers used a slow-neutron nuclear reactor and a naturally occurring calcium isotope to produce the calcium-41 tracer for their experiments. Collaborators at UC San Diego prepared the collected samples for analysis. AMS samples must be in solid form, but elemental calcium is unstable and difficult to produce. Therefore, the UC San Diego researchers mixed calcium from the samples with hydrofluoric acid to produce



The AMS process for analyzing calcium-41 begins with cesium ions producing negative calcium trifluoride (CaF_3^-) and potassium trifluoride (KF_3^-) ions. Because KF_3^- is less stable than CaF_3^-, this step effectively reduces the isotope potassium-41 (^{41}K) that otherwise would interfere with the analysis. A mass spectrometer separates these molecules, which accelerate and collide with a carbon foil. This collision destroys all of the molecules and leaves only positively charged particles, which are separated by a second mass filter. Each calcium 41 particle ($^{41}Ca^{8+}$) is positively identified and counted in a gas ionization detector, providing clear separation from the remaining $^{41}K^{8+}$. Stable calcium-40 particles ($^{40}Ca^{8+}$) are separately measured, and the ratio of the two calcium isotopes is compared to baseline levels.



Skeletal calcium was measured in six postmenopausal women who received a medication for osteoporosis. AMS measurements clearly show the expected drop in the rate of bone destruction for each individual tested, confirming that the drug is effective. Results also demonstrate that the calcium-41 technique is the most sensitive marker available to diagnose bone turnover.

a precipitate of calcium fluoride and added silver powder to the mixture so it would conduct a charge effectively.

With AMS, a beam of cesium ions bombards the calcium fluoride mixture, producing negatively charged calcium trifluoride. These molecules are attracted to a 9-megavolt charge in the linear accelerator and collide with a carbon foil, which causes them to dissociate into high-energy calcium particles. Large magnetic and electrostatic filters then separate the particles. The calcium-41 particles enter a gas ionization detector, where they are individually counted. The stable calcium-40 isotope is measured at the same time by a Faraday-cup detector. By working with ratios of calcium-41 to calcium-40, researchers can ensure that results are insensitive to changes in instrument parameters, especially negative-ion output among different samples. The ratio of the two isotopes is then compared to the baseline calcium level to determine the rate of calcium loss. The Livermore spectrometer can analyze about 100 samples of calcium-41 every day. Knezovich says, "No other instrument has the speed and throughput to analyze the thousands of samples necessary for calcium-41 studies of human health."

To validate the technique, the team injected prostate cancer cells from a human into the tibia of mice. As tumors grew and destroyed bone, the rate of calcium-41 release increased. Results from these experiments indicate that the technique can effectively diagnose changes in bone turnover with a precision of ±3 percent.

The team will soon begin trial studies on humans using prostate cancer patients with and without confirmed bone metastasis. Patients will take a 1.2-microgram dose of calcium-41 and provide 11 urine samples over a 6-month period. Hillegonds says, "Preliminary data and the kinetic model predict that our approach will detect a change of 10 percent in bone turnover. Such a small change would be completely invisible to other diagnostics."

Improving Therapeutic Drugs

The technique may also help pharmaceutical companies assess the effectiveness of drug treatments. For example, some medications designed to treat osteoporosis reduce bone breakdown by "sealing" the bone. Hillegonds's team confirmed that calcium-41 release from bone dropped dramatically when one type of medication was administered, indicating that the treatment was effective.

According to Hillegonds, the calcium-41 assay for prostate and breast cancer could easily be tailored for malignancies affecting other organs of the body as well as for diseases in which treatment increases bone loss. He adds that the collaboration with UC researchers allows the Laboratory to extend the reach of its innovations. "UC's expertise in clinical research and medicine enables us to apply our scientific breakthroughs toward helping improve the health of hundreds of thousands of people each year."

—Gabriele Rennie

Key Words: accelerator mass spectrometry (AMS), bone disease, calcium-41, cancer, Center for Accelerator Mass Spectrometry (CAMS).

