

'METHOD OF THE YEAR' Intramural Cryo-EM Lab Achieves Atomic Resolution

BY CARLA GARNETT

In the late 1990s, Dr. Sriram Subramaniam began to feel restless at work. After a few years of studying how fruit flies see, the then-junior faculty member at Johns Hopkins University was looking for something new to do. He found himself one day sitting across from NIH deputy director for intramural research Dr. Michael Gottesman and NIH distinguished investigator Dr. William Eaton of NIDDK.

For some time, explained Subramaniam—a biochemist at heart and by training—he had wanted to “walk inside” a

retina cell (or any cell, for that matter) and be able to see all of it, inside and out. He had an idea to employ electron microscopy in this quest, he told the two veteran scientists. His interests seemed to match Eaton's and Gottesman's desire to bring more electron microscopy to the NIH campus. Intrigued, Eaton, a longtime structural biologist, asked whether Subramaniam had much experience with electron microscopy. Not really, Subramaniam admitted, but “nobody had told me I couldn't do it. I thought it was a worthwhile thing to do...I had never done anything like this, but that didn't seem to bother them.”

The time was ripe. NIH was amid its historic budget-doubling era. Funds for high-risk research were available for intrepid investigators with a solid pitch. NIH took a chance on Subramaniam. By 2000, he was on staff at NCI. A decade and a half later,

SEE **CRYO-EM**, PAGE 6



Dr. Sriram Subramaniam reveals the innards of a Titan Krios, used to produce atomic-resolution cryo-EM images.



Jazz comes to the Clinical Center. See p. 2.

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EXERCISE CAN COUNTERACT Columbia's Fried Describes Syndrome of Frailty

BY RICH MCMANUS

You get the feeling that if Dr. Linda P. Fried, dean of the Mailman School of Public Health at Columbia University, were in charge of things, exercise classes for frail adults would be as common across the land as kindergarten enrollment is for youngsters.

There's a canard among those who study older adults: A gerontologist can spot frailty at 50 yards. Fried examined it much more closely—“from cells



Dr. Linda P. Fried of Columbia University discusses frailty.

SEE **FRAILITY**, PAGE 8

Bldg. 7 Demolition Halted by Discovery of Asbestos

BY ERIC BOCK

How do you demolish Bldg. 7—an outdated 3.5-story lab facility with 12-inch thick, steel-reinforced concrete walls—in the crowded center of NIH's campus?

“You chip it down piece by piece,” said the Office of Research Facilities' chief engineer Tony Clifford about the ongoing demolition. The slow process helps ensure the safety of demolition workers as well as employees who might be passing by.

Recently, though, progress was halted when a demolition crew broke through a concrete wall and found pipes insulated with asbestos. Unfortunately, Clifford said, demolition cannot resume until the asbestos is completely removed.

Bldg. 7 was designed to prevent—or at least limit—the spread of infectious diseases in laboratories. The thick, reinforced

SEE **BLDG. 7**, PAGE 4

Michie To Give Next 'Mind the Gap' Seminar, Mar. 7

Dr. Susan Michie, professor of health psychology, director of the Centre for Behaviour Change at University College London and co-director of the U.K.'s National Centre for Smoking Cessation and Training, will present on the topic "Reducing Waste in Research: Use of Taxonomies and Frameworks of Behaviour Change" at the next Medicine: Mind the Gap seminar. Her presentation is Monday, Mar. 7 from 11 a.m. to noon via NIH Videocast, <http://videocast.nih.gov/>.



Dr. Susan Michie

Michie will discuss how interven-

tions to change behavior can improve health and well-being. Better answers are needed to the big question: What interventions are effective in changing what behaviors, for whom, in what circumstances and how? Her presentation will describe a method for specifying the "active ingredients" of interventions.

Michie will accept questions before and during her presentation via email at prevention@mail.nih.gov and on Twitter with #NIHMTG. Register for the event at <https://prevention.nih.gov/programs-events/medicine-mind-the-gap>.

Informatics Lecture Features Craven

Mar. 9

The next speaker in the National Library of Medicine Informatics Lecture Series will be Dr. Mark Craven, discussing "Inferring Host-Pathogen Interactions from Diverse Data Sources" on Wednesday, Mar. 9

from 2 to 3 p.m. in Lister Hill Center Auditorium, Bldg. 38A.

Craven is a professor in the department of biostatistics and medical informatics at the University of Wisconsin and an affiliate faculty member in the department of computer sciences. He will discuss his work in three studies



Dr. Mark Craven



Jazz Quartet Entertains at CRC

The Hamilton Springs Quartet offered an hour-long jazz concert at noontime in the atrium of the Clinical Research Center on Feb. 3. The musicians, most of whom are NIH'ers, include (from l) Christopher Booher (NIMH), drums; guest bassist Ethan Phillion, a two-time Downbeat Award winner who currently performs and teaches in the D.C. area; Christophe Ludet (NLM), piano; and Grant Izmirlian (NCI), tenor saxophone. Patients, family members, visitors and staff enjoyed the performance.

PHOTO: RICH MCMANUS

that involve developing and applying predictive methods in order to characterize host-pathogen interactions.

Sign language interpreters will be provided. Individuals who need reasonable accommodation to participate should contact Ebony Hughes at (301) 451-8038 or Ebony.Hughes@nih.gov or the Federal Relay (1-800-877-8339).

Sailing Association Open House

The NIH Sailing Association invites everyone to its open house on Wednesday, Mar. 9 from 5 to 8 p.m. at the FAES House at the corner of Old Georgetown Rd. and Cedar Ln.

Explore your interest in learning to sail and discover opportunities for sailing with NIHSA. There will be information about 6-week basic training classes, boat chartering, the club's racing program and social activities offered by NIHSA.

A fee of \$5 at the door includes pizza, drinks and snacks. Cash bar for beer and wine—\$2 each. Look for NIHSA posters and flyers around campus.

Registration is now open for the spring (April-May) and summer (July-August) basic training classes. For more information, visit www.nih sail.org/.



