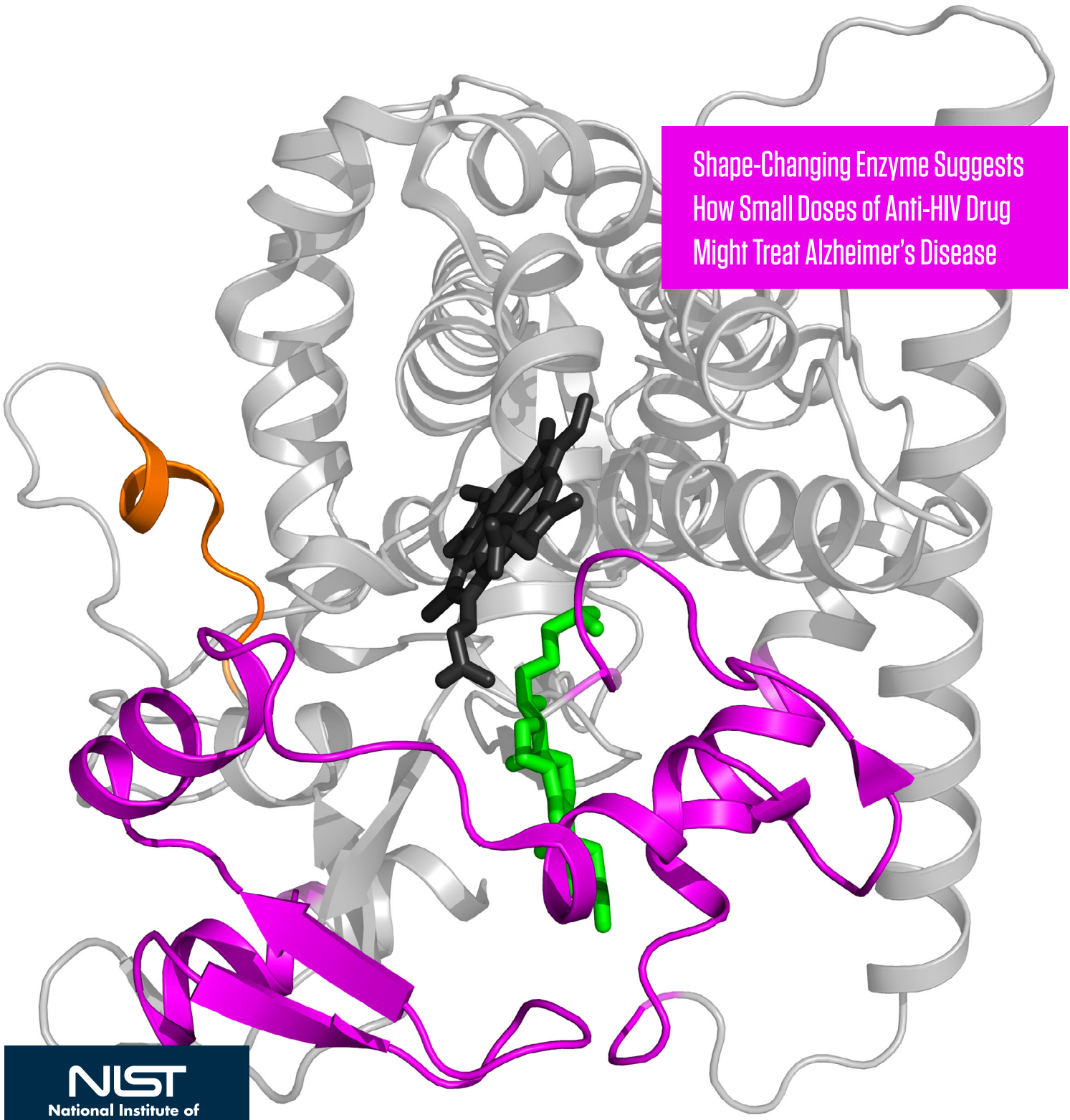
SUMMER 2016

MATERIAL MATTERS

THE QUARTERLY MAGAZINE OF NIST'S MATERIAL MEASUREMENT LABORATORY

Shape-Changing Enzyme Suggests How Small Doses of Anti-HIV Drug Might Treat Alzheimer's Disease



NIST
National Institute of Standards and Technology
U.S. Department of Commerce

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CONTRIBUTORS

Editor | Torey Liepa

Contributors | Leah Kauffman | Mark Bello | Rich Press

Cover Image | Kyle Anderson/NIST

Contact MML | mmlinfo@nist.gov

A MESSAGE FROM THE MML DIRECTOR

Laurie Locascio, Ph.D.
Director
Material Measurement Laboratory
NIST

The chemical industry, which accounts for more than 25% of the U.S. gross domestic product, relies heavily upon catalysts, substances that speed the rate of chemical reactions. Without catalysts, most chemical reactions happen so slowly or at such high temperatures and pressures that the resulting products wouldn't be profitable. Ninety percent of all chemical products are made with catalysts.

Small improvements in the efficiency of a catalyst can result in significant savings in the use of energy, feedstock material, and water, and so yield a competitive advantage and higher profits, and potentially lead to lower prices for consumers and more jobs. In addition to seeking higher rates of efficiency, the chemical industry is looking for new catalysts that minimize the environmental impact of industrial processes and reduce emissions of greenhouse gases to meet regulations in U.S. and global markets.

MML's experts in the chemical sciences and engineering have been talking with industry members about these issues and will soon do what NIST does best: convene stakeholders to understand their measurement needs so we can meet them with solutions that will benefit the entire industry. That workshop is scheduled to take place in fall 2016. We already know that the chemical industry needs better data on the mechanisms of reactions as they happen in real working conditions so they can build accurate, reliable, and fast models of new catalysts before undertaking large-scale, costly trials of new catalysts on their production floors. This goal will require an industry-wide effort to attain and share fundamental knowledge of complex reactions, which MML has the knowledge and experience to help lead.

Better simulations of potential catalysts will also need catalyst reference materials, physical artifacts that have been intensively characterized under controlled conditions with documented methods and validated data, more realms in which MML staff members, who oversee the NIST-wide Standard Reference Material program, are experts. These reference materials will allow researchers in the chemical industry to validate their own measurements and help ensure the reliability of their data.

The transfer of technical expertise from a lab like MML to industry is, ideally, an ongoing process that doesn't end with the sale of a reference material. To keep the knowledge exchange going, we're forming an alliance with several universities in the region to provide measurement services and data to the chemical industry. University students will have the opportunity to train at NIST while working on industry's top problems, and mingle with industry chemical engineers working in NIST labs to perfect new measurement science, a continual exchange of ideas that results in more American innovation.

SHAPE-CHANGING ENZYME SUGGESTS HOW SMALL DOSES OF ANTI-HIV DRUG MIGHT TREAT ALZHEIMER'S DISEASE

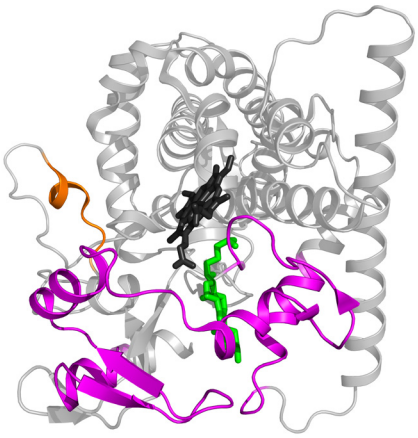
For a promising pathway to treating Alzheimer's patients, "aim here." That's what NIST researchers advised collaborators hunting for molecules that, by linking to a normally occurring enzyme, rev up the brain's capacity for clearing cholesterol—a boost associated with improvements in memory and other benefits in animal studies.

The target pinpointed by the NIST scientists is where an approved anti-HIV drug—efavirenz—latches to the enzyme already responsible for about 80 percent of the cholesterol elimination from the human brain. Obtained with a cutting-edge atom-substitution technology called hydrogen-deuterium exchange (HDX), the molecular roadmap shows how small amounts of the drug can kick the enzyme, called CYP46A1, into higher gear.