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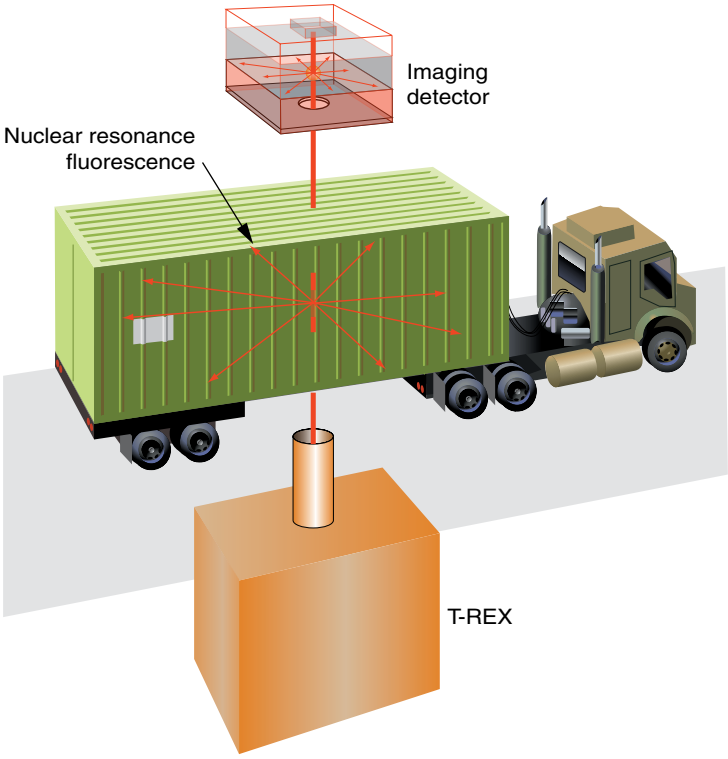
Taking a Gander with Gamma Rays

SINCE their discovery in 1895, x rays have been used in countless applications to make the unseen visible—bones beneath skin and tissue, metal beneath plastic. These electromagnetic waves can penetrate low-density materials (such as skin and plastic), but higher density materials (bone and metal) significantly scatter or absorb photons. Recording the photons that pass through only some materials creates the distinctive "shadow picture" of an x-ray image, which shows a feature previously hidden from view. In special cases, scientists can use x-ray imaging to determine the atomic composition of matter—that is, its constituent elements. Determining the isotopic variety of observed elements would also be useful for some applications, for example, to distinguish depleted uranium from weapons-grade uranium. However, developing those capabilities requires a radiographic source that uses the next higher energy range in the electromagnetic spectrum.

Christopher Barty, a physicist in Livermore's National Ignition Facility Programs Directorate, has brought together Laboratory experts in lasers, optics, accelerators, and nuclear physics to design such a source. Called T-REX, the Thomson-radiated extreme x-ray system will produce photons at extremely high energies with the brightness, or photon spectral, spatial, and temporal density, needed to study isotopes. This capability will allow researchers to address challenges in fields such as nonproliferation, homeland and international security, and waste identification.



Livermore researchers are developing a system that combines the capabilities of a Thomson-radiated extreme x-ray (T-REX) system with a nuclear resonance fluorescence technique to detect small amounts of nuclear materials and image their isotopic distribution. The system could be used to inspect well-shielded objects, such as cargo containers moving through a terminal.

From X to Gamma Rays

T-REX builds on a past Livermore project called Picosecond Laser–Electron Interaction for the Dynamic Evaluation of Structures (PLEIADES), which was funded by the Laboratory Directed Research and Development (LDRD) Program. The goal of PLEIADES was to develop a system for generating high-energy x rays to study the dynamic processes in biological and energetic materials. The project team used a 100-megaelectronvolt (MeV) accelerator to create a beam of energetic electrons that were then smashed into photons generated from an ultrashort-pulse, 10-terawatt laser. (See *S&TR*, October 2001, pp. 13–15.) The collision of electrons and photons produces pencillike beams of x rays by the so-called Thomson-scattering process. With the PLEIADES system, the energy of the Thomson x rays can be adjusted, or tuned, by changing the electron bunch energy or the laser photon energy, resulting in picosecond-long pulses of bright, tunable x rays between 10 and 100 kiloelectronvolts (keV).

"Photons in this range can excite or ionize even the most tightly bound atomic electrons," says Barty. "We could use these photons to probe the atomic-scale dynamics of various physical, chemical, and biological phenomena and to develop element-specific tools for radiography and radiology." In 2003, the PLEIADES system generated record pulses of 70-keV x rays.