NIH Celebrates Pi Day, Mar. 14

NIH will hold a Pi Day celebration on 3.14 (Monday, Mar. 14). The goal of the event is to increase awareness across the community of the role that the quantitative sciences play in biomedical science.

The day will be packed with events, including a keynote address by Dr. Carlos Bustamante, chair of Stanford's new department of biomedical data science (1 p.m., Lipsett Amphitheater, Bldg. 10). The lecture will be open to the public and available by videocast.

For more information, including a schedule of events, visit <https://datascience.nih.gov/PiDay2016>. You can also join the Pi Day conversation—include #NIH_PiDay in your tweets.



Portrait Honors Lindbergs at NLM

On Feb. 10, the National Library of Medicine was the scene of a special unveiling ceremony for a portrait of former NLM director Dr. Donald Lindberg and his wife, Mary. Lindberg retired in 2015 after more than 30 years of service as NLM director. During his tenure, the Lindbergs were a much-admired team, always closely involved with the people and activities of the library. The painting was created by Virginia artist Bradley Stevens, one of America's leading realist painters and a noted portraitist. Commissioned and sponsored by the Friends of the NLM, the painting will hang in a prominent location at NLM.

PHOTO: ERNIE BRANSON

NIH Accountants Volunteer at Food Bank

Nine accountants from NIH's Division of Financial Advisory Services (DFAS) volunteered Saturday, Jan. 30 to help sort donated canned foods at Manna's Gaithersburg food distribution center. Manna describes itself as "the premier food bank of Montgomery County, providing food to 40,000 individuals each year and helping distribute rescued food to soup kitchens, food pantries and emergency shelters."

It was the first weekend community service project for the group, most of them CPAs, whose day job is to negotiate indirect cost rates with companies receiving grants and contracts from NIH.



Volunteering at Manna Food Center were (from l) Manuel Garcia, Marie Novak, Dan Milstead, Ray Hart, Alan Lichtman, Hruta Virkar, Angel Wang, Diana Huang and Kyle Kronenberger.

Nearly half of the department volunteered. Their assignment was to sort recently volunteered foodstuffs into one of 24 different bins of food being readied for distribution. They also had to check the dates on the products to ensure the donations were still usable. The project was organized by Angel Wang, one of the department's newest hires.

Management Intern Program Recruits

The NIH Management Intern Program, a way to unlock a new career path, is recruiting Apr. 4-8. It is a highly competitive, 2-year career-development program for current NIH employees. MIs come from a variety of job backgrounds including both scientific and administrative fields. Upon completion of the program, MIs transition into an administrative-management career in one of many areas throughout NIH. Eligible employees are invited to apply. For program FAQs and details about eligibility, visit <http://trainingcenter.nih.gov/intern/mi/>.

Learn more by attending any of these information sessions, all of which are held from noon to 1 p.m.:

- Mar. 22, Bldg. 31, 6C, Rm. 6
- Mar. 23, Bldg. 45, NIH Training Center (adjacent to cafeteria)
- Mar. 28, Rockledge 1, Suite 4000, RT1



ON THE COVER: Detail of artwork used for 2011 NIMH poster featuring a visual interpretation of high-throughput technologies.

IMAGE: MEDICAL ARTS

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Bldg. 7

CONTINUED FROM PAGE 1

concrete walls and specialized air-handling system were supposed to stop contaminated air from circulating from one lab to another.

Like many aging buildings, Bldg. 7 contains asbestos, a naturally occurring, strong, heat-resistant and fibrous mineral found in rocks. Because of these properties, it was widely used for insulation and as a fire retardant. As long as it's not disturbed, asbestos poses little threat. If disturbed, however, asbestos fibers and particles can be released into the air. Over time, exposure increases the risk of lung diseases such as mesothelioma and lung cancer.

Before demolition began, Clifford said, NIH contracted with a Maryland department of the environment (MDE)-licensed firm to remove asbestos. The asbestos abatement contractor then removed and disposed of all known asbestos and other hazardous materials in the building according to its abatement plan.

On Sept. 4, demolition started. To minimize dust, workers sprayed water on the parts of the building they were tearing down. Shortly thereafter, Clifford said, a crew found previously undiscovered pipes in a hidden shaft. The pipes were suspected to be insulated with asbestos. Work stopped immediately and MDE was notified. Tests



Exposed face of partially flattened building



Work came to a halt on the demolition of Bldg. 7 after asbestos was found in the debris. The project will resume once abatement is complete.

PHOTOS: RICH MCMANUS

later confirmed the presence of a small amount of asbestos on the pile of rubble. The pile is now covered so the asbestos cannot be disturbed.

Clifford said air-monitoring tests continue to confirm the absence of asbestos particles or fibers in the air during this construction delay. All water runoff from the site is filtered to avoid migration of sediment into the surface water, he added.

The asbestos abatement contractor came back and conducted additional surveys inside Bldg. 7. ORF has also briefed MDE on steps taken to avoid asbestos exposure and on the plan to remove the debris safely. Clifford said ORF is now in negotiations with a contractor that specializes in asbestos waste removal.

"We will treat the entire pile as if it's contaminated with asbestos," he said. "In an abundance of caution, the entire pile will be removed from the area as if it were all asbestos-containing material."

After the asbestos is gone, demolition will

resume. Eventually, new research facilities will take the place of Bldg. 7 and the building next to it, Bldg. 9, which is also slated for demolition.

When a building is demolished on NIH's campus, up to 90 percent of building materials are normally recycled. "We don't just put materials in a landfill," Clifford said. In the case of Bldg. 7, that means separating steel from concrete before the materials can be recycled. The exception is that the existing pile of rubble with the trace amounts of

asbestos-containing material will be safely disposed of in an asbestos-licensed landfill.

Originally, demolition was to be complete by June. Currently, Clifford said, a new timeframe has not been set. Earl Johnson, the ORF project officer for Bldg. 7, publishes regular email updates to the neighbors surrounding the building. He will continue to provide updates, announcing when all abatement work is complete and when demolition will resume. **R**

★ ★ ★
"We will treat the entire pile as if it's contaminated with asbestos."