With this information, a team led by Irina Pikuleva of Case Western Reserve University now has the full story behind the drug's mechanism of action, key evidence in their proposal to launch clinical trials of efavirenz as an Alzheimer's treatment. The analytical sleuthing that exposed the dynamics of the cholesterol-clearing connection was reported in a recent issue of the *Journal of Biological Chemistry*.

Analyses of NIST's HDX data and follow-on experiments helped to explain why, in studies of mice, tiny doses of efavirenz ramped up CYP46A1's cholesterol-removal capability while larger doses had an inhibiting effect.

The explanation: At low doses, efavirenz binds to a site on the enzyme that boosts cholesterol breakdown at another location on the enzyme, an increase enabled by changes in shape initiated by the drug. At higher doses, however, drug molecules begin to compete with cholesterol for the same site where cholesterol normally binds.



When efavirenz binds to CYP46A1 at the site shown in orange, it increases the flexibility of the protein in the region (magenta) around cholesterol (green). Regions with no changes are shown in grey and iron-containing heme in black. Credit: Kyle Anderson/NIST

The shape-changing effect of efavirenz "is a classic example of a basic tenet of biology—structure determines function," Pikuleva said. And the effect can be dramatic.

In mouse studies, the enzyme-drug connection triggered a 40 percent increase in cholesterol breakdown and removal from the brain. In people, the boost is likely to be significantly higher, Pikuleva said, since the enzyme plays a larger disposal role in the human brain than in the mouse's.

Studies of over the past 15 years persuaded Pikuleva's team to pursue an Alzheimer's treatment strategy focused on ratcheting up the cholesterol-clearing capabilities of CYP46A1, part of a large family of iron-containing enzymes that strongly influence how the body processes drugs.

Studies by other scientists that used genetic manipulations in mouse models of Alzheimer's disease showed that cranking up CYP46A1's activity reduced development of plaque, or clumps of protein pieces called beta amyloids. These studies also reported improvements in memory and learning. And, even in plaque-free, normal mice, increased cholesterol removal resulted in memory improvement. Conversely, mouse studies also found that suppressing CYP46A1 led to learning deficiencies.

Focusing on efavirenz as part of its strategy to "repurpose" already-approved drugs, the Case Western team set out to uncover how the drug stimulates the enzyme's activity. Computational simulations and modeling suggested more than 30 locations on the enzyme where efavirenz molecule might bind. Seeking to winnow down the options, Pikuleva turned to Kyle Anderson and colleagues at the Institute for Bioscience and Biotechnology Research, a partnership between NIST and the University of Maryland.

In HDX analyses, proteins are immersed in "heavy water," in which normal hydrogen, containing a single proton in its nucleus, is replaced by deuterium, a rarer type of hydrogen whose nucleus holds both a proton and neutron. Protein and heavy water exchange hydrogen and deuterium. As the protein swaps out hydrogen for heavier deuterium, its mass increases.

The process involves a series of steps that include quenching—or locking in the deuterium in the protein—and then breaking the protein into electrically charged fragments for analysis. With a device called a mass spectrometer, researchers can measure the mass of these fragments to determine how quickly these protein pieces exchange hydrogen for deuterium. A protein fragment that is largely exposed to water will have a fast exchange rate, but a fragment that comes from a site buried inside the protein or is covered up by a molecule binding to the protein will have a slower exchange rate.

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NEW MODEL MAY HELP SOLVE THE MYSTERY OF HOW LITHIUM STABILIZES MOODS

New measurements may have lifted the veil on the vexingly elusive interactions through which lithium can moderate the manic highs and debilitating lows experienced by people who suffer from bipolar disorder—about 2.6 percent of Americans, according to the National Institute of Mental Health.

Through a series of nuclear magnetic resonance (NMR) experiments, scientists from the Institute for Bioscience and Biotechnology Research (IBBR) and the Center for Biomedical Engineering and Technology (BioMET) at the University of Maryland, Baltimore, have proposed a new molecular model of lithium's biologically active form. Writing in the new issue of *Biophysical Journal*, they also report evidence that this bioactive form can significantly prolong the activity of a signaling pathway in the brain's nerve cells (neurons), while also connecting seemingly disparate results of previous studies of the drug.

Although not effective in all patients, lithium is the "first-line pharmacologic treatment" for acute bipolar disorder cases, as recommended by the American Psychiatric Association. But nearly five decades after the Food and Drug Administration approved lithium as a long-term treatment in 1970, just how salts formed from this common silver-white metal work in the brain continues to be debated.

The new model provides a fresh perspective that can sharpen research aimed at pinning down lithium's biochemical targets, and the pathways through which it exerts its beneficial psychological effects, the team explained. The model also could guide design of new treatments of mood disorders that are as effective as lithium but with fewer side effects.

Credit: istockphoto.com

"No one has yet found the binding site on a protein through which lithium exerts its pharmacological effects, which means we still don't have a target that might be used to steer drug development," said John Marino, the NIST researcher who leads the Biomolecular Structure and Function Group at IBBR, a joint institute of NIST and the University of Maryland. But the bullseye that Marino's team found is not your typical binding site.

"In our model," he explained, "lithium acts as a kind of force multiplier," exerting the equivalent of a gentle, yet very helpful nudge to abundant molecular complexes essentially composed of phosphate and magnesium. In a sense, lithium may be a performance modulator for these functionally diverse complexes.

Perhaps the most ubiquitous and influential of these complexes is the molecule that serves as the body's "chemical fuel" and as an essential cellular signaling agent—adenosine triphosphate, or ATP. Positively charged magnesium ions must bind to ATP so that cells can tap the energy it stores, a prerequisite for most biological functions and processes.

Lithium ions also have an affinity for phosphate-containing compounds, including ATP, and a number of proteins, known as enzymes, that use or make ATP. On the basis of earlier research, some scientists have suggested that lithium could compete with and displace magnesium and, thus, inhibit these enzymes, although the evidence was far from conclusive.

So, in the new study, the researchers began with the hypothesis that lithium could cooperate—or, at least, co-exist—with magnesium in these phosphate complexes. In a series of NMR experiments, which exploit the same magnetic properties of atoms that yield MRI images in hospitals and clinics, the team assembled evidence indicating that rather than competing, lithium ions can form an "intimate association" with magnesium ions and phosphates.

At concentrations corresponding to normal dosage levels, lithium ions were found to be attracted to ATP-magnesium to form an ATP-magnesium-lithium complex. This complex might influence how ATP functions in the brain and elsewhere in the body, the researchers reported. And this same three-way interaction—lithium, magnesium and phosphate—might "provide a common link among previous studies that have identified seemingly unrelated enzymes as targets for lithium ions," Marino said.

One place where this interaction might be significant is on the surfaces of neurons, which have diverse cell-surface receptors that bind ATP. To explore this possibility, the team exposed rat nerve cells in a solution containing ATP, magnesium and lithium ions, separately and in combination. For each of these mixtures,

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A CALL FOR DEVELOPING—AND USING—CONSENSUS STANDARDS TO ENSURE THE QUALITY OF CELL LINES

Mainstays of biomedical research, permanent lines of cloned cells are used to study the biology of health and disease and to test prospective medical therapies. Yet, all too often, these apparent pillars of bioscience and biotechnology crumble because they are crafted from faulty starting materials: misidentified or cross-contaminated cell lines.

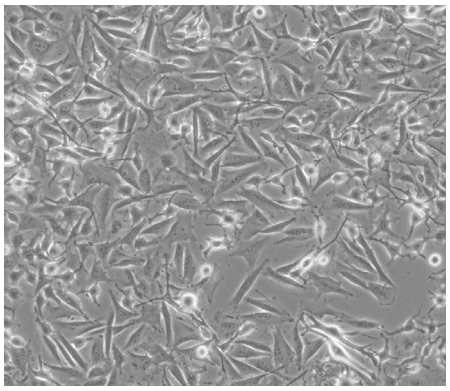
Writing in the June 2016 issue of *PLOS Biology*, NIST scientists call for "community action" to assemble a "comprehensive toolkit for assuring the quality of cell lines," employed at the start of every study.

As important, they assert, more researchers and laboratories should use the tools that already exist. The NIST authors point to the American National Standard for authentication of human cell lines, which can be implemented to detect cell-line mix-ups and contamination before embarking on studies of cancer or other research using human cells.

