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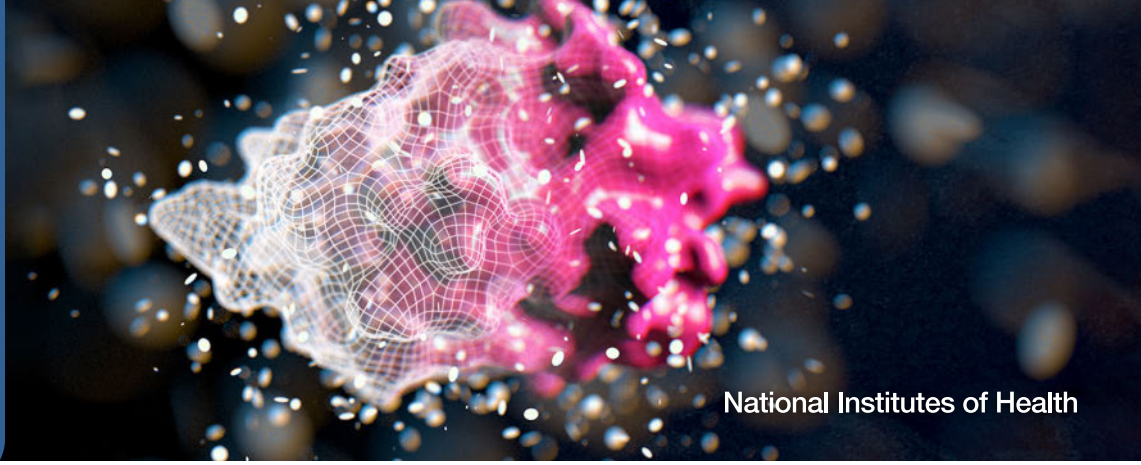


A SENSE OF IMPORTANCE

Levy Discusses Smell as a Diagnostic Tool

BY DANA TALESNIK

Many people stop to smell the roses, but what happens when we can no longer physically smell the roses? Loss of smell is a common, self-reported symptom that too often gets overlooked in the medical field, yet it can sometimes indicate a more serious health problem.

Loss of smell is a symptom associated with dozens of diseases, said Dr. Joshua Levy, clinical director of NIH's National Institute of Deafness and other Communication Disorders (NIDCD), and co-director, the National Smell and Taste Center. He discussed the impact of smell on health at a recent Beyond the Lab speaker series talk.

The ability to smell is critical for safety, nutrition, quality of life and overall health. It can warn us of danger—such as from smoke or fumes or spoiled food. Smell loss can affect taste, appetite and eating habits, which subsequently can lead to nutritional deficiencies. There's an emotional connection as well. Chronic smell loss is closely associated with depression, anxiety and social isolation.


Dr. Joshua Levy

What's more, noted Levy, loss of smell is a biomarker for more than 130 diseases and disorders—from viral infections to neurodegenerative disorders.

Levy, a sinus surgeon, offered real-world examples of the importance of smell, sharing patient stories from his practice in Atlanta, where he worked prior to coming to NIH. In April 2020, he said, a healthy woman came in complaining of a loss of smell with no other viral symptoms.

"As a field, we hadn't fundamentally connected the dots" that smell loss was a defining symptom of Covid-19, Levy said. "The rest of that story is history."

In fact, he said, following a viral infection, "self-reported change in smell is not only an early sign, it's actually more predictive than a fever."

SEE **SMELL**, PAGE 4


Bhattacharya visits the Blood Bank, see p. 2.

ALSO THIS ISSUE

Genomic Sequencing Reveals Complexity of Microbial World

BY ERIC BOCK

The microbial world encompasses a vast array of undiscovered microorganisms that live in many different ecosystems, including some of the harshest environments on Earth.

Scientists now have a wide variety of genomic sequencing tools to identify and gain insights into their past, said Dr. Purificación López-García, research director in the ecology, systematics and evolution unit at the French National Centre for Scientific Research. She spoke at an NIH Director's Wednesday Afternoon Lecture Series (WALS) talk earlier this summer in Lipsett Amphitheatre.


Dr. Purificacion Lopez-Garcia

These advances allow scientists to reconstruct the evolutionary relationships of all life on Earth through genetic information. The relationships are often depicted as phylogenetic trees, which are branching diagrams that show how species or groups of organisms have diverged from each other over time. The trees illustrate how species are related through a common ancestor. If two organisms branch off from the same node, it's thought they evolved from the same ancestor.