-TONY CLIFFORD

★ ★ ★

Capital Bikeshare Coming to Campus

BY DANA TALESNIK

It's a crisp, clear day, perfect for a bike ride on your lunch break. But your bicycle is at home.

Well, there's a new option coming to satisfy your urge to pedal around in the fresh air. Soon you can rent a bike whenever you want, right by the Medical Center Metro station.

The new Bikeshare station, with 10 bikes and 19 bike docks, will sit on the island between the Metro entrance and the Kiss and Ride parking lot. You'll be able to grab a bike and cycle over to a meeting, traverse the 3.25-mile bike path around campus, run some errands or ride into downtown Bethesda to grab a bite. You can return the bike to any of the more than 350 Bikeshare stations across the greater Washington area.

"It's an opportunity to access transit, get around near work, ride around at lunch hour and get some exercise," said Gail Tait-Nouri, manager for pedestrian and bicycle projects for the Washington Metropolitan Area Transit Authority (WMATA).

Sponsored by the Montgomery County department of transportation and Capital Bikeshare, in cooperation with NIH and WMATA, the new station is one of more than 50 stations across Montgomery County. There are several around nearby Battery Park and another new one on Old Georgetown Rd. and Southwick St., across from Suburban Hospital.

To rent from Bikeshare, you first become a member. When you join—at any Bikeshare kiosk or at <https://secure.capitalbikeshare.com/register>—you receive a key to access a bike at any Bikeshare location, 24 hours a day. Choose from a 1-day, 3-day or 30-day pass or annual membership; the first 30 minutes of any trip is free for members.

So grab your helmet and you're off. Montgomery County law requires anyone 18 or younger to wear a helmet, but every bicyclist should wear one, especially if riding alongside traffic. Also, check your surroundings and be careful at the new Bikeshare site.

"That's a busy area. Buses go through there regularly," said Tait-Nouri. "We encourage people to look and be more vigilant as vehicles may not realize Capital Bikeshare has arrived."

If you're new to Bikeshare, or a novice cyclist, Tait-Nouri recommends contacting the Washington Area Bicyclist Association (www.waba.org), which offers bicycle training and safety classes.

A 2014 Bikeshare user survey showed most riders reported renting from Bikeshare to get around more easily and especially enjoyed the program's one-way travel option. Most respondents also cited biking for the enjoyment of it and the exercise.

Riding a bike, even at a leisurely pace, is great exercise. NHLBI studies show that an hour of cycling



A Capital Bikeshare dock (l) across from Bldg. 35 provides a model of what the new one will look like at a site (r) near the Medical Center Metro plaza.

PHOTOS: BILL BRANSON

(at about 5.5 mph) burns 460 calories in men and 370 calories in women. Just 30 minutes of moderate-intensity physical activity daily boosts energy and mood, reduces stress and tones muscles.

"Bikeshare is for NIH, Walter Reed and the entire community," said Tony Clifford, chief engineer in NIH's Office of Research Facilities. "It provides a hub for transportation. You can rent a bike when you get off of Metro or a bus. Now people who work or live nearby have an alternative form of transportation."

Installing the station was expected to be a fairly fast process once the weather cooperated. In mid-February, once the cement was poured, the bike brackets and electronics were to be lowered by crane. Clifford, who co-chairs NIH's Green Team, proudly points out that all nearby trees were preserved.

In addition to the exercise and sustainability, biking is just a convenient way to get around. NIH received a 2013 regional award for encouraging alternative commuting options. One of the first federal agencies to offer a bicycle subsidy program, NIH also is still riding out the success of its Bike to Work Day each spring. That is the NIH Bicycle Commuter Club's signature annual event.

Tait-Nouri emphasized the role Montgomery County played in making the new Medical Center Bikeshare station a reality. "The county did all the legwork and paid for it," she said. "Cost isn't insignificant here. It's a great public service."

Bikeshare Is Latest Project with Montgomery County

When you're walking or pedaling around the campus perimeter, ever wonder about that big pond on the south side of campus? That stormwater retention pond serves an important purpose for nearby residents and, along with the new Bikeshare station, is among the good-neighbor projects between NIH and the town of Bethesda.

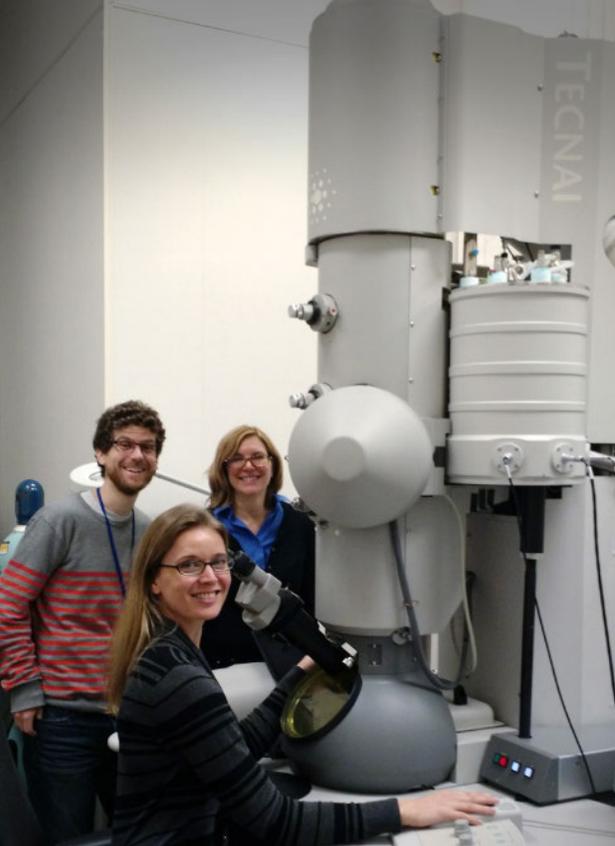
NIH has long worked with Bethesda Urban Partnership on good-neighbor campaigns to make Bethesda a desirable place to live and do business, said ORF's Tony Clifford. The pond, for example, located on NIH property but paid for by the county, collects and drains more than 200 acres of downtown Bethesda's storm runoff, which paved the way in part for expanding the development of downtown Bethesda's business and residential high-rises.