That success led Barty and Livermore physicist Fred Hartemann to consider using the Thomson-scattering process to create photons with energies above 100 keV. Their calculations indicated that a beam's brightness could be increased rapidly by using more energetic electrons and by reducing the interaction region between the laser and electrons.

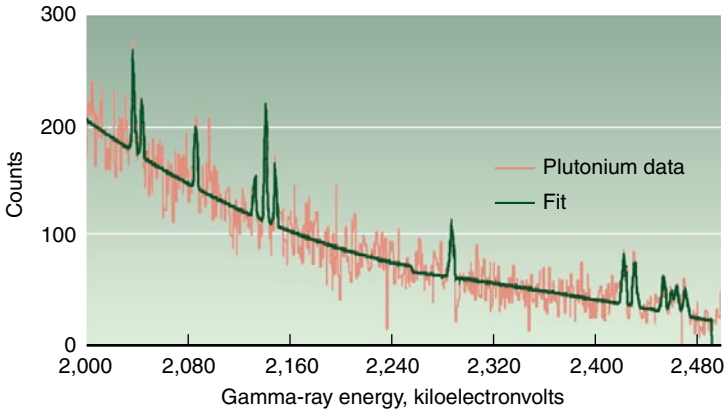
"The number of photons generated from the Thomson-scattering process increases as a square of the electron energy," says Barty. "We calculated that, by using relativistic electrons and energetic photons from a laser, we could generate a tunable, nearly single color, bright beam of photons between 100 keV and several megaelectronvolts."

Traditionally, beams in this particular energy regime are created in synchrotron facilities. The problem with synchrotron-generated radiation is that the brightness of the generated beam declines rapidly as a function of photon energy, and the photons produced span a wide, continuous spectral range. Thomson scattering would alleviate this problem if the technical issues in building a system could be resolved. According to Barty, conservative estimates indicate that, at 1 MeV, a system using Thomson scattering could generate a beam of photons with a spectral, spatial, and temporal density a quadrillion (10^{15}) times greater than that from the Advanced Photon Source at Argonne National Laboratory, which is the brightest synchrotron machine in the Department of Energy's (DOE's) complex.

Detecting Concealed Nuclear Materials

Barty and Hartemann are working with Dennis McNabb, Jason Pruet, and others on an LDRD project to develop a 15- by 3-meter T-REX system capable of producing tunable pulses of 700-keV photons. "We visualize applications in radiography, spectroscopy, imaging of special nuclear material, microcrack failure analysis, and more," says Barty. The team expects such systems to provide new research opportunities in much the same way that tunable lasers revolutionized atomic spectroscopy.

Bright gamma-ray pulses tuned to specific nuclear energy levels could be used to detect specific nuclei and isotopes, through a process called nuclear resonance fluorescence (NRF). Most nuclei have a set of nuclear "fingerprints"—several photon-excited states unique to that type. When a photon with the defined energy hits a targeted nucleus, the photon is absorbed. The excited nucleus then decays, radiating photons of the characteristic energy in all directions. The emitted energy spectrum thus identifies the nuclear species or isotope of the target.



These nuclear resonance transitions for plutonium-239 occur at energy levels that can be reached by a T-REX gamma-ray source.

Maurice Goldhaber and Edward Teller described the basic physics of NRF in 1948. In 2003, William Bertozzi from the Massachusetts Institute of Technology proposed using the technique to detect nuclear materials, such as highly enriched uranium, in shipping containers and trucks. At that time, however, no available system could generate tunable gamma-ray beams for this application. Barty's team wants to combine fully developed T-REX capabilities with the NRF technique to detect the presence of specific isotopes and image their distribution.

The Department of Homeland Security's Domestic Nuclear Detection Office is funding research to explore this imaging and detection capability. The proposed system, called fluorescence imaging in the nuclear domain with extreme radiation (FINDER), could be used to image the isotopic composition of materials inside well-shielded objects, such as cargo containers moving through an inspection terminal. If successful, a FINDER system based on T-REX technology could provide a solution to the challenge of detecting concealed highly enriched uranium.

Calculations by Pruet and others indicate that the technology has tremendous potential for verifying the contents of cargo containers without interrupting the flow of commercial traffic. In addition, this isotopic imaging method, which the team calls isotope photography, could be used in stockpile surveillance and as a safer method for evaluating legacy nuclear waste streams. "We're also exploring ways to apply T-REX technology to important DOE science missions, such as next-generation light sources and high-intensity megaelectronvolt photon beams for fundamental nuclear science measurements," says Barty.