There are three domains of life: archaea,

SEE **LOPEZ-GARCIA**, PAGE 5

All of Us Accelerates Discovery for Chronic Disease Solutions

Dr. Josh Denny (l) and Dr. Rick Woychik

What does it take to revolutionize how we understand and treat chronic conditions like diabetes and heart disease? In a recent *Research!America Alliance* discussion, NIH leaders shared how NIH's *All of Us* Research Program is accelerating progress by capturing the full picture of health: genetics, environment, nutrition, lifestyle and more.

"We think about chronic disease as composites of genetic influence, environmental exposures and lifestyle habits," said Dr. Josh Denny, CEO of the *All of Us* Research Program. "We're able to look at that intersectionality," thanks to one of the most data-rich research platforms ever built.

Dr. Holly Nicastro, nutrition scientist and coordinator of the Nutrition for Precision Health study, highlighted the program's value as a national research infrastructure:

"We estimate, conservatively, that our study is saving on the order of tens of millions of dollars by embedding within the *All of Us* Research Program," she said.

Dr. Rick Woychik, director of NIH's National Institute of Environmental Health Sciences, emphasized that understanding where people live and work is just as critical as understanding their biology.

"My physician has never asked me where I work or live, and what we're discovering is that where you live and work actually can predict what some of your environmental exposures are," Woychik said.

Together, these insights are helping to reshape the way we think about chronic disease. To watch the full discussion and learn more about how *All of Us* is transforming chronic disease research, see: https://bit.ly/3GS3mna.

Director Donates Blood at the CC

NIH Director Dr. Jay Bhattacharya recently rolled up his sleeves for an important cause: donating blood at the Clinical Center's Blood Bank. He said he hopes his donation might inspire others who are able to give.

There's often a critical need for multiple types of blood as well as platelets at the CC Blood Bank, which serves protocol patients who need blood for surgeries, emergency transfusions and treatments.

NIH Director Dr. Jay Bhattacharya donates blood at the CC Blood Bank on Aug. 4. **PHOTO: JUSTIN BAKER**

To schedule a donation appointment: call 301-496-1048, email nihblood-bank@cc.nih.gov or visit www.cc.nih.gov/blood-bank to book online. Walk-ins are also welcome.

CC Blood Bank hours are Monday – Friday, 7:30 a.m. to 4:00 p.m.

NIH Research Festival Returns — Sept. 9-12

The NIH Research Festival will be held Sept. 9-12, in Bldg. 10 in the Lipsett Amphitheater, the FAES terrace and classrooms, the NIH Library and the South Lobby. All are welcome.

Clockwise from l, former NIH Director Dr. Elias Zerhouni and NIH investigators Dr. Paule Joseph and Dr. Gisela Storz are featured speakers at this year's NIH Research Festival.

Started in 1986 as "NIH Research Day," the festival is an annual, multi-day event that highlights the scientific discoveries and advances made by scientists in NIH labs and clinics. The event provides an opportunity for NIH scientific staff, including trainees, not only to share their work with their peers at lecture and poster sessions, but also to get to know their "neighbors."

This year's Research Festival will kick off with a short TED-style talk by Dr. Paule Joseph, an NIH senior investigator who studies how smell and taste are altered in conditions such as alcohol use disorder, obesity and viral infections. The opening day also includes lectures by independent research scholars and staff clinicians, four poster sessions and myriad scientific workshops and information tables. And the NIH Library will again host virtual reality demos.

The agenda on Wed., Sept. 10 includes a series of special lectures, including the Victoria A. Harden Lecture in NIH history to be delivered by John Burklow, senior vice president, Foundation for the NIH; the Anita B. Roberts Lecture by Dr. Kelly Ten Hagen, an NIH senior investigator who studies how sugar influences biological processes; the G. Burroughs Mider Lecture by Dr. Gisela Storz, an NIH distinguished investigator who researches small regulatory RNAs and proteins; and a special event with former NIH Director Dr. Elias Zerhouni.

Thursday and Friday bring biomedical vendor exhibits and scientific workshops, sponsored by the NIH R&W.

See the full agenda at researchfestival.nih.gov. Direct questions to Research Festival coordinator, Diana Gomez, at researchfest@mail.nih.gov.