Unfortunately, the four-year-old standard has not been widely adopted, even though cell-line authentication is a growing priority among funders and publishers of research.

Cell lines are populations of clones: genetically uniform animal or plant cells that are bioengineered to proliferate indefinitely in culture. First used in the early 1950s, these immortalized cell lines, each with different properties or features, now number well into the thousands and are used as simple models for studying disease and for testing the toxicity of compounds, producing biological drugs, and other applications.

Cell-line contamination and misidentification can undermine research results, spur additional studies of questionable value and waste research



A cross-contaminated cell line, identified as such through STR profiling. Credit: CellBank Australia

funds—accounting for a significant portion of the estimated $28 billion of irreproducible preclinical research conducted each year in the United States alone, according to a 2015 economic analysis.

A "high level of confidence" in published research results requires valid underpinning data on methods and materials—cell lines, instrument performance and more, explain the researchers, who work in the Biosystems and Biomaterials Division of NIST's Material Measurement Laboratory. "One might argue that these control data are as important as the study data themselves."

The critical importance of authenticating cell lines is widely recognized, due, in part, to publicized reports on the costs and damaging research consequences of cell-line contamination, which could have been avoided by confirming the identity of cell lines at the outset of research projects. The National Institutes of Health, other funding agencies and organizations, and many scientific journals have established requirements for reporting on the authentication and purity of cell lines.

Still, cell-line authentication is poorly reported. In 2015, the Global Biological Standards Institute reported that 52 percent of the life sciences researchers it surveyed never validate their cell lines.

The American National Standards Institute and American Type Culture Collection have developed, according to the authors, a "very thorough and helpful" standard on authenticating human cell lines using short tandem repeats—a DNA "fingerprinting" method borrowed from forensics in which cells can be identified by how many times particular DNA sequences repeat within their genome. "Lack of awareness," the NIST authors suspect, may account for limited use of the standard, as suggested by disappointingly low levels of human cell-line authentication in studies. They recommend using the standard in training and education programs, which may get a push from authentication requirements set by funders and publishers.

Comparable authentication standards are needed for mouse, rat and other important nonhuman cell lines used in research and biomanufacturing.

The authors advocate using inclusive, consensus standards-setting processes—like the one used for human cell-line authentication—to address these needs as well as to seize new opportunities that are arising with the commercialization of genome-sequencing technologies.

"Consensus standards that are produced in a careful, open and official process are an integral part of the success of this endeavor," they write. "Standards help to assure that data are sharable and can be the basis of decisionmaking and compliance."

J.L. Almeida, K.D. Cole, A.L. Plant, Standards for Cell Line Authentication and Beyond, *PLOS Biology*. **June 14** (2016) http://dx.doi.org/10.1371/journal.pbio.1002476

NIST AND STANFORD LAUNCH LONG-TERM MEASUREMENT INITIATIVE TO BOOST THE U.S. BIO-ECONOMY

NIST and Stanford University recently announced that they are embarking on a long-term partnership to develop the measurement capabilities central to research, innovation and commercialization in a budding bio-economy of products and services in sectors ranging from health care to energy to electronics.

The new NIST-Stanford Joint Initiative for Metrology in Biology, or JIMB, brings together academia, industry and government to advance the knowledge and tools that will make up biotechnology's equivalent of the weights and measures that enabled modern manufacturing and materials engineering. To signify JIMB's focus on 21st century measurement infrastructure, the organizations chose to launch the initiative on May 20th, World Metrology Day, which marks the anniversary of the Treaty of the Meter, the 1875 international agreement on globally accepted units of measurement.

"JIMB exemplifies how 21st century government can partner with academia and industry to promote the public good," said Under Secretary of Commerce for Standards and Technology and NIST Director Willie E. May. "Additionally, I'm personally very pleased to see this effort come to fruition. The notion of NIST working together with a partner like Stanford to help strengthen the measurement foundations of biology and biotechnology and foster innovation and a marketplace that will drive future prosperity was the vision of my former bioscience advisor, Michael Amos, who passed away four years ago."

"We have long considered NIST to be a key public partner in advancing

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Lindsay Vang (top) inspects a sequencing run of NIST Reference Material 8398, Human DNA for Whole-Genome Variant Assessment (bottom), created by NIST, Stanford, and their partners in the Genome in a Bottle Consortium, which JIMB now manages. The reference material provides a well-characterized standard that can help laboratories measure the performance of the equipment, chemistry, and data analysis involved in DNA sequencing. Credit: T. Liepa/NIST

AN EXTRAORDINARY STANDARD: NEW NIST PROTEIN COULD SPUR BIOPHARMACEUTICAL INNOVATION

NIST recently issued one of the world's most intricate measurement standards: an exhaustively analyzed antibody protein that the biopharmaceutical industry will use to help ensure the quality of treatments across a widening range of health conditions, including cancers, autoimmune disorders and infectious diseases.

The standard is an antibody protein—consisting of more than 20,000 atoms—analyzed so thoroughly that the material can be used by organizations around the globe to verify and improve their analytical methods for quality control.

Donated by MedImmune, the global biologics research and development arm of AstraZeneca, and then characterized by NIST and collaborators, the new reference material (RM)—NIST RM 8671—is a monoclonal antibody, or mAb. This class of therapeutic compounds is produced in the lab by living cells, usually from mouse or hamster cell lines. Uniform in composition and structure, mAbs account for five of the 10 top-selling drugs and over $75 billion in annual sales worldwide. According to one estimate, about 300 monoclonal-antibody-based therapeutics are being evaluated for safety and effectiveness in clinical trials.

Antibodies work by binding to and inactivating proteins involved in disease pathways. mAbs also can act like guided missiles that precisely deliver therapeutic payloads of chemicals or radiation.

Chosen for development in consultation with industry, NIST RM 8671 is an important addition to the toolkits of biological drug manufacturers and their suppliers and regulators. It serves as a representative molecule that can be used to determine that methods for assessing product quality are working properly and to evaluate new methods or technologies. It also provides an industry very mindful of intellectual property concerns with a standard benchmark for everyone, from aspiring startup to multinational firm to regulator.

As such, "it can serve as a common benchmark for future innovation," explained NIST research chemist John Schiel, who led an international effort that explored and demonstrated uses of the reference mAb. "The material has many anticipated applications—in establishing industry-recognized best practices, for example—and we are hoping that there will be many future uses that we can't predict from the current state of practice in biopharmaceutical research and production."

A USEFUL TOOL

Industry experts have indicated that a universally available 'public' mAb, characterized and distributed by NIST, will allow better assessment of existing analytical methods and potentially faster adoption of new technologies.

In fact, the utility of the reference material already has been demonstrated by more than 100 collaborators from companies, regulatory agencies and universities around the world. As documented in a three-volume book set published by the American Chemical Society (ACS), the partners engaged in a "crowdsourcing" exercise. Research teams used current and emerging analytical methods to, in effect, take measure of the mAb from many different vantage points before NIST formally released it as a standard.

"NISTmAb, will act as a shared catalyst for developing, troubleshooting, adapting and bridging analytical technologies," explained Oleg Borisov, director of analytical development at Novavax. "The book from ACS demonstrates this. It presents extensive information and data on a single monoclonal antibody, and describes the methodologies that enabled this state-of-the-art characterization. The result is a comprehensive characterization dossier that should serve as a valuable reference to researchers."

Schiel, Borisov and Darryl Davis, associate director of biologics research at Janssen R&D, LLC, Pharmaceutical Companies of Johnson & Johnson, are editors of the set, *State-of-the-Art and Emerging Technologies for Therapeutic Monoclonal Antibody Characterization*.

Each vial of NIST RM 8671 will contain 800 microliters of the NISTmAb at a concentration of 10 milligrams per milliliter. The standard comes with the results of NIST measurements that provide a thorough profile of the standard protein, Schiel said, providing details on size, concentration, composition, structure, purity, stability and other attributes.

Kurt Brorson, a research biologist in the Office of Biotechnology Products at the Food and Drug Administration (FDA), said the new standard can be used as a "universal system suitability test" for many of the assays and test methods used to assure the quality of mAbs. "The biotech industry can more efficiently cross-validate (measurement) methods at different sites or more efficiently develop platform analytics for related molecules," he explained.