Bethesda and NIH also have a reciprocal agreement for emergency services. The Bethesda Fire & Rescue Squad on Cedar Ln. sits on a half-acre of land NIH transferred to it 60 years ago. NIH's own fire department often responds to emergency requests beyond campus. In fact, in 2013, NIH responded to more than 1,000 emergencies throughout the Bethesda/Rockville area.

"If a house is on fire or someone has a medical emergency in nearby Bethesda, there's a good probability that NIH's Fire Department, under its mutual aid agreement with the county, could be one of the first responders," said Clifford.

Another symbol of collaboration between NIH and Bethesda is the Woodmont exit ramp off of Rockville Pike. NIH owns and does landscaping to maintain the surrounding area, the gateway to downtown Bethesda. It's all part of NIH's Sustainability Management Plan.

So as you bike around campus or into downtown Bethesda, you'll be passing these and other symbols of sustainability as NIH continues its efforts to be a good neighbor.



Team players. Dr. Doreen Matthies, postdoctoral fellow, is seated at one of the lab's cryo-electron microscopes, with postdoctoral fellow Dr. Jean-Philippe Demers (l) and electron microscopist Lisa Hartnell.

PHOTO: VERONICA FALCONIERI

Cryo-EM

CONTINUED FROM PAGE 1

results from NIH's investment in EM are being hailed throughout the science world. Not only does Subramaniam's lab now hold the world record for the highest resolution achieved using cryo-electron microscopy (cryo-EM), the team also holds the spots for the second- and third-highest resolution structures obtained using this technique. But that's jumping ahead of the story.

The Early Years

Over the 10 years after Subramaniam joined NIH, he built a highly diverse team, with expertise ranging from microbiology and protein biochemistry to imaging, computer programming and electrical engineering.

"Our lab has always been full of people with myriad and eclectic interests, and spanning a wide age range," he said. "Early work that I and Dr. Jacqueline Milne did resulted in a molecular model for the enzyme pyruvate dehydrogenase and insights into how this molecule worked in mitochondria. Then-NIH director Dr. Elias Zerhouni actually showed this data on the floor of Congress."

Another major breakthrough came in 2008, when the lab developed powerful computational tools and a technique called cryo-electron tomography. This enabled them to publish the first 3D structure of the intact HIV envelope glycoprotein, the complex responsible for allowing the virus to invade host cells. That same year, they also used these methods to describe arrangements of membrane protein assemblies in intact bacteria.

The Better to See You

As they continued their forays into imaging intact HIV, influenza, Ebola and related viruses, the team also continued to sharpen efforts to see the inner details of proteins at higher resolution. A novel "Living Lab" partnership with a microscope manufacturer led to further innovations in technology and methods to achieve high resolution.

With the latest generation of microscopes, cameras and analysis tools, suddenly the protein image quality leapt forward.

In early 2015, starting with a few drops of purified protein, the Subramaniam group was the first to publish the structure of a small enzyme at atomic resolution obtained by cryo-EM—a level of detail where

you can essentially make out the individual atoms in proteins. Last month, *Nature Methods* magazine named the cryo-EM technique "Method of the Year." NIH director Dr. Francis Collins posted a blog about the achievement on Jan. 14.

Visualizing proteins and other molecules in the cell can be a little tricky. In the mid-20th century, scientists first started getting glimpses of the internal workings of proteins using X-ray crystallography. That technique became the go-to structural biology method. But even though the structures of a great many proteins have been studied this way, some molecules—big, wobbly or dynamic proteins or complexes that just won't crystallize—have foiled crystallographers.

Now, cryo-EM, as the Subramaniam group and many others world-wide are beginning to show, may be ready to challenge crystallography in the 3D imaging resolution domain.

Location, Location, Location?

One important goal in advancing these methods is to find better drug targets. If, for example, you can learn how a protein involved in cancer—or any disease—is shaped, where it is situated in a cell, how it moves in its environment and what its neighboring biomaterial is like, then you can figure out the best way to alter the protein's function and thus treat the disease.

FREEZE FRAME

How the Method Works

The contrast is striking. The cryo-EM microscope that the Subramaniam team uses for high-resolution structural work, a Titan Krios manufactured by FEI Co., stands more than 13 feet high and weighs in excess of 2,000 pounds. It's designed to study individual molecules and even visualize single atoms—material far too tiny to be seen without high-tech help.

The first step in generating a structure, says Subramaniam, is suspending the chosen molecules in a solution and placing them on a fine mesh screen called a "grid." Next the grid is plunged into liquid ethane to form a thin film of ice with the proteins in it. The film gets inserted into a cassette, which then goes into a cryo-capsule device that gets inserted into the Titan. Next, the microscope takes thousands of pictures, delivered every 60 seconds or so.

Because of the way electrons can interact with biological molecules like proteins, it can be complicated to get a very clear signal in any single



Subramaniam is helping the NCI intramural program expand its use of cryo-EM. The Center for Molecular Microscopy (<https://cmm.nci.nih.gov/>), which he directs, hosts both transmission and focused ion beam microscopes and works with intramural collaborators to study cells, viruses and molecules in 3D at high resolution.

image. In addition, all those images are in 2D. So to get a 3D picture of the protein at atomic resolution, "we [computationally] assemble all of those pictures together," Subramaniam explains. When



Subramaniam (seated, l) and members of his team discuss the Krios microscope with FEI Co. representatives. Shown (from l) are Alan Merk, Kieran Moynihan, Gijs Janssen and Dr. Joseph Darling.

PHOTO: RHODA BAER

“The interesting part is the interpretation of the structure,” Subramaniam explained. “[Protein] structure is useful in many different contexts. We like to understand how cells work. We like to understand how viruses get into cells...The structure and dynamics are generally interesting biologically across the board, but our present interest, keeping the future in mind, is to leverage this information to accelerate drug discovery.”