Conference to Explore Future of Health Behavior Theories — Sept. 8

NIH's Office of Behavioral and Social Sciences Research (OBSSR) is hosting a virtual conference titled, "Unlocking the Future of Health Behavior Theory: Toward Innovations in Understanding and Practice" on Sept. 8 from noon to 4:30 p.m. ET.

Health behavior theories are used to describe, predict and understand health behaviors, and inform the development and use of behavior change strategies. Recent tech advances and increased focus on social and structural determinants of health challenge traditional approaches to developing and applying health behavior theories.

NIH's Health Behavior Theories Project aims to identify core needs for advancing health behavior theory quality and use as well as establish a foundation for future progress. During the conference, project members and other NIH leaders will report on recent efforts and facilitate discussions to explore cross-cutting challenges and opportunities.

To register for this conference, visit: https://go.nih.gov/PINfXMW. People who need reasonable accommodations to participate should email ahurst@scgcorp.com at least 5 days in advance.

Honoring the Healing Totem Pole's Legacy at NLM

In 2011, a striking new addition appeared in the heart of the National Library of Medicine (NLM) grounds: a hand-carved, brightly painted healing totem pole, flanked by carved benches. It quickly became a focal point of the NLM herb garden—an artistic landmark and a spiritual presence that drew admiration and reflection from staff and visitors alike.

The healing totem pole's story began with a vision to celebrate Native American heritage and honor the vital role of tribal communities in advancing medicine, healing and health—and the deep interconnectedness of wellness, illness and cultural life across generations.

Commissioned by NLM, the totem pole was carved by master carver Jewell Praying Wolf James, a member of the House of Tears Carvers of the Lummi Indian Nation in Bellingham, Washington. Each figure carved into the wood—from the sky, the earth and water—represents a story, a lineage and a connection between people, land and spirit.

The healing totem was installed with great care and meaning near the NLM herb garden, a space dedicated to healing plants and traditional knowledge, offering a powerful connection between culture and medicine. Made from red cedar—a wood chosen for its significance and traditional use—the healing totem pole was always intended to return to the earth, following the cycle of life and renewal that is central to many Indigenous worldviews.

After nearly 14 years standing tall in the sun, wind, rain and snow, the healing totem pole and accompanying benches have reached an advanced stage of natural decay. Unfortunately, the rate of deterioration has accelerated in recent years. Safety assessments have determined the structure now poses a risk to staff and visitors who enjoy the NLM herb garden.

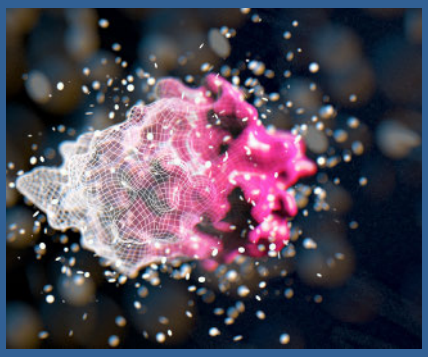
Rather than preserving or relocating the structure, NLM has decided to gently retire the healing totem pole and carved benches to an area adjacent to the garden. The healing totem will be allowed to decay naturally and return to the Earth—a practice rooted in the belief that totems, like all living things, are part of a greater cycle.

This process will be carried out with care, and the approach aligns with the values expressed by the carvers themselves when the healing totem pole was first raised and echoes the spirit of the NLM herb garden it has graced for more than a decade.

While the physical healing totem may return to nature, its legacy will remain part of NLM's story. Photographs, stories and historical materials will continue to be preserved as part of NIH's institutional memory and archives.

This healing totem pole has served as more than a work of art—it has been a symbol of healing, partnership and respect. As we say farewell, we do so with gratitude for the stories it told and the space it held. R

The healing totem pole and carved benches that have graced NLM's herb garden since 2011 will soon be retired, due to decay.



ON THE COVER: *A 3D mediator protein structure, generated from data*

IMAGE: ALAN HOOFRING, DIVISION OF MEDICAL ARTS

The NIH Record

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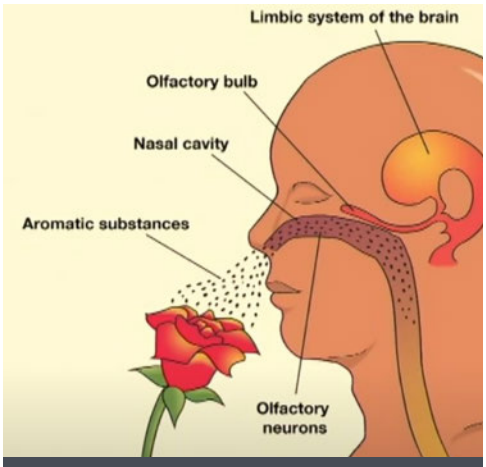
Turning Discovery Into Health

Smell

CONTINUED FROM PAGE 1

In another case, a 70-year-old man reported a declining sense of smell for two years. It could've been normal. Smell tends to decline with age. But four years later, the man developed a tremor and had difficulty speaking. He had Parkinson's disease.