"The NISTmAb should help in answering a simple, yet critical, question that can consume a disproportionate amount of time when deviations arise with testing; is it the sample or the method that is varying?" said Michael Tarlov, chief of NIST's Biomolecular Measurement Division and leader of the NIST-wide Biomanufacturing Program.

During the NISTmAb's meticulously recorded audition, NIST and its

collaborators developed data comparable to that found in a Biologics License Application submitted to the FDA when a company seeks approval for a new mAb-based therapeutic. These data are available online, along with results of analyses done with still-experimental tools, providing a historical record of NIST RM 8671 that will be updated as more analyses are done and as questions arise and spawn new studies.

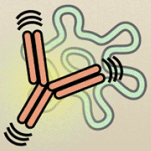
Combined with the three-volume book set, the reference material and data repository provide a comprehensive—yet updateable—picture of the state-of-practice in the fastest-growing area of biopharmaceuticals.

"We hope that this compilation serves as a baseline for many years of future collaboration, continued development and ultimately a routine analytical pipeline for rapid time-to-market for mAb therapeutics," Schiel, Davis and Borisov state in the preface of their book set.

What are **MONOCLONAL ANTIBODIES?**

The body tailor-makes antibodies to combat specific foreign substances, such as **viruses and bacteria.**

Therapeutic monoclonal antibodies are highly specific protein molecules designed to mimic the human body's immune response.

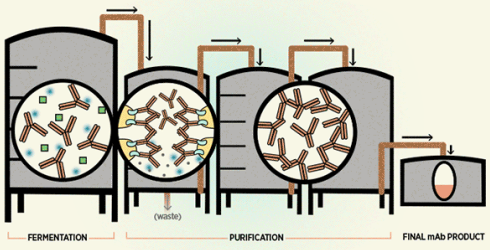


They also can act like **guided missiles** that precisely deliver **therapeutic payloads** of chemicals or radiation to cancer tumors.

How are **MONOCLONAL ANTIBODIES** made?

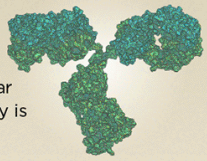
Monoclonal antibodies are **nearly identical copies of a single type of antibody** produced by living systems, typically **mammalian cells**.

Mass producing these complex molecules requires building a "**biological factory**."



It entails developing processes and scaling them up—from research to manufacturing. Tests and assays are built into each step.

Why did NIST develop a **MONOCLONAL ANTIBODY REFERENCE MATERIAL?**



Manufacturers rely on many different **chemical and bio-chemical assays** to determine that each batch of their particular therapeutic monoclonal antibody is safe and effective.

The **NISTmAb** will **help manufacturers** know that their assays are working properly.

The **NISTmAb IgG1** (*aka* NIST RM 8671)

is a **first-of-its-kind measurement tool** for the biopharma-ceutical industry;

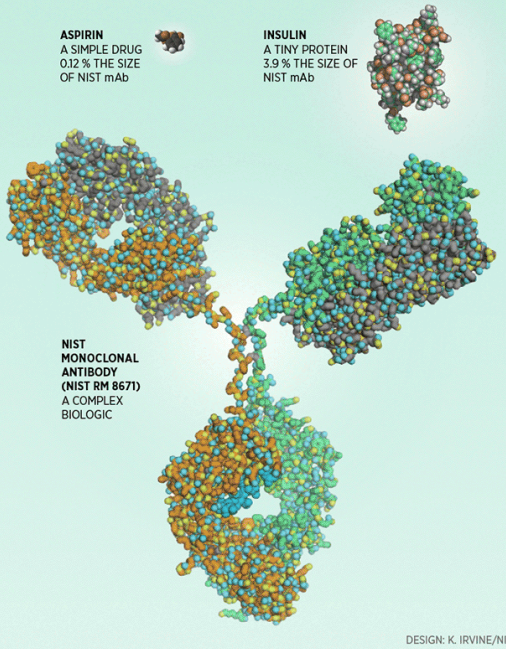
provides a **standard reference** for everyone;

will **aid the development, quality control, and testing of biological drugs**.

Biological drugs are **BIG**

"In terms of size and rough complexity, **if an aspirin were a bicycle**, a small biologic would be a Toyota Prius, and **a large biologic would be an F-16 fighter jet."**

—W. Nicholson Price II and Arti K. Rai, "Manufacturing Barriers to Biologics Competition and Innovation."



NIST FORENSIC SCIENTIST HELPS VIETNAMESE COUNTERPARTS IDENTIFY WARTIME REMAINS

In a Hanoi, Vietnam, hotel conference room, Mike Coble led a group of scientists through a series of calculations. Coble's presentation was heavy on the statistics, and this created a lot of work for the translators. It took two of them, working tag-team, to keep up.

Coble is a scientist at NIST and an expert in forensic DNA analysis. Before NIST, he was the research director at the U.S. Armed Forces DNA Identification Laboratory, where he supported U.S. efforts to identify the remains of servicemen killed in Vietnam and other wars.

Today, Vietnam is undertaking a similar effort to identify its war dead, and Coble was in Hanoi this April presenting the latest methods to Vietnamese scientists.

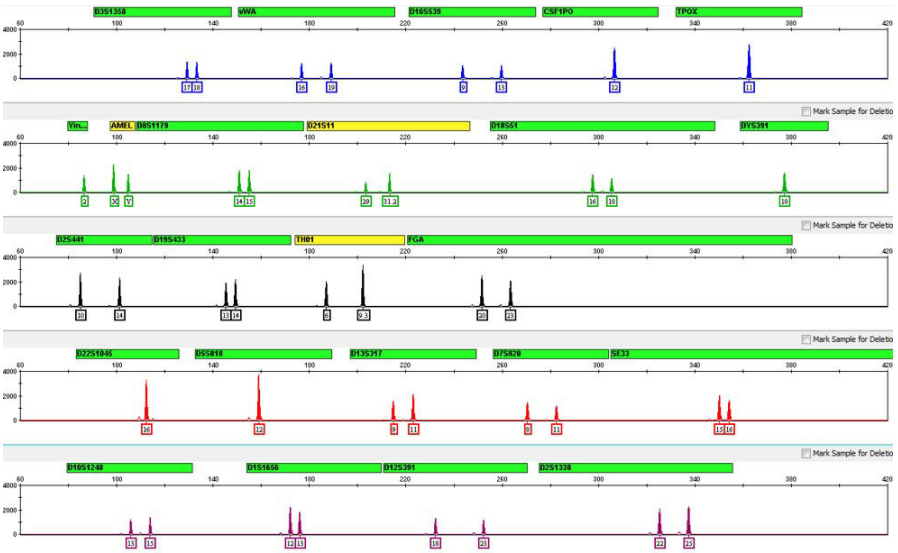
"The U.S. solved a lot of cases," Coble said, including many that became solvable only in the last decade as research led to powerful new techniques for analyzing DNA. "But the Vietnamese are at the beginning of the process."

That process is likely to be a long one. The war left 300,000 Vietnamese unaccounted for, their remains either missing or unidentified. That process will also be a very personal one. "Many of the scientists who participated in the workshop were children during the war, and they and their families experienced it firsthand," Coble said.

For these scientists, the project may have great historical and personal significance, but it is also presents some difficult technical challenges.

EXTRACTING INFORMATION FROM DEGRADED DNA

For example, scientists create a genetic profile by looking at stretches of DNA that repeat themselves, like the same word typed over and over again. These sections



This DNA profile is based on 24 genetic markers (stretches of DNA found at specific locations in the genome). Each genetic marker contains a short tandem repeat (STR)-a section of DNA that repeats itself, like a word typed over and over again, with the number of repeats varying from person to person. In this graph, the peaks represent the number of repeats at each marker. Most markers show two peaks-one inherited from each parent (where only one peak appears in a marker, the individual has inherited the same number of repeats from each parent). These 24 markers produce a series of 48 numbers that can be used to uniquely identify an individual. Credit: B. Steffen/NIST

are called short tandem repeats, or STRs, and the number of repeats in each STR varies from person to person.

By measuring the length of several different STRs, forensic analysts generate a series of numbers that are like a code. In the FBI's national DNA database, for instance, a genetic profile is made up of a series of numbers that can be used to identify an individual or vastly narrow the range of suspects.

But in tropical countries such as Vietnam, soils tend to be acidic, which hastens the decomposition of DNA. When that happens, the STRs fall apart like a ribbon cut to pieces, and scientists might only be able to measure a handful of them—not enough to generate a unique genetic profile.

IMPROVED ACCURACY IN DNA TYPING

Coble worked on this problem in the years following the events of 9/11, when investigators had to identify human remains that were exposed to intense heat, which also causes DNA to fragment. Coble and several colleagues at NIST identified miniSTRs—ones so short that they are more likely to remain intact even as the larger DNA fragments around them degrades. This advance allowed scientists to identify remains that would have otherwise been impossible to identify.

Coble discussed miniSTR testing with his Vietnamese counterparts. The technique is useful in many situations. Because they allow for more precise and accurate matching, miniSTRs have also begun to be used in criminal investigations. For instance, three of the miniSTRs identified by NIST scientists in the years after 9/11 will be required when uploading DNA profiles to the FBI's national DNA database starting Jan. 1, 2017.

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A CRACK IN THE MYSTERY OF 'OOBLECK'—FRICTION THICKENS FLUIDS

By revealing missing details behind the odd behavior of a science fair favorite—a soupy mixture known as "oobleck" that switches back and forth between liquid and solid— scientists from NIST and Georgetown University could help to end a long-running scientific debate and improve processes ranging from pouring concrete to making better body armor.

Oobleck's name is borrowed from a Dr. Seuss classic (*Bartholomew and the Oobleck*). Squeeze or pound it and, in an instant, the slurry of cornstarch and water becomes solid, only to revert to ooze once the stress is relieved.

The NIST and Georgetown scientists have developed a new picture to describe oobleck and similar mixtures of fine particles suspended in liquids. Based on flow measurements of tiny silica beads dispersed in solution, the model invokes two competing theories to explain the phenomenon of "shear-thickening" fluids, which stiffen in response to stress.

Known more formally as non-Newtonian substances, shear-thickening fluids are more than just curiosities. "They dictate how much stuff you can move and at what speed," said Daniel Blair, a Georgetown University physics professor and co-author of an article published in *Physical Review Letters*. "In the chemical processing industry, you're looking for the most efficient way to move something through a pipe, without breaking a pump. To do that, you want to know as much as you can about shear thickening so you can control it."

Opposing theories—one drawing mostly on experimental evidence, the other on results of modeling studies—have been proposed to explain shear thickening in suspensions of microscopic particles, also called colloids. Rather than competing, it turns out that the two are complementary, according to the new research.

Credit: istockphoto.com

"The ongoing debate concerns the role of lubrication-based hydrodynamic interactions versus frictional contact forces," explained lead author John Royer, a NIST materials scientist.

At low concentrations of silica beads, Royer, Blair and NIST materials scientist Steven Hudson found that measurements of stress were consistent with the hydrodynamic model. The model posits that impact forces particles to pack into assemblies called hydroclusters.

As stress increases, the hydroclusters contract and the fluid thickens, or becomes more viscous. Liquid is squeezed out of the clusters, creating an ever-thinner lubricating layer separating the particles and making the scattered clusters more rigid.

But as in earlier experiments, Royer says, the amount of shear thickening observed exceeded the levels that models indicated could be achieved with hydroclusters.

A competing model invokes frictional contacts—essentially, particle collisions caused by stress—as the primary driver of thickening. But, the friction model requires materials to expand—or dilate—once stress surpasses a threshold and particles lock into place so that they are unable to squeeze by each other, as in the hydrodynamic model.

Therein lies the rub. Experiments to date have not yielded evidence of stress-caused expansion, leading some scientists to rule out friction as playing a significant role in shear thickening.

Royer and colleagues tackled these quandaries by measuring how colloids with different concentrations of bacterium-sized spheres responded to stresses ranging from slight to large. These measurements, done on a state-of-the-art rheometer, or flow-measurement device, at Georgetown's Institute for Soft Matter Synthesis and Metrology, unmasked "a previously hidden transition from hydrodynamics-dominated to friction-dominated interactions as the shear thickening becomes more pronounced," Royer says.

They found a transition from contraction to expansion, which occurs without fanfare—or no observable change in shear-thickening behavior itself.

"This transition demonstrates that shear thickening is driven primarily by frictional contacts, with hydrodynamic forces playing a supporting role at lower concentrations of particles, when mixtures are less dense," Royer explained. "These results now motivate new microscopic approaches to control shear thickening in industrial applications, by either minimizing thickening when steady flow is needed or controlling thickening for use as in flexible body armor applications."

Protective clothing applications under development aim to exploit shear thickening to, for example, strengthen defense against knife wounds in the case of body armor and to further enhance protection against penetration by projectiles and blast debris.

J.R. Royer, D.L. Blair and S.D. Hudson, A rheological signature of frictional interactions in shear thickening suspensions, *Physical Review Letters*, **5 May** (2016). http://dx.doi.org/10.1103/PhysRevLett.116.188301

HOW DO NATURE'S MATERIALS STACK UP? "PATCHY" FRAMEWORK OFFERS NEW INSIGHTS INTO SELF-ASSEMBLY

Nature's toolkit includes its still-matchless ability to effortlessly assemble proteins, membranes and other complex structures from parts of atoms, molecules, and particles of various sizes and shapes. Researchers have worked for several decades to understand the mechanisms behind this almost magic-like construction process.

New research, published by scientists at NIST and a colleague, moves researchers a big step toward the aim of devising comprehensive theories and realistic models of self-assembly. The advances provide insights to guide efforts to harness and manage self-assembly in artificial materials and reliably make structures as designed. These could include entirely new structures composed of subunits specially tailored to self-assemble in predictable ways. Similarly, the work could help prevent unwanted structures from forming, a concern especially during the production of biopharmaceuticals.

Debra Audus, a NIST materials scientist, and two colleagues have come up with a new approach for predicting the clustering behavior of particles in fluids, an environment in which self-assembly frequently occurs. They describe their theoretical framework in a recent issue of the *Journal of Chemical Physics*.

Applying the framework to experimental results, other researchers can cut to the chase more quickly and predict the shape, size and distribution of particle clusters as conditions change in liquid mixtures.

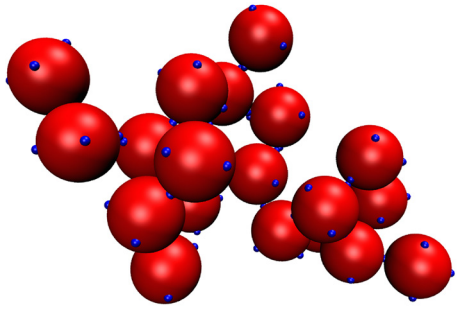
Audus, NIST materials scientist Jack Douglas and Francis Starr of Wesleyan University in Connecticut added another layer of realism to a so-called patchy particle model, a popular tool for investigating how particles interact in liquids. These models are simplified representations that show how inter-particle forces steer self-assembly processes. They can streamline efforts to identify the basic principles at work, saving researchers from having to piece them together through trial-and-error experiments.

Typically, patchy particles are spheres whose surfaces are precisely "decorated" with several patches—each possessing a directional attractive force, or bond. Usually, the models stop there, but the team went one better. They cloaked their five-patch particles with a pervasive, uniform force—akin to the ubiquitous van der Waals forces arising from molecular interactions. Though feeble, these attractive forces exert significant influence on the ultimate shape of multi-particle structures.

Including both types of forces in the model set the stage for a dynamic competition that defined where cluster formation and self-assembly occur, Audus explained.

Changing the size of the particle-encompassing attractive force significantly altered how particles were distributed into areas of low and high concentration, also known as phases. As the uniform force increased, the temperature at which particles began to separate also increased, and the region where self-assembly took place decreased. These relationships were revealed through a computer-intensive simulation method used to explore the behavior of complex and often disordered systems through repeated random sampling. Crunching numbers to measure the behavior of some particles as they separated into phases engaged multiple computers for nearly a month—testimony to the bewildering intricacies of self-assembly.