Staying with the architectural theme, Subramaniam compares macromolecular drug discovery to buying real estate. The protein you’re studying is the house you’re interested in purchasing. Of course you want

to tour the inside, look at how the space flows and see all of the nooks and crannies invisible from outside. Just as important, however, is the neighborhood and environment around your potential residence. You want to know what else is nearby—streams and ponds, other structures—that might affect your house.

Welcome to the Neighborhood

“Very often when drugs bind, the proteins that we are targeting bind in the context of interacting with lots of other partners, so when we look at just the local target we don’t have a feeling for what’s happening,”

“We need to look at much larger complexes and be able to look at them at much higher resolution,” Subramaniam says. “The atomic resolution structures we have been posting are still of fairly well-defined complexes. But when you go to more complex systems, we have only achieved lower resolutions.”

The key for the future will be to capture all of the movement and dynamics of protein complexes, without losing resolution. The group will use methods they pioneered over the last decade to image whole cells at high resolution to better understand how these complexes function in the context of the whole cell.

So far, the NIH team is doing what it can to stay at the forefront of a very crowded and growing area of research.

“It’s just taken off,” Subramaniam enthuses. “There’s exponential growth in the field. Until 2013...it was really a niche field.” And now? “There’s a real buzz across many disciplines that this could be a very powerful addition to the biologist’s toolkit.”

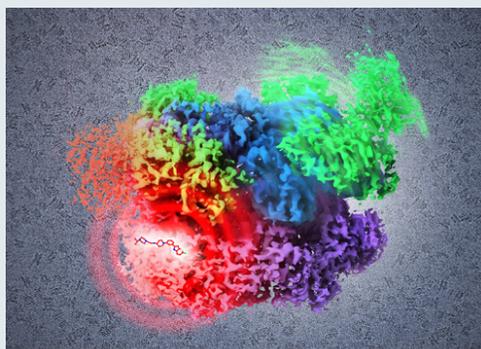


Illustration of the structure of p97, a target for cancer therapy, trapped in an inactive state by a newly designed inhibitor. The structure is a composite of multiple states derived by cryo-EM analysis, blended to highlight the dynamic nature of this molecular machine.

IMAGE: VERONICA FALCONIERI

there’s enough information and everything is done correctly, “out comes the structure of the protein” at atomic resolution.

Cryo-EM is still mostly uncharted territory, however.

Subramaniam said. “What’s happening with the neighbors? What’s happening downstream? We want to look at drugs bound to native proteins. Generally we want to focus on things that are hard to do by crystallographic methods, but are nevertheless important. So we want the structures of protein in as close a state as possible to what they are in the cell. Because when drugs work or don’t work, we want to know why. That’s what we’re after.”

Just this past month, the Subramaniam lab, in coordination with the NCI NExT program and several labs around the country, published the first complete structure of the cancer target protein p97 at atomic resolution. Other groups had analyzed the structure of parts of p97, but because inhibitors can bind at the junction between different sections of the protein, it was critical to image the whole protein complex.

“Being able to see in detail how this protein machine works, and how the inhibitor throws a wrench in the works, using cryo-EM—it’s a whole new world,” said Subramaniam.

So, how does his cryo-EM team decide which of the thousands of macromolecules to image?

“We cast a wide net,” he said. “Proteins important in brain function, in cancer, in viral infection, vaccines—it’s quite a broad spectrum. We’ve tried to pick important examples, where if it works, we learn something new. That’s why we picked receptors in the brain. We picked HIV. We picked cancer targets. In each case, as we push the frontier of the technology a bit more, we also at the same time try to advance a particular biological mission.”

What’s Next?

Subramaniam also intends for NIH to maintain its head start on the rest of the cryo-EM field. The goals now, he said, “are to get this method to be more broadly applicable and to accelerate the rate of drug discovery.”

Already he has the germ of a new idea forming. “I do see in the next decade a way to take on that problem [of studying drug interactions] seriously, by applying these methods,” he said. “So we can get a much more calibrated view of how drugs interact with cells. Maybe we’ll understand what works and what doesn’t work.” **R**

Frailty

CONTINUED FROM PAGE 1

to society”—and reported her findings Jan. 14 for an NIH audience in the Porter Bldg.

“This is something I’ve been trying to figure out for several decades,” said Fried, who explained that, for the past 60 years, the descent from resilience to frailty in some older people has been the “raison d’être” of geriatric medicine in the United States. “Who are these people and why is this going on?”

Everyone who ages experiences some degree of loss of resilience, but not every senior citizen becomes frail, a state highly predictive of death within 3 years. Fried is interested in preventing the advance of frailty syndrome in those most vulnerable to its ravages.

“We know that frailty increases with age,” she said. “It appears to be a distinct physiological state” characterized by a constellation of markers. “We all think we know it when we see it. However, the science of characterizing the phenotype of frailty and its underlying biology takes us beyond our assumptions.”

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“We know that frailty increases with age. It appears to be a distinct physiological state...We all think we know it when we see it. However, the science of characterizing the phenotype of frailty and its underlying biology takes us beyond our assumptions.”

-DR. LINDA P. FRIED

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Markers include loss of: muscle mass (sarcopenia); strength and power; energy motor speed; and activity. In advanced stages, it includes chronic undernutrition, which accelerates the cycle of decline.

A phenotype for a new clinical syndrome has emerged with 5 characteristics; a person with 3 to 5 of them is clinically frail, while 1 to 2 is considered pre-frail. These include shrinking (unintentional weight loss), weakness, poor endurance, slowness and low activity.

Fried filled in the frailty picture with

results from three major population-based studies of older adults; one focused mainly on cardiovascular health and the other two were women’s health and aging studies.

She found that frail adults were at “high risk of a lot of bad outcomes,” including death, falls, hospitalization, burns and surgery. In short, frailty appears to predict high risk.

Further, it is a chronic, progressive process, whereby a frailty score of 1 or 2 is likely to advance to a 3 within 3 years. A score of 5 is highly predictive of death within 6 months.

“We have found that frailty is a vicious cycle of dysregulated energetics,” said Fried. In 2013, physical frailty was declared a

clinical syndrome. Fried thinks everyone over age 70 should be screened for it.

Peering below the waterline of overt symptoms, Fried and her colleagues have found “a large number of physiological systems being disrupted” in frailty. These include anemia, inflammation, immune deficits, nutrient deficiency, abnormal blood tests, altered insulin-glucose dynamics and dysregulation of hormones, among other problems.

“Something is going on beyond any one symptom,” she said. “There is a large amount



Fried and her colleagues have found that, even at the molecular and genetic level, frailty is characterized by an inability to adapt to stressors.

PHOTOS: RICH MCMANUS

of dysregulation across many systems for people who are frail. And the odds go up more than linearly as the number of frailty markers rises—there is an acceleration as more systems are involved, so that the whole is greater than the sum of the parts...What is driving this aggregate loss of reserves?”

Fried and her colleagues have found that, even at the molecular and genetic level, frailty is characterized by an inability to adapt to stressors. “Dysregulation of energy metabolism may be the root of frailty,” she said. “These patients have far fewer reserves and less resilience.”

Frailty tends to be a background vulnerability rather than the presenting disease for which one is typically hospitalized, Fried explained. But sadly, “Putting a frail person in the hospital is perhaps the ultimate stress test.”

The good news is that frail adults respond to exercise, sometimes in dramatic fashion. “Physical activity up-regulates all kinds of functions,” Fried said. “It’s a very nice model of what we would be driving for...If we understand the syndrome accurately, there are lot of ways to intervene.”

So, have you signed grandma and grandpa up for “kindergarten” yet? **R**



Ixodes scapularis tick engorged with blood. Some genes allow ticks to quickly expand their stiff outer coats to accommodate a 100-fold increase in total body size during blood feeding.

PHOTO: CDC

Tick Genome Reveals Secrets of a Successful Bloodsucker

With tenacity befitting their subject, an international team of nearly 100 researchers toiled for a decade and overcame tough technical challenges to decipher the genome of the blacklegged tick (*Ixodes scapularis*).

The National Institute of Allergy and Infectious Diseases contributed primary support to the research, which appeared in the online journal *Nature Communications*.

“Ticks spread more different kinds of infectious microbes to people and animals than any other arthropod group,” said NIAID director Dr. Anthony Fauci. “The spiral-shaped bacterium that causes Lyme disease is perhaps the best known microbe transmitted by ticks; however, ticks also transmit infectious agents that cause human babesiosis, anaplasmosis, tick-borne encephalitis and other diseases. The newly assembled genome provides insight into what makes ticks such effective disease vectors and may generate new ways to lessen their impact on human and animal health.”

The researchers’ focus was a creature that is extremely difficult to maintain and that lives a long time—up to 2 years in the wild and 9 months in the lab.

Another challenge was the sheer size of the tick genome—some 2.1 billion DNA base pairs—and expansive regions where sequences are repeated.

“The genome gives us a code book to

the inner workings of ticks. With it, we can now begin to hack their system and write a counter-script against them,” said Dr. Catherine A. Hill of Purdue University, who headed the team of investigators.

Hill admits to a grudging admiration for her 8-legged subjects. “I find them almost endearing in the way they stick so firmly to the business of parasitizing their hosts. They are persistent and resilient. In a way, our team took a page from the tick’s book in working together over so many years until we achieved our goal.”

Criminal Justice Alcohol Program Linked to Decreased Mortality

A criminal justice program that requires offenders convicted of alcohol-related offenses to stop drinking and submit to frequent alcohol testing with swift, certain and modest sanctions for a violation was linked to a significant reduction in county-level mortality rates in South Dakota. These results came from a study funded by the National Institute on Alcohol Abuse and Alcoholism.

The 24/7 Sobriety program, launched in South Dakota in 2005, was associated with a 4.2 percent decrease in all-cause mortality over 6 years, with the largest reductions occurring among women and individuals over 40. Deaths from circulatory conditions, which include heart disease and stroke, declined significantly.

“The study suggests that effective programs for alcohol-involved offenders may have benefits, not only for the participants themselves, but [also] for the community as a whole,” said Dr. George Koob, NIAAA director. “If these results are replicated in future studies, it could advance our understanding of how interventions within the criminal justice system can be used to improve public health.”

The study results appeared online in *The Lancet Psychiatry*.

NIH Researchers Identify Striking Genomic Signature Shared by 5 Types of Cancer

NIH researchers have identified a striking signature in tumor DNA that occurs in 5 different types of cancer. They also found

evidence that this methylation signature may be present in many more types of cancer.

The specific signature results from a chemical modification of DNA called methylation, which can control the expression of genes like a dimmer on a light switch. Higher amounts of DNA methylation (hypermethylation), like that found by the researchers in some tumor DNA, decreases a gene’s activity. Based on this advance, the researchers hope to spur development of a blood test that can be used to diagnose a variety of cancers at early stages, when treatments can be most effective. The study appeared Feb. 5 in the *Journal of Molecular Diagnostics*.

“Finding a distinctive methylation-based signature is like looking for a spruce tree in a pine forest,” said Dr. Laura Elnitski, a computational biologist at NHGRI. “It’s a technical challenge to identify, but we found an elevated methylation signature around the gene known as ZNF154 that is unique to tumors.”

In 2013, her research group discovered a methylation mark (or signature) around ZNF154 in 15 tumor types in 13 different organs and deemed it a possible universal cancer biomarker. Biomarkers are biological molecules that indicate the presence of disease. Elnitski’s group identified the methylation mark using DNA taken from solid tumors.

“No one in my group slept the night after that discovery,” Elnitski said. “We were so excited when we found this candidate biomarker. It’s the first of its kind to apply to so many types of cancer.”

Elnitski will next begin screening blood samples from patients with bladder, breast, colon, pancreatic and prostate cancers to determine the accuracy of detection at low levels of circulating DNA. Tumor DNA in a person with cancer typically accounts for 1 to 10 percent of all DNA circulating in the bloodstream. The group noted that when 10 percent of the circulating DNA contains the tumor signature, the detection rate is quite good. Because the methylation could be detected at such low levels, it should be adequate to detect advanced cancer as well as some intermediate and early tumors, depending on the type.

Record Number of Events for 'Drug Facts' Week

NIDA conducted its annual National Drug & Alcohol Facts Week Jan. 25-31 with its new partner this year, the National Institute on Alcohol Abuse and Alcoholism. NDAFW is an annual health observance week for teens to shatter myths about drug and alcohol use through community events, Drugs & Alcohol Chat Day and other partnerships.

This year, NIDA reached an all-time record number of events—more than 1,800 in all 50 states and 10 countries. During the week, NIDA also hosted Drugs & Alcohol Chat Day (Jan. 26), a live online chat between teens and NIH scientists. Despite the inclement weather, more than 60 high schools participated from 25 states. The blizzard did not stop NIDA, NIAAA and NIMH experts from participating remotely, with more than 25 scientists answering more than 1,400 questions.

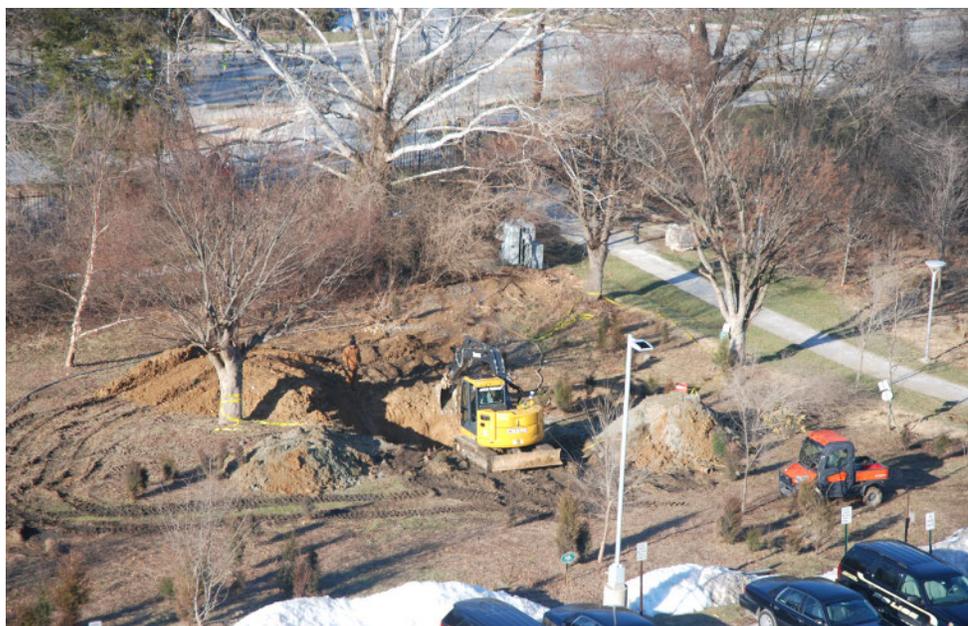
In addition, NDAFW activities were



Students from Marathon (Fla.) Middle School participate in a National Drug & Alcohol Facts Week event.

promoted throughout the week via social media outreach on Twitter and Facebook. Online resources included five new drug-specific toolkits for event holders to use and the popular National Drug IQ Challenge,

an interactive quiz accessible on mobile devices, for teens to test their knowledge about drug and drug abuse. Visit <http://teens.drugabuse.gov/national-drug-facts-week> for more information.



Water Main Repair Puts Another 'Deere' in Field

The meadow between Bldg. 31 and Cedar Ln. is often dotted with deer. But it was a John Deere backhoe that the Office of Research Facilities' utility distribution group used to repair a main water line that ruptured on Feb. 4 behind Bldg. 31. The 12-inch pipe provides water to the NIH campus and connects to the Washington Suburban Sanitary Commission water supply on West Cedar Ln. ORF had to wait for the ground to dry out before bringing in heavy equipment to repair the line on Feb. 10. Above, workmen dig a hole around the ruptured pipe. At right, the backhoe delivers the specially cut length of pipe into the pit. By the next day, little evidence of the effort remained, except tractor tracks.

PHOTOS: RICH MCMANUS



NIEHS Alumnus Nettesheim Mourned

Former NIEHS senior science advisor Dr. Paul Nettesheim passed away peacefully at his home on Jan. 16. His contributions to NIEHS were numerous and significant. He came to the institute in 1977 and served as head of the Laboratory of Pulmonary Pathobiology. He stepped up to serve as acting scientific director from 2000 to 2001, then as senior science advisor to the institute director from 2001 until he retired in 2003.



Dr. Paul Nettesheim

PHOTO: STEVE MCCAIV

A pulmonary biologist, Nettesheim was internationally recognized. In 2002, he received the Humboldt Research Award, a lifetime career achievement award for his outstanding contributions to science. "Paul made seminal contributions to our understanding of the adverse effects of environmental agents on the respiratory system, particularly abnormal growth in the airways induced by carcinogens, as well as the process of differentiation of airway epithelial cells," said Dr. Anton Jetten, head of the NIEHS Immunity, Inflammation and Disease Laboratory.

One of Nettesheim's important achievements was the development of new experimental models for studying cell behavior, which enabled better assessment of environmental risks to health and supported the development of novel therapies. The more than 220 scientific papers he published illustrated consistent cutting-edge thinking; many of his publications came from his work at NIEHS.

Highly regarded by national and international colleagues for his objectivity, scientific knowledge and research excellence, Nettesheim led productive teams of scientists and mentored and trained numerous researchers who now carry on his work to improve human health.

Nettesheim was born 82 years ago in Cologne, Germany, and completed his studies at the University of Bonn. The family moved to Oak Ridge, Tenn., in 1962, where he joined Oak Ridge National Laboratory as a research biologist. He served there as head of the respiratory carcinogenesis group from 1969 to 1977.

Nettesheim is survived by his wife, Barbara, and sons Ulrich of Los Angeles, Klaus of Durham, N.C., and Christoph of Ventura, Calif., and nine grandchildren. **R**



At NSC, Old Glory Flies Again

Last spring, the flag that normally flies in front of the Neuroscience Center Bldg. developed a tear and needed to be replaced. John Hamill, retired former chief of NIDA's Research and Development Contracts Management Branch, reached out to U.S. Sen. Ben Cardin's office for a replacement. Within a day, Cardin's staff responded with a promise to send a flag. Shortly thereafter, the new flag arrived, along with a certificate stating that it had previously flown over the U.S. Capitol dome. The certificate (r) is now on view at the entrance to NSC.



Become a Healthy Volunteer

An NIH study is enrolling healthy persons 18-65 who are free of psychiatric disorders and certain medical conditions. Researchers will evaluate the effects of the experimental medication ketamine on brain receptors in healthy and depressed adults. Study includes 1 to 6 weeks of outpatient procedures: screening visit, computer tasks, rating scales, neuropsychological testing, two intravenous infusions, blood draw, brain scans (MEG & fMRI) and may include optional 2-4 overnight stays for a sleep study. The study is conducted at the Clinical Center. There is no cost and compensation is provided. To find out if you qualify, email moodresearch@mail.nih.gov or call 1-877-MIND-NIH (1-877-646-3644), TTY 1-866-411-1010. Refer to study 04-M-0222.

Study Seeks Healthy Older Adults

Healthy older adults ages 55-75 are invited to participate in an outpatient research study investigating the benefits of omega-3 oil and blackcurrant supplements on vascular health. The goal of the study is to determine whether the supplements improve blood flow and blood vessel function that can affect your heart. Eligible participants must be medication-free and in good general health. The study will be carried out in an outpatient clinic and includes 4 visits over 6 months. Compensation is provided. For more information, call 1-800-411-1222 (TTY 1-866-411-1010) and refer to study 14-NR-0034.

Liver Disease Patients Needed

An NIDDK research team seeks people with fatty liver disease to participate in a study. Researchers are looking at a breath test to measure how the body breaks down food in people with fatty liver disease. If you have been diagnosed with non-alcoholic fatty liver disease or steatohepatitis, you may be interested in participating. Compensation is provided. For more information, call 1-866-444-2214 (TTY 1-866-411-1010) and refer to study 15-DK-0080.

Volunteers Needed for Energy Study

NIDDK seeks healthy Caucasian men, 55-75 years old, and women 18-35 to participate in a research study. Doctors want to learn how the body burns energy at different temperatures. You will have an 8-day inpatient stay at the Clinical Center. Compensation is provided. For more information, contact the Office of Patient Recruitment, 1-866-444-2214 (TTY 1-866-411-1010). Refer to study 12-DK-0097.

NHGRI Seeks Volunteers

NHGRI researchers seek people with chromosome abnormalities involving the sex chromosomes for a research study. Compensation is provided. For more information, call 1-866-444-2214 (TTY 1-866-411-1010) and refer to study 12-HG-0181.



NIH director Dr. Francis Collins adds his advice to the “For the Heart, From the Heart” chalkboard. “NIH’ers: Be an ambassador for health!” he counseled employees.

NIH Celebrates ‘Wear Red’ Day, Kicks Off American Heart Month

On Feb. 5, the NIH campus turned into a virtual sea of red—from employees wearing red clothes to the prominent display of red food in the cafeterias. Why? Because NHLBI celebrated National Wear Red Day and kicked off the start of American Heart Month to raise awareness of heart disease, which is the number one cause of death in this country.

Among the notable highlights of the celebration was a special event at the Clinical Center, where an artist created a mural on a giant chalkboard and encouraged guests to write and share their advice about heart health. The event, hosted by NHLBI director Dr. Gary Gibbons, encouraged everyone to share advice for the heart, “From the Heart.” Gibbons wrote “Know your numbers” on the chalkboard, urging people to know their blood pressure and cholesterol measurements.

The Rockledge II lobby and Bldg. 31 cafeteria had similar chalkboard-signing events and the cafeteria also featured a display of red, heart-healthy foods, including apples and peppers.

Later that day, NHLBI helped paint the Internet red. The institute teamed up with the Heart Truth campaign and the American Heart Association for a #HeartChat hosted by *Woman’s Day* magazine on Twitter to raise awareness about heart disease in women. Despite research advances, heart disease remains the leading cause of death for women in the United States.

On Feb. 11, NHLBI also co-hosted the Red Dress Fashion Show in New York City, which featured celebrities walking the runway in red dresses created by fashion designers. Guests included Vanna White, Fran Drescher, Florence Henderson, Misty Copeland and many others. Gibbons attended the star-studded event and was joined by U.S. Surgeon General Vivek Murthy.—**Mark Sampson**



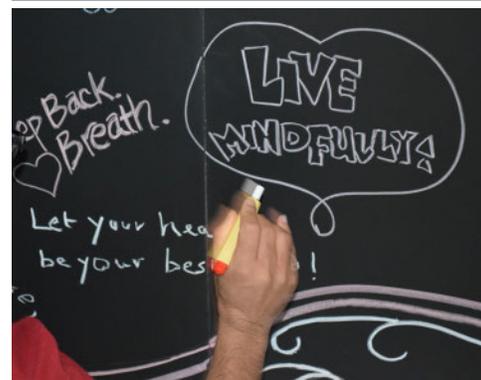
ABOVE: The Bldg. 31 cafeteria staff adds their hearts to the spirit of the day, joining ORS director Dr. Alfred Johnson (third from r) for a photo op. RIGHT: The cafeteria also featured a display of red, heart-healthy foods.



Showing their colors for the day are (from l) NIDDK director Dr. Griffin Rodgers, Collins, ORWH director Dr. Janine Clayton and NHLBI director Dr. Gary Gibbons.



NHLBI also participated in the Red Dress Fashion Show in New York City, which featured celebrities walking the runway in red dresses created by fashion designers. Gibbons attended the star-studded event and was joined by U.S. Surgeon General Vivek Murthy.



One of several chalkboard-signing messages offers good advice.