This case illustrates the opportunity to test and diagnose Parkinson's earlier, before the neurologic symptoms develop. Nearly 90% of Parkinson's patients experience smell loss years prior to developing classic motor symptoms, Levy said. In Alzheimer's disease, even early on when cognitive impairments are mild, the majority of patients report a diminished sense of smell.



Perceiving a specific smell involves a system of neural processing between the nose and brain.

When sense of smell works, that sweet (or foul) smell arrives at the nose through chemicals—or, odorants—that we breathe in. In the nose, there's a structure called the olfactory epithelium. The receptors there bind the specific odorants that allow us to distinguish the smell.

From there, the signaling moves to the olfactory bulb up to the brain and to the central nervous system. In the brain, the smell travels through olfactory pathways that include the limbic system, the home of emotion. This helps explain why there can be such strong memory components associated with the sense of smell, noted Levy.

Inside the olfactory epithelium, there are millions of receptors capable of detecting thousands of different odorants. But there are not unique receptors for every odor we smell, explained Levy. Rather, each odorant activates several—sometimes dozens—of receptors, which tell the brain what you're smelling.

Each neuron has the receptor for one specific odorant. "That's important because we believe that one-to-one relationship is disrupted in other forms of disease," he said.

An example of this is a qualitative smell dysfunction called parosmia that can develop after recovering from a viral infection.

"The prevalence of qualitative smell disorders has dramatically increased over the last five years," Levy said, and is a defining symptom in patients with Long Covid.

People with parosmia develop strongly negative perceptions when exposed to a common triggering odor such as shampoo or coffee.

"Imagine waking up one morning to have your favorite cup of coffee but it [suddenly] smells like sewage," Levy said. "Not only that, it has triggered a panic attack and you have to remove yourself from the room."

Treatment for parosmia is limited to supportive care. A new clinical trial, launched by NIH's Smell and Taste Center, is recruiting 80 volunteers to investigate the cause and potentially identify therapeutic targets for future studies.

"We believe [parosmia occurs due to] a miswiring where that one olfactory sensory neuron, maybe because of recovery from viral injury, no longer attaches to the right glomerulus [structure in the olfactory bulb]," Levy hypothesized. "There's a mix-up in the code and [therefore] in the perception of the smell."


Levy speaks at Beyond the Lab lecture in July.

Thanks to research by NIH postdoc Dr. Akshita Joshi, it's now clear that, with parosmia, the brain structurally changes. There's reduced volume of the olfactory bulb, atrophy of cortical regions and reduced connectivity in the pathways through which the brain interprets smell.

"We know that smell is directly connected to memory and emotion, critical for detecting environmental hazards, essential for flavor perception and nutrition, and an emerging biomarker for neurologic health," summarized Levy. So why doesn't it get more attention?

There's a lack of understanding and training in the medical community, said Levy. Sense of smell can be a remote warning sign but doctors either aren't making the connection or are outright ignoring smell as a symptom.

Levy emphasized the need to pay closer attention to loss of smell. "There's a big disconnect in how we're communicating—how we're teaching both each other as clinicians and scientists and—with our patients," he said. "We need to do better."


At the inaugural seminar of the National Smell and Taste Center last year, olfactory investigators and meeting participants gather in Bldg. 35. **PHOTO: CHIA-CHI CHARLIE CHANG**

Lopez-Garcia

CONTINUED FROM PAGE 1

bacteria and eukaryotes. Archaea and bacteria are prokaryotes, meaning they are single-cell organisms that don't contain a nucleus or other membrane-bound organelles. All organisms whose cells contain a nucleus and other membrane-bound organelles are eukaryotes.

López-García and her team travel the world searching for new lineages of these domains. They've taken samples from the deep-sea floor, volcanic hot springs and crater lakes. The more they learn about these lineages, the greater detail they can add to phylogenetic trees.

Bacteria make up most of the microbes on the planet. She studies one group of bacteria called the Candidate Phyla Radiation (CPR). These bacteria have small genomes and depend on other microbes to obtain many essential cellular components to survive.

"CPR bacteria have an important ecological role in controlling the host population size of other bacteria," López-García said.

CPR bacteria are found in a variety of ecosystems, she said. They prefer oxygen-poor environments and are particularly abundant in subsurface aquifers, sediment and soil.

The existence of this group was first discovered in the 1980's. Back then, two scientists were studying microbes in a tiny lake in Catalonia, Spain. Each year, the lake turns a pinkish-purplish color for several months. A microorganism belonging to the purple sulfur bacteria is responsible for the color change.

The scientists took a sample from the lake and observed it under a microscope. They saw smaller bacteria latch onto the purple sulfur bacteria and suck out the cell's components. They named the bacteria *Vampirococcus* after the mythical creature that feeds on the living. This was the first time anyone had observed a bacteria exhibiting this kind of predatory behavior.

More than 30 years later, López-García and her team collected samples from microbial mats from another lake in Spain. The mats contained a type of bacteria that could photosynthesize without producing oxygen. They placed what they brought into tanks in the lab.

A few days later, the bacteria bloomed. They looked at the bacteria under a microscope and, in addition to bacteria that caused the bloom, they found another microbe—one that resembled *Vampirococcus*. They collected the newly discovered bacteria and a genomic analysis revealed the bacteria was also part of the CPR group. They named their discovery *Vampirococcus lugosii* after Bela Lugosi, the actor who played Dracula in the 1931 film of the same name.

The Danakil Depression in Ethiopia

DDPHOTO: KATJA TSVETKOVA/SHUTTERSTOCK

"Vampirococcus is violent. It terminates the bloom of its host rapidly," López-García said.

They since discovered more members of the CPR bacteria group. These findings have allowed them to learn more about the bacteria's biology and mechanisms of action.

López-García's research is also revealing important clues about archaea's evolutionary history. Archaea were initially grouped with bacteria due to their size and shape. In the 1970s, the biologist Carl R. Woese discovered that archaea have genetic and biochemical differences, which justified their classification as an independent domain of life.

At first, there were two groups of archaea known. "We now recognize four major groups of archaea," she said.

Archaea are well known for their ability to live in the world's most inhospitable places. Different groups have adaptations to survive. They can, for instance, tolerate high concentrations of salt, scalding temperatures and acidic conditions.

Some archaea maintain symbiotic relationships with other microorganisms, she said. Their living conditions influence whether they are mutualistic, parasitic or possibly commensal.

To learn more about the types of archaea that live in these extreme ecosystems, López-García collected samples from the Danakil depression in northeast Ethiopia. Sitting at the intersection of three tectonic plates, the depression is a volcanically active region that sits below sea level. It's home to hot springs and lava lakes. Due to its thick salt, deposits coat the depression's bottom.

An analysis of samples taken from hypersaline lakes found that most of the microorganisms living in these salty ecosystems were halophilic archaea. Halophilic describes organisms that thrive in high-salt environments. Her lab also discovered new lineages of halophilic archaea.

Genomic analyses of these organisms have revealed "there are at least four independent adaptations to extreme halophily in archaea," she said.

The phylogenetic information gathered from these samples allows them to produce more and better data to better understand the evolution of archaea that's providing clues to the domain's origin.

López-García is also using genomic information to fill out the phylogenetic tree for eukaryotes, the vast majority of which are unicellular. Only a few of them gave rise to multicellular organisms at some point in their evolutionary history.

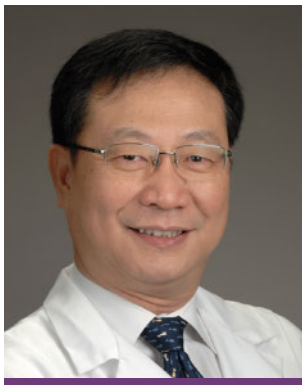
Eukaryotes come in many shapes and sizes, so scientists thought they "more or less knew all of the big groups." But genomic sequencing is revealing new lineages.

The inclusion of these lineages into the phylogenetic tree is shifting scientists' views about eukaryogenesis, the process by which the eukaryotic cell and lineage evolved. López-García posited that the first eukaryotic cells were the result of a symbiotic relationship between an archaeon and at least a bacterium (her syntrophy hypothesis proposes two bacteria involved), where the metabolic products of one partner were used by the other. Her hypothesis is just one of several about how the process occurred. Many open questions remain about how eukaryogenesis took place.

López-García concluded, discovering the origins of eukaryotes "can only be done by integrating these different aspects of the diversity ecology and evolution of microorganisms that have populated the planet for most of the history of the Earth and still dominate today."

NCI's Zhuang Retires

Dr. Zhengping Zhuang, a world-renowned expert in experimental pathology, cancer genetics and cancer therapeutics, retired in June after working at NCI for 32 years.



Dr. Zhengping Zhuang

Throughout his career, Zhuang focused on investigating the role of inherited and somatic mutations in tumor pathophysiology, particularly in tumors of the central nervous system. This work led to the characterization of four genes linked to cancer causation, one of which is associated with a disease now named after him and his colleague. Zhuang has also contributed to biotechnological advancements, drug development and clinical translation of his work in tumor biology.

Zhuang received his M.D. at the Shanghai Jiao Tong University School of Medicine in Shanghai, China. He completed his Ph.D. in pharmacology at Wayne State University in Detroit, Mich., followed by a fellowship at Massachusetts General Hospital. Zhuang then moved back to Michigan, where he completed his residency in transitional medicine at the Henry Ford Hospital, a training program associated with the University of Michigan.

Zhuang served as a research associate at the University of Michigan before coming to NCI in 1993, where he started as a resident in anatomic pathology in the Department of Pathology. He served as a staff pathologist and special expert for the Surgical Neurology Branch for 17 years. In 2017, Zhuang joined the Neuro-Oncology Branch as a senior investigator and head of the Cancer Stem Cell Biology Research Program.

Throughout his career, Zhuang has published more than 400 articles. He co-discovered the role of the menin gene in multiple endocrine neoplasia type 1; the role of the c-MET gene and trisomy in papillary renal cell carcinoma; and the role of the HIF2A gene in a novel tumor-associated syndrome of multiple paraganglioma, somatostatinoma, and polycythemia, a disease now referred to as Pacak-Zhuang syndrome. Recently, he also co-discovered a role for the gene SF3B1 for pituitary prolactinoma. He holds eight patents and has 17 more pending.

In a Q&A with NCI colleagues, Zhuang reflected on his proudest scientist achievement.

"One early invention I'm pretty proud of is a technology called laser capture microscopy (LCM). When we talk about cancer tissue, it's not just cancer cells; you also see all different varieties of vascular cells and immunoreactive cells," he explained. "At the time of my residency training, people just took the whole piece of tissue to do the genetic analysis or protein study. I thought that was inaccurate, so I started thinking about how to develop a technology to separate individual cells in the tissue.

"I developed a tool from a pipette that could be used to isolate tumor cells under a microscope. And then, with Dr. Lance A. Liotta and fellow pathology resident Dr. Michael Emmert-Buck, we developed an automated machine that could isolate cells without having to do everything manually. We started around 1995, and almost 30 years later, it's still very popular."

Zhuang and his colleagues used this tissue microdissection technology to identify several important cancer genes. The research eventually led to having a syndrome named after him and his colleague, Dr. Karel Pacak.That condition, Pacak-Zhuang syndrome, is now taught in medical school. "How often in a lifetime do you get to find a completely new disease and have it named after you?"

In his retirement, Zhuang plans to still work with some labs to continue some research and help train young scientists. He is also working with a Japanese company to develop a high-throughput device that can image-capture a tumor tissue on a film or tape, allow AI to reconstruct the images and create a 3D model.

"I want this machine to go to every hospital, so that pathologists will not have to look at the microscope anymore; they will see 3D images on their computer like CT scans for a radiologist. I'm very excited about this."

To read the full Q&A with Zhuang, see: https://go.nih.gov/VjlO2n0.

Zhuang (front, c) poses with lab members and other NIH colleagues.

NIH Mourns the Passing of Prominent Retrovirologist

Dr. Syed Zaki Salahuddin

Dr. Syed Zaki Salahuddin, who closely collaborated with Dr. Robert Gallo at NIH on his groundbreaking studies of human immunodeficiency virus (HIV), died on July 8 in Ventura, Calif. He was 84 years old.

Salahuddin, born in pre-independence India, graduated from the University of Dacca (now in Bangladesh, then East Pakistan). He then moved to the United States to gain research experience. Salahuddin worked at Walter Reed Army Medical Center before joining Gallo's research team at NIH. He quickly established himself as one of the leading retrovirologists in the country.

It is hard to imagine today how much fear the emergence of an unknown pandemic caused in the early 80s, mainly affecting young men, and almost always being fatal. Physicians and epidemiologists observed that all patients experienced a catastrophic breakdown of their immune systems.

A fierce race among virologists worldwide ensued to identify the cause. French scientists, led by Montagnier at the Pasteur Institute, isolated a new retrovirus from AIDS patients in 1983 and named it Lymphadenopathy-associated virus (LAV), which was later proven to be the cause of AIDS.

At NIH, on Gallo's team, Salahuddin also reported the identification in 1984 of a virus, HTLV III, that caused AIDS. The controversy over which laboratory should be credited with the discovery was resolved when it was demonstrated that the viruses isolated by the two laboratories were identical. A neutral name, HIV, was adopted.

Salahuddin's other research concentrated on human herpesvirus 6 (HHV-6). His numerous publications on HHV-6 and similar viruses helped clarify their roles in various clinical scenarios, including AIDS and other viral infections.

Salahuddin left NIH in the late 1980s and moved to California, where he founded the California Institute of Molecular Research. In his free time, he pursued painting as a hobby. Later in life, he rediscovered his spiritual heritage and began regularly attending religious services at a mosque in Ventura.

—**Syed Amir**, who retired from NIH's Center for Scientific Review in 2010

Beta-HPV Can Cause Skin Cancer

Ulcer on neck with suspicion of squamous cell carcinoma

PHOTO: CASA NAYAFANA/SHUTTERSTOCK

NIH researchers have shown for the first time that a type of human papillomavirus (HPV) called beta-HPV commonly found on the skin can cause a form of skin cancer called cutaneous squamous cell carcinoma (cSCC) when certain immune cells malfunction.

cSCC is one of the most common cancers in the U.S. and worldwide. Previously, scientists believed HPV facilitated the accumulation of DNA mutations caused by ultraviolet (UV) radiation, the primary driver of cSCC. The findings were published in *The New England Journal of Medicine.*

NIH researchers made their discovery in a 34-year-old woman who came to the NIH Clinical Center for evaluation and treatment of recurrent cSCC on her forehead. She had undergone multiple surgeries and a round of immunotherapy to try to kill the tumor, but it repeatedly grew back. The tumor was one of many progressively worsening HPV-related diseases the woman was experiencing.

The researchers analyzed her genome and discovered a beta-HPV had integrated into the tumor DNA and was producing viral proteins. This contradicted the prevailing theory that beta-HPV facilitates the establishment of cSCC without integrating into cellular DNA and plays no role in maintaining the cancer. Further genetic analysis of the woman's cells showed they were capable of repairing DNA damage from UV radiation, suggesting the virus alone had caused cSCC.

The investigators found her genetic mutations hampered T cells from activating in response to skin-cell infection by beta-HPV, suggesting the immune disorder itself was responsible for the woman's worsening HPV-related diseases, and that treating this disorder might cure all of them.

NIH investigators gave the woman a stem cell transplant to replace her defective T cells with healthy ones. After, all her HPV-related diseases including the recurrent, aggressive cSCC resolved and have not recurred since the transplant. This confirms the woman's inherited disorder had prevented her T cells from keeping beta-HPV in check, allowing the virus to directly cause and sustain cSCC.

The study finding suggests other people with defective T-cell responses may also be susceptible to cancer caused directly by beta-HPV.

Researchers Develop New Brain Scanner

A scientific team supported in part by NIH has developed a new, ultra-high-resolution brain imaging system that can reconstruct microscopic brain structures that are disrupted in neurological and neuropsychiatric brain disorders. The new system is a significant advance over conventional magnetic resonance imaging (MRI) scanners that cannot visualize these tiny but clinically important structures.

The system, called the Connectome 2.0 human MRI scanner, overcomes a significant hurdle for neuroscientists: to bridge different brain regions and probe tiny structures necessary to define the "connectome," the complex matrix of structural connections between nodes in the nervous system, and to do it noninvasively in living humans.

The scanner is innovative in two major ways: it fits snugly around the heads of living people and it has many more channels than typical MRI systems. These advances greatly increase the signal-to-noise ratio of the system, providing much sharper images of very small biological brain structures than previously possible. These technical upgrades will enable scientists to map human brain fibers and cellular architecture down to nearly single-micron precision to study how subtle changes in cells and connections relate to cognition, behavior and disease.

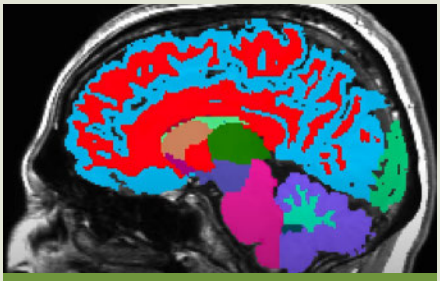
In addition, the team showed the scanner was safe in healthy research volunteers, revealing subtle microstructural differences (individual axon diameter or cell size) between individual brains. Before this new system, this was only feasible in postmortem or animal studies.

This work is an important step toward developing a complete wiring diagram of the brain. It also opens the door for future advances in precision neuroscience, in which noninvasive brain stimulation may help treat brain disorders tailored to an individual's unique brain circuitry.

The research was funded in part by The BRAIN Initiative®. It supports the BRAIN Initiative Connectivity Across Scales (BRAIN CONNECTS) program, which aims to develop the research capacity and technical capabilities to generate wiring diagrams that can span entire brains across multiple scales. The findings were reported in *Nature Biomedical Engineering.*

Measuring Aging with Brain Scans

Many past attempts to measure biological age relied on biomarkers that capture various aspects of a person's health. A chemical change to DNA called methylation is now the most widely used method for measuring differences in aging.



Researchers develop a tool to measure aging and predict future risk of dementia.

IMAGE: ETHAN WHITMAN/DUKE UNIVERSITY

In a new study, researchers at Duke University developed a tool to measure aging based on a single brain scan. Their findings were reported in *Nature Aging.*

The researchers built their new tool on the foundations of their previous breakthroughs. Using data from the Dunedin study, they first developed a method to measure biological aging called the Pace of Aging, which measures the decline in function over time of 19 health-related biomarkers. Next, they found a way to correlate DNA methylation patterns at a single time point with the Pace of Aging measure. They called this measure DunedinPACE. However, it depends on having DNA methylation data, which many neuroscience aging studies do not collect. In their new study, the researchers aimed to capture aging rates from brain images instead.

The team used MRI scans collected from participants in the Dunedin study. They used those images and their earlier data on declining function over time to develop a model for measuring aging rates from brain scans alone. They call their new measure, which uses 315 structural measures in the brain scans, Dunedin Pace of Aging Calculated from Neuroimaging (DunedinPACNI).

DunedinPACNI predicted aging rates with similar accuracy to past tests of DNA methylation. Higher DunedinPACNI scores were associated with declining physical and cognitive function as well as facial aging.

The tool can also measure aging rates in other groups of people. DunedinPACNI accurately predicted cognitive impairment, faster brain atrophy and dementia. Higher DunedinPACNI scores also predicted physical frailty, poor health, future diseases and mortality.

While more study is needed before the test could be used in the clinic, it could ultimately help to identify those at greater disease risk to allow for increased monitoring and earlier interventions.

Above l, local news outlets covered Santa's summertime visit to the Children's Inn at NIH. Above r, an Inn family shows off their toy haul at the day's "Shop with a Cop" event. Below, Inn residents and officers ride the carousel at Rio.

Children' Inn Celebrates Christmas in July

PHOTOS: CHILDREN'S INN AT NIH

The Children's Inn at NIH brought a dose of holiday cheer in the heat of summer by welcoming Santa Claus and his motorcycle elves for its annual Christmas in July celebration.

On July 16, the NIH Police Department joined the Montgomery County Police Department to escort Santa's motorcade through the county to the Inn. Once there, they picked up families and departed for a fun afternoon at the Rio Lakefront shopping center.

While at Rio, the families rode the carousel and then met officers for a "Shop with a Cop" event at Target. Each child received a gift card to shop for toys and other gifts. Each family was paired with an officer from Montgomery County. Many residents shopped not only for themselves but also for friends and family. Afterward, they ate dinner at Silver Diner and then enjoyed gelato pops for dessert.

The Inn is a residential "Place Like Home" for families with children, teens,and young adults participating in leading-edge research studies at the NIH Clinical Center. While the NIH takes care of the child's medical needs, the Inn tends to the child's heart, soul and spirit.

Officers from the Montgomery County Police Department joined Inn families for the "Shop with a Cop" event at a store in Rio.