From there, the team used a theory-guided approach to distill the simulation results and look for overarching lessons-learned that other researchers can apply.



Model patchy particles self-assemble and provide guidance for understanding the nature of self-assembly in more complicated systems such as protein solutions. Credit: Audus/NIST (made with VMD)

For one, they determined that their five-patch particles behaved like swollen, branched polymers, a well-studied class of materials. The researchers also identified the thermodynamic conditions under which self-assembly behavior will emerge, and they describe methods for determining the average molecular weight of clusters and their size distribution.

Employing these methods, other researchers can probe the behavior of particles in solution by measuring how they scatter light, for example, and compare their results to patchy particle models. For instance, do the experimental particles behave like theoretical particles with five patches, rather than seven?

"From there, researchers can use theory to predict how particles in their mixtures will cluster under different conditions," Audus explained. "With our framework, they can gain insights into clustering phenomena."

D.J. Audus, F.W. Starr, and J.F. Douglas, Coupling of isotropic and directional interactions and its effect on phase separation and self-assembly, *Journal of Chemical Physics* **144**, 074901 (2016). http://dx.doi.org/10.1063/1.4941454

SIMPLER, FASTER, AND CHEAPER: A FULL-FILLING APPROACH TO MAKING CARBON NANOTUBES OF CONSISTENT QUALITY

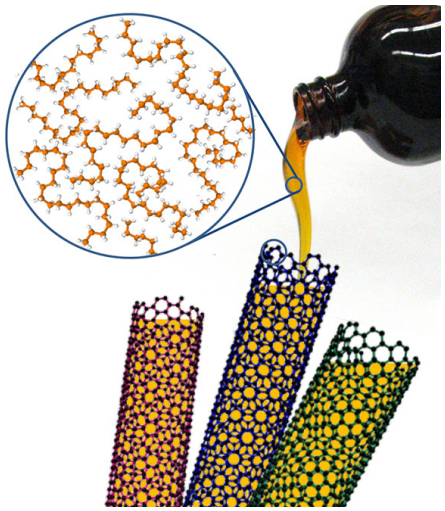
Just as many of us might be resigned to clogged salt shakers or rush-hour traffic, those working to exploit the special properties of carbon nanotubes have typically shrugged their shoulders when these tiniest of cylinders fill with water during processing. But for nanotube practitioners who have reached their Popeye threshold and "can't stands no more," NIST has devised a cheap, quick, and effective strategy that reliably enhances the quality and consistency of the materials—important for using them effectively in applications such as new computing technologies.

To prevent filling of the cores of single-wall carbon nanotubes with water or other detrimental substances, the NIST researchers advise intentionally prefilling them with a desired chemical of known properties. Taking this step before separating and dispersing the materials, usually done in water, yields a consistently uniform collection of nanotubes. In quantity and quality, the results are superior to water-filled nanotubes, especially for optical applications such as sensors and photodetectors.

The approach opens a straightforward route for engineering the properties of single-wall carbon nanotubes—rolled up sheets of carbon atoms arranged like chicken wire or honey combs—with improved or new properties.

"This approach is so easy, inexpensive and broadly useful that I can't think of a reason not to use it," said NIST chemical engineer Jeffrey Fagan.

In their proof-of-concept experiments, the NIST team inserted more than 20 different compounds into an assortment of single-wall carbon nanotubes with an interior diameter that ranged from more than 2 down to about 0.5 nanometers. Led by visiting researcher Jochen Campo, the scientists tested their strategy by using hydrocarbons called alkanes as fillers.



To prevent cores of single-wall carbon nanotubes from filling with water or other detrimental substances, the NIST researchers advise intentionally prefilling them with a desired chemical of known properties. Taking this step before separating and dispersing the materials, usually done in water, yields a consistently uniform collection of nanotubes, especially important for optical applications. Credit: Fagan/NIST.

The alkanes, which include such familiar compounds as propane and butane, served to render the nanotube interiors unreactive. In other words, the alkane-filled nanotubes behaved almost as if they were empty—precisely the goal of Campo, Fagan, and colleagues.

Compared with nanotubes filled with water and possibly ions, acids and other unwanted chemicals encountered during processing, empty nanotubes possess far superior properties. For example, when stimulated by light, empty carbon nanotubes fluoresce far brighter and with sharper signals.

Yet, "spontaneous ingestion" of water or other solvents by the nanotubes during processing is an "endemic but often neglected phenomenon with strong implications for the development of nanotube applications," the NIST team wrote in a recent article in *Nanoscale Horizons*.

Perhaps because of the additional cost and effort required to filter out and gather nanotubes, researchers tend to tolerate mixed batches of unfilled (empty) and mostly filled single-wall carbon nanotubes. Separating unfilled nanotubes from these mixtures requires expensive ultracentrifuge equipment and, even then, the yield is only about 10 percent, Campo estimates.

"If your goal is to use nanotubes for electronic circuits, for example, or for fluorescent anti-cancer image contrast agents, then you require much greater quantities of materials of consistent composition and quality," Campo explained, who was exploring these applications while doing postdoctoral research at the University of Antwerp. "This particular need inspired development of the new prefilling method by asking the question, can we put some passive chemical into the nanotube instead to keep the water out."

From the very first simple experiments, the answer was yes. And the benefits can be significant. In fluorescence experiments, alkane-filled nanotubes emitted signals two to three times stronger than those emitted by water-filled nanotubes. Performance approached that of empty nanotubes—the gold standard for these comparisons.

As important, the NIST-developed prefilling strategy is controllable, versatile, and easily incorporated into existing methods for processing single-wall carbon nanotubes, according to the researchers.

J. Campo, Y. Piao, S. Lam, C.M. Stafford, J.K. Streit, J.R. Simpson, A.R. Hight Walker and J.A. Fagan, Enhancing single-wall carbon nanotube properties through controlled endohedral filling, *Nanoscale Horizons*, Published online **May 10** (2016). http://dx.doi.org/10.1039/C6NH00062B

SHAPE-CHANGING ENZYME SUGGESTS HOW SMALL DOSES OF ANTI-HIV DRUG MIGHT TREAT ALZHEIMER'S DISEASE (CONT'D.)

"HDX mass spectrometry opens a window that allows you to look in on how proteins behave under physiologically relevant conditions," Anderson explained. "It provides the pieces to a puzzle that you can assemble to show how their three-dimensional shape changes over time."

The NIST team used HDX to compare and contrast CYP46A1 in four different states: alone, with cholesterol only, with efavirenz only, and with cholesterol and efavirenz. Subsequent analyses of the resulting torrents of experimental data—a computationally intensive process that Anderson performed in triplicate to ensure accuracy—revealed not only where the drug attached to the enzyme but also how the cholesterol-binding site adjusted in response. The structural changes enabled CYP46A1 to bind cholesterol molecules more tightly than in the absence of the drug.

Following up with a study using a different method, Pikuleva's team further confirmed the site of efavirenz binding as determined with HDX. The evidence strongly suggests, she said, at doses a hundred times lower than prescribed for treating HIV, efavirenz might be an effective therapy for stimulating cholesterol turnover from the brain and slowing or preventing Alzheimer's disease.

Pikuleva and colleagues now are seeking to obtain funding for a clinical trial on humans to investigate the effects of small doses of efavirenz.

K.W. Anderson, N. Mast, J.W. Hudgens, J.B. Lin, I.V. Turko and I.A. Pikuleva, Cholesterol Hydroxylase CYP46A1: Mapping of the Allosteric Site for Efavirenz, a Drug that Stimulates Enzyme Activity, *Journal of Biological Chemistry*, **May 27** (2016). http://dx.doi.org/10.1074/jbc.M116.723577

NEW MODEL MAY HELP SOLVE THE MYSTERY OF HOW LITHIUM STABILIZES MOODS (CONT'D.)

they monitored the behavior of a type of ATP receptor that opens a channel to allow the flow of calcium ions into the neurons, a key activity in neuronal signaling. All elicited the same initial response. However, the ATP-magnesium-lithium combination caused the receptor to remain activated 40 percent longer than did the ATP-magnesium stimulus. Whether and how this prolonged signaling response contributes to lithium's mood-stabilizing effects remains to be studied.

"We're not saying this is the whole story. There's a broad swath of other possibilities, as well," Marino said. "But this physical model provides an intriguing new way to broadly view lithium's bioactive form—as working in tandem with magnesium by co-binding to phosphate-containing ligands, and thereby influencing the function of cellular receptors and enzymes."

K.T. Briggs, G.G. Giulian, G. Li, J.P.Y. Kao and J.P. Marino, A Molecular Model for Lithium's Bioactive Form, *Biophysical Journal*, **26 July** (2016). http://dx.doi.org/10.1016/j.bpj.2016.06.015

NIST AND STANFORD LAUNCH LONG-TERM MEASUREMENT INITIATIVE TO BOOST THE U.S. BIO-ECONOMY (CONT'D.)

biomeasurement science," said Dr. Ann Arvin, Stanford's vice provost and dean of research. "We are delighted that NIST is now establishing a permanent West Coast presence to help advance basic science and promote innovative commercial developments."

JIMB sprouted from an initial three-year collaboration focused on biological measurements. Thanks to these research connections, JIMB begins with a complement of 16 NIST staff members. They include NIST postdoctoral researchers embedded in Stanford faculty members' labs. In addition, eight Stanford graduate students are supported by NIST grants that encourage research that integrates measurement and biological engineering objectives.

"To realize biotechnology's tremendous promise, we need to develop measurement platforms—standards, methods, and data—that support innovation within existing and entirely new industries," said Laurie Locascio, director of NIST's Material Measurement Laboratory. "Stanford's strong relationships with area biotechnology companies will continue to inform JIMB's work so that it is as widely applicable as possible."

The partnership already has yielded practical benefits, including the world's first reference material to help ensure laboratories accurately "map" DNA for genetic testing, medical diagnoses, and future customized drug therapies. The "measuring stick" for the human genome—NIST RM 8398—was created by NIST, Stanford, and their partners in the Genome in a Bottle Consortium, which JIMB now manages.

Since it was issued in May 2015, NIST's reference human genome has been helping medical labs to ensure the accuracy of genetic tests. The reference material also served as the comparative tool that the Food and Drug Administration used in its PrecisionFDA Consistency Challenge. Intended to improve the reliability, accuracy, and utility of DNA testing, the challenge is a key element of President Obama's Precision Medicine Initiative.

Besides Genome in a Bottle, two other NIST-hosted consortia—Synthetic Biology Standards and External RNA Controls—provide direct means for companies and other organizations to engage with JIMB.

Initially, JIMB will focus on human genome sequencing and synthetic biology. NIST is in the process of establishing a West Coast facility where researchers will develop and prototype biometrology tools and produce validated tools and reagents for the biology sector.

NIST FORENSIC SCIENTIST HELPS VIETNAMESE COUNTERPARTS IDENTIFY WARTIME REMAINS (CONT'D.)

But for one week in April, Coble stepped away from his research at NIST to share his knowledge. It was his first trip to Vietnam.

Coble's trip was organized by the International Criminal Investigative Training Assistance Program of the U.S. Department of Justice, which helps foreign governments develop professional and transparent law enforcement institutions. That program is funded by the U.S. Agency for International Development, the U.S. Department of State, and the U.S. Department of Defense.

A SHARED LANGUAGE

If it's true that war can dehumanize one's enemies, then perhaps giving fallen enemies a name can humanize them again. If so, Coble's trip, and other efforts like it, are especially fitting gestures of peace between formerly warring nations.

In fact, the assistance that Coble offered the Vietnamese runs in both directions. When U.S. specialists excavate sites in Vietnam to search for the remains of U.S. servicemen, Vietnamese experts participate in the work.

But whatever the deeper meaning of this exchange, Coble said that in the classroom, it was just a bunch of scientists sharing ideas.

"We didn't speak the same language, and we didn't have the same experience in terms of history," Coble noted. "But we were speaking the language of science, and that helped to transcend the differences."

OUTREACH AND PARTNERING

MML PART OF NEW NATIONAL MICROBIOME INITIATIVE, RECEIVES FDA GRANT

MML's program in microbiome metrology, led by Scott Jackson, is part of the new National Microbiome Initiative, announced by the White House Office of Science and Technology Policy in May 2016. The initiative will help advance microbiome applications for health care, food safety and security, environmental protection, bioenergy production, and other areas.

Also in microbiome news, MML received a grant from the Food and Drug Administration's (FDA) Center for Devices to develop a mixed-pathogen DNA reference material so that developers of new diagnostic tools can assess analytical sensitivity, specificity, and relative performance of pathogen detection devices and assays that use next generation sequencers.

MML EXPERTISE TO HELP ADVANCE SYNTHETIC GENOME

MML's Elizabeth Strychalski attended the invitation-only HGP-write: Testing Large Genomes in Cells meeting in May 2016, to contribute to discussion of the underlying technology and knowledge required to design and create synthetic human genomes, which have the potential to lead to innovative medical treatments and platforms for research and production of new materials, energy feedstocks, and sources of nutrition. NIST's expertise in synthetic and engineering biology will help meet critical measurement needs to realize this vision.

RISK ASSESSMENT TO MOVE NANOTECHNOLOGIES TO THE NEXT LEVEL

The White House's National Nanotechnology Initiative is moving into its next phase. MML's Elijah Petersen chaired a breakout session at the initiative's 2016 Strategic Planning Stakeholder Workshop on "Risk Throughout the Product Life Cycle." Participants discussed the need for measurement methods to assess the environmental, health, and safety implications of nanomaterials with increased complexity.

GENOME EDITING WORKSHOP EXPLORES MEASUREMENT NEEDS

In early May 2016, MML's Samantha Maragh hosted the first Genome Editing Standards Workshop, in partnership with the American Society of Gene and Cell therapy and sponsored by Microsoft Corporation and Editas Medicine. Participants from FDA, NIH, academia, and industry discussed measurement assurance needs to help genome editing mature into a tool for the study and treatment of human disease. Participants discussed FDA requirements; increasing confidence in editing, sample measurements, and assessment of off-target edits; and informatics needs.

SUPPORT FOR STEM EDUCATION

MML's Jeanita Pritchett returned to Grahamstown, South Africa, where she served as an Embassy Science Fellow in 2015, for SciFest Africa 2016, South Africa's largest national science festival. Pritchett coordinated the Workshop and Etcetera portions of the program. Pritchett also performed a number of demos at iRhini Township Festival and at the Nelson Mandela Bay Science Center (Uitenhage, South Africa) for students and teachers that could not attend SciFest. As part of the United States Diplomatic Mission to South Africa, Pritchett also presented at the Nelson Mandela Metropolitan University alongside scientists from NASA and other organizations.

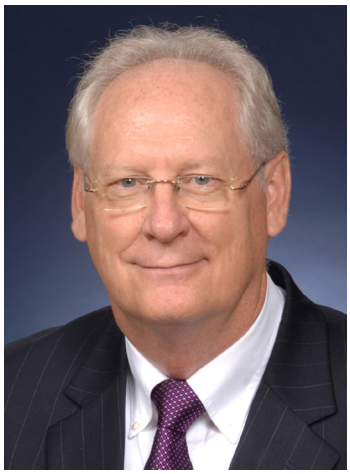
KEYNOTES

MML's Edward Garboczi delivered the Frontiers of Engineering lecture in May 2016 at the Leeds University School of Chemical and Process Engineering in the United Kingdom, explored their world-renowned complex particulate products and processes research area, and initiated several potential collaborations in the area of particle shape, which is vital to additive manufacturing.

Rebecca Pugh, leader of the joint Environmental Specimen Bank at Hollings Marine Lab (a partnership among NIST, the National Oceanic and Atmospheric Administration, the South Carolina Department of Natural Resources, the College of Charleston, and the Medical University of South Carolina) gave the keynote address at the Trends and Advancements in the Sampling and Preservation of Samples for the Identification of Contaminants of Emerging Concern Workshop held in March 2016 at the Norwegian Institute for Water Research.

AWARDS

WISE SELECTED FOR 2015 HILLEBRAND PRIZE



Stephen A. Wise, who recently retired after 40 years of service to NIST, is the recipient of the 2015 Hillebrand Prize from the Chemical Society of Washington. The annual Hillebrand Prize, awarded for original contributions to the science of chemistry, is named for William F. Hillebrand (1853-1925), former chief chemist at NIST. Wise is recognized for career achievements in separation science, particularly in the field of polycyclic aromatic hydrocarbons, and for contributions to the NIST Standard Reference Materials (SRM) Program in support of an accurate national measurement system for chemistry. Wise has been involved in the development of over 90 SRMs to support accurate measurement of environmental contaminants in such varied matrices as air and diesel particulate matter, coal tar, sediments, mussel tissues, fish oil and tissues, whale blubber, human serum and milk, and house dust. In the mid-1990s, he facilitated development of food SRMs to support newly issued food labeling regulations. He also provided leadership in establishing the critical partnerships among NIST, the National Institutes of Health Office of Dietary Supplements, FDA, and other stakeholders to produce reference materials for dietary supplements.

FASOLKA, SATTERFIELD RECOGNIZED BY WASHINGTON ACADEMY OF SCIENCES

MML Deputy Director Mike Fasolka received the Washington Academy of Sciences 2016 Award for Engineering Sciences, in recognition of his exceptional research contributions to the field of materials science and engineering and his influential and sustained technical leadership in the global materials science enterprise.

MML Chief of Staff Mary Satterfield received the 2016 Krupsaw Award for Non-Traditional Teaching in recognition of her groundbreaking work in creating a series of programs to educate students, teachers, and NIST staff members in measurement science. Both Fasolka and Satterfield were also recognized as fellows of the Washington Academy of Sciences.

MML-AUTHORED ARTICLE SELECTED AS EDITOR'S PICK

An article by MML scientists published in the *Journal of Vacuum Science and Technology A* was recently featured as an Editor's Pick and appears in the "Most Read" list on the journal's website. A write-up of the article appeared in the Publication Highlights section of the May 2016 edition of the "Beneath the AVS Surface" newsletter. The article, by Tariq Ahmido, William Kimes, Brent Sperling, Joseph Hodges, and James Maslar and entitled "In-Situ Metrology to Characterize Water Vapor Delivery during Atomic Layer Deposition" (*J. Vac. Sci. Technol. A* 34, 031512 [2016]), describes the performance of an *in situ* tunable diode laser absorption spectroscopy scheme for performing rapid, quantitative measurements of water vapor in a gas delivery system representative of those employed in laboratory and commercial atomic layer deposition systems. This work demonstrates that such a metrology could provide the basis for the development of a mass flow meter for use in closed-loop control of water delivery during thin film metal oxide deposition processes. Such control would allow a decrease in the range of film properties obtained during microelectronics fabrication processes, which could potentially lead to an increase in device yield and performance.

NIST STANDARD STORY

NIST scientists have thoroughly measured and characterized more than 1,300 physical products, NIST Standard Reference Materials®, to help people in industry, academia, and government agencies calibrate instruments, verify their test methods, and develop new measurement methods. NIST reference materials, for example, help manufacturers make interoperable parts in far-flung facilities, medical labs check the accuracy of cholesterol and other clinical tests, and scientists monitor environmental threats.

FOR LABORATORY USE ONLY

WHAT

Standard Reference Material® 1849a, Infant/Adult Nutritional Formula

Each packet contains approximately 10 grams of a milk-based powder, a blend of material similar to the infant and adult versions of just-add-water nutritional powders you can buy in the grocery store. The material, provided by a manufacturer, is close to the consumer versions, but is "not an actual infant formula, because you don't want it to be confused with anything real," says Melissa Phillips, one of the NIST scientists who coordinated the analysis of this reference material. It's not so important that the material matches an actual consumer product, just that it's been assessed with NIST's usual rigor and is available for others to do the same.

WHY

Infant formula is "one of the most regulated foods in the world," according to Phillips, "with strict requirements for how much of each nutrient the powders should contain. When manufacturers report those nutrient values to regulators, they have to be within a narrow range, so manufacturers need accurate and precise analytical methods." Manufacturers seek guidance from AOAC International, which works with food manufacturers, among many other sectors, to set industry standards. While NIST is not a regulatory body, its scientists participate in AOAC standards committees alongside manufacturers to understand their needs. NIST then develops reference materials to help manufacturers comply with regulations both in the U.S. and in foreign markets, so that their products can be exported. Manufacturers like it when NIST provides reference materials and data because they can trust NIST's products are free of bias that might favor a competitor. This reference material continues work that NIST has done since the 1990s to support formula manufacturers.

WHO

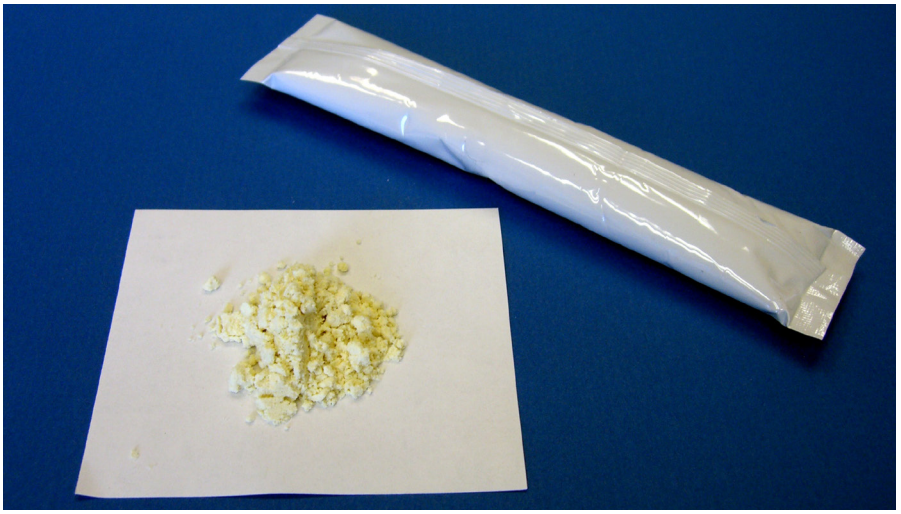
NIST scientists collaborated with the Grocery Manufacturers Association to organize more than a dozen laboratories in a round robin, an interlaboratory comparison test where all the participants test the same material with the same methods and the results are compared. The data contributes to the calculation of values for each nutrient analyzed, and helps NIST understand what kind of values to expect from the typical industry test methods in daily use.

HOW

Manufacturers and testing labs use Standard Reference Material 1849a to validate their methods, or to confirm the composition of the in-house reference materials they make themselves for validating their analytical methods. The NIST reference material is also used when two manufacturers or other test labs don't agree on the values in a sample. To settle the dispute, they'll use Standard Reference Material 1849a and AOAC official methods to understand which method needs correcting. About 550 units of Standard Reference Material 1849a are sold each year.

Learn more: https://www-s.nist.gov/srmors/view_detail.cfm?srm=1849a

Technical Contacts:
Melissa Phillips, melissa.phillips@nist.gov
Laura Wood, laura.wood@nist.gov



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MATERIAL MEASUREMENT LABORATORY

The Material Measurement Laboratory supports the NIST mission by serving as the national reference laboratory for measurements of matter, providing broad support for chemical, biological, and materials sciences. Our fundamental and applied measurement science research expands possibilities for determining the composition, structure, and properties of manufactured, biological, and environmental materials, and the processes that create them. In addition, MML drives the development and dissemination of tools—including measurement protocols, certified reference materials, critically evaluated data, and best practice guides—that help assure quality measurements of matter. Our research and measurement services support progress in areas of national importance including advanced materials, energy, environment, food safety and nutrition, forensic science, health care, manufacturing, physical infrastructure, and safety and security. MML also coordinates the NIST-wide Standard Reference Materials® (SRM) and Standard Reference Data programs.

TO LEARN MORE, CONTACT:

Material Measurement Laboratory
100 Bureau Drive, M/S 8300
Gaithersburg, MD 20899-8300
Tel: 301-975-8300
Fax: 301-975-3845
mmlinfo@nist.gov
or visit http://www.nist.gov/mml

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