The Future Looks Bright

The T-REX team is designing and constructing the gamma-ray source that will be used to demonstrate the FINDER concept. In addition, researchers at Lawrence Livermore and Pacific Northwest national laboratories and Passport Systems, Inc., in Acton, Massachusetts, have identified NRF transitions in uranium-235 and plutonium-239 at energy levels that can be reached by a 2-MeV-class T-REX source. Says Barty, "Completing this research will place the Laboratory in a leading position with respect to gamma-ray source capability and the development of novel applications in nuclear photo science."

—Ann Parker

Key Words: cargo inspection, gamma-ray spectrum, isotope photography, nuclear resonance fluorescence (NRF) imaging, Thomson-radiated extreme x-ray (T-REX) system, Thomson scattering.

For further information contact Christopher Barty (925) 423-8486 (barty1@llnl.gov).

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

Method and System of Integrating Information from Multiple Sources

Francine A. Alford, David L. Brinkerhoff

U.S. Patent 7,092,948 B1

August 15, 2006

This method integrates information from multiple sources in a document-centric application system. Many applications are connected through an object request broker to a central repository, which then posts information to a Web page. An example implementation of this method is an online procurement system.

Inductrack Configuration

Richard Freeman Post

U.S. Patent 7,096,794 B2

August 29, 2006

A simple permanent-magnet-excited geometry for a magnetically levitated (maglev) train provides levitation forces and is stable against vertical displacements from equilibrium, but it is unstable against horizontal displacements. An Inductrack system used in conjunction with this geometry stabilizes the vehicle from horizontal displacements. It also provides centering forces to overcome centrifugal forces when the vehicle is traversing curved sections of a track or when another transient horizontal force is present. In some proposed embodiments, the Inductrack track elements are also used as the stator of a linear induction-motor drive and braking system.

Thin Film Transistors on Plastic Substrates with Reflective Coatings for Radiation Protection

Jesse D. Wolfe, Steven D. Theiss, Paul G. Carey, Patrick M. Smith, Paul Wickboldt

U.S. Patent 7,112,846 B2

September 26, 2006

Silicon thin-film transistors (TFTs) are fabricated on low-temperature plastic substrates using a reflective coating so that these inexpensive substrates may be used in place of standard glass, quartz, and silicon wafer–based substrates. The TFTs can be used in large-area, low-cost electronics such as flat-panel displays and portable electronics such as video cameras, personal digital assistants, and cell phones.

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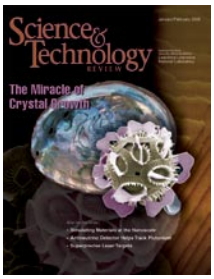

January/February 2006

March 2006

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May 2006

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September 2006

October 2006

November 2006

December 2006

Abstracts

Diagnosing Flu Fast

A new instrument developed at Lawrence Livermore can differentiate five types of respiratory viruses in about two hours after a sample is taken. The FluID$_x$ diagnostic system, with its multiplexed polymerase chain reaction nucleic-acid-based assays, was designed specifically for fast, easy use at the point of patient care. FluID$_x$ uses carefully vetted nucleic-acid assays developed in part with KPATH, the Laboratory's whole-genome comparative analysis software system. Minimal Set Clustering, another software tool, augments KPATH by identifying the smallest number of signatures required to recognize all members of a target set of genomic sequences. Tests of FluID$_x$ at the Emergency Department of the University of California at Davis Medical Center show that the system's assays are as sensitive as viral culturing, the best available method for viral diagnosis. The FluID$_x$ technology can be adapted to other systems that use biological assays.

Contact:
Mary McBride (925) 423-2299 (mcbride2@llnl.gov).

U.S. Government Printing Office: 2006/670-074-10024

Titan's Dual-Pulse Power

Livermore introduces the first laser in the world with both long- and short-pulse capability.

Also in January/February

• Nuclear forensics has become an important tool in the fight against illegal smuggling of nuclear and radiological materials.

• Membranes made from billions of carbon tubes, each 50,000 times thinner than a human hair, allow liquids and gases to flow at astonishingly fast speeds.

• In an abandoned mine, where the pH approaches zero, communities of microbes produce hundreds of unusual proteins.

Coming Next Month

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