

Immunotherapy Pioneer Tells All

Steven A. Rosenberg, M.D., Ph.D.

BY EMILY PETRUS, NINDS

STEVEN ROSENBERG IS WIDELY considered the father of cancer immunotherapy. His 40-year scientific journey has led to an explosion of immunotherapy treatments for numerous cancer types both at the NIH and across the globe.

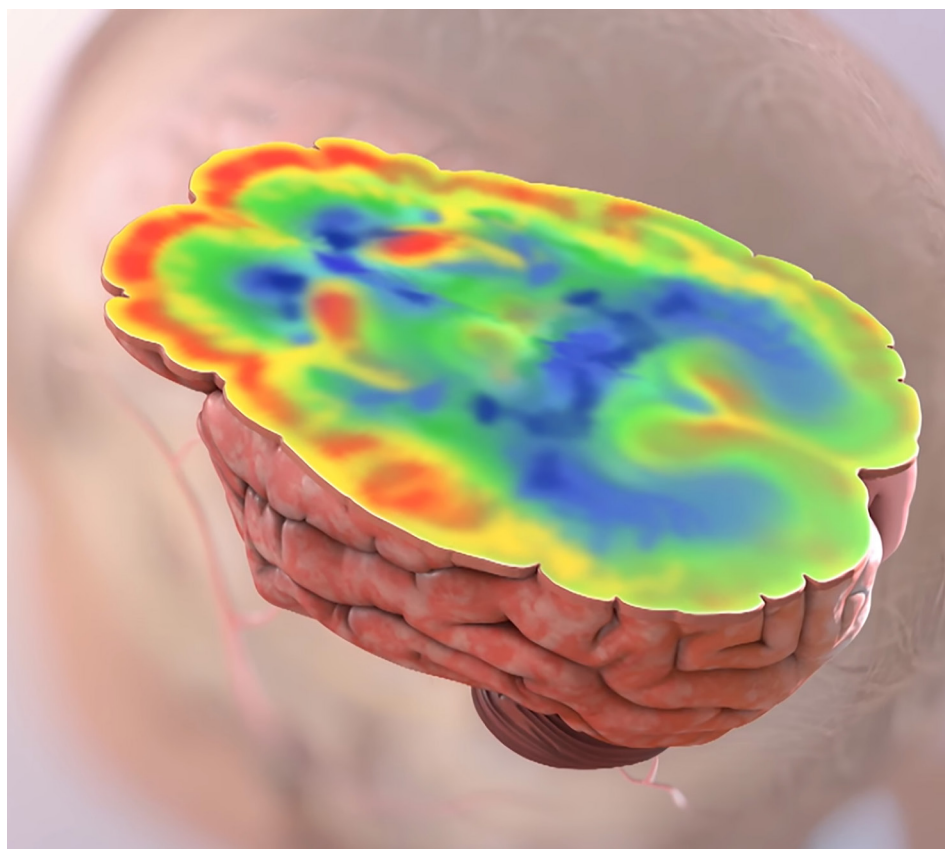
His journey began when he witnessed one of the rarest events in medicine—the spontaneous regression of a tumor. Early in his career, he had encountered a young man whose cancer had disappeared. Rosenberg, who’s now the chief of surgery in the National Cancer Institute (NCI), believed that the answer had to lie in the patient’s own immune system.

Rosenberg started his pioneering work on immunotherapy in the late 1970s when almost nothing was known about T lymphocyte function in cancer and there was no convincing evidence that any immune reaction existed in patients against their cancer. Shortly after the description of a T-cell growth factor now called interleukin 2 (IL-2), Rosenberg began studies of the ability of IL-2 to generate cells with anti-cancer activity in the laboratory and in tumor-bearing mice.

In a series of clinical trials based on these findings, he injected IL-2 or cells grown in IL-2 into patients with advanced cancer who had progressed through all available therapies. In the first 66 patients with metastatic cancer in whom the

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Higher Brain Glucose Levels May Mean More-Severe Alzheimer Disease



NIH scientists found potential connections between problems with how the brain processes glucose and Alzheimer disease: glucose processed normally (red); glucose processed poorly (blue) so there’s excess in some areas of the brain.

SCIENTISTS HAVE FOUND A CONNECTION BETWEEN ABNORMALITIES IN HOW THE BRAIN breaks down glucose and the severity of the signature amyloid plaques and tangles in the brain, as well as the onset of eventual outward symptoms, of Alzheimer disease. The study was led by researchers at the National Institute on Aging.

READ MORE ABOUT THIS AND OTHER RESEARCH BRIEFS ON PAGE 8

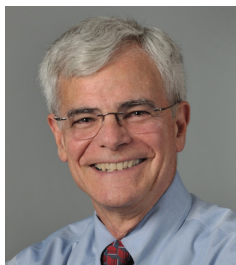
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Of Assays and Surveys:

Tools to Inform Decision-Making

BY MICHAEL GOTTESMAN, DDIR

FOR BASIC SCIENTISTS AND CLINICIANS, reproducible, accurate, and sensitive assays are the gold standard for evaluating *homogenous* populations of molecules. For social scientists and administrative decision-makers, surveys are the gold standard for evaluating information from *heterogeneous* populations of people. Assays can yield accurate data based on a relatively small sample of homogeneous molecules.

Surveys, however, can only yield useful data if they are based on larger samples of heterogeneous populations.

Biostatisticians tell us that a 10 percent truly random sample is a good representation of the response of an entire large population. The problem is that it is very difficult to achieve random samples in all substrata of a large population. So we must rely on a high response rate in order to obtain meaningful information to inform decision-making.

This argument is not purely theoretical. At the NIH we make decisions at all levels that profoundly affect the organization's mission and the conduct of science here. We need to have input from all our NIH workforce to make informed decisions. One of the ways to obtain such input is through surveys. But all too often, staff either ignore the surveys we send or cannot find time to respond to them. I will promise to limit the number of surveys

that we send broadly to NIH staff if you promise to respond to the best of your ability to those surveys we do send out.

Let me illustrate the importance of this request with a few examples:

- Each year the federal government asks you to fill out the Federal Employees Viewpoint Survey (FEVS). The survey results help us determine whether work conditions at the NIH match your

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expectations and, more specifically, identifies areas in need of remediation. For example, several years ago, the FEVS results emphasized the need for programs that increase work-life balance (such as flexible work hours and telework). In consequence, NIH now has a very robust program in these areas.

- The NIH is assembling an important survey on workplace climate and harassment, including sexual harassment. You will receive it later this winter or early spring. The results will have a profound impact on the programs we develop to ameliorate unacceptable situations. Please participate fully.

- Recently, the Assembly of Scientists sent out a survey asking its constituents to comment on the relative importance of many of the challenges faced by scientists at the NIH. The responses will be used to limit, insofar as possible, some of the administration burdens faced by our scientific and clinical investigators.

- Under the direction of the Women Scientists Advisors, a survey was created to assess the experiences of our postdoctoral fellows. The fellows will fill out the survey when they check out through the Foundation for Advanced Education in the Sciences (FAES). The results will help us understand the factors affecting career decisions by our fellows.

I am well aware that some of the surveys are complex and lengthy (in some cases this approach is needed to verify the statistical accuracy of the responses), but we cannot get an overall view of your circumstances unless everyone is willing to take some time to complete the surveys. The result will be more informed decision-making and more effective NIH management.

As always, your comments will be appreciated. ●

New NIMHD Scientific Director: Anna María Nápoles, Ph.D., M.P.H.

Nápoles Is NIH's First Latina Scientific Director



EDGAR DEWS III, NIMHD

Anna María Nápoles, who was a professor and behavioral epidemiologist at the University of California at San Francisco, was recently appointed scientific director for the National Institute on Minority Health and Health Disparities.

THE NATIONAL INSTITUTE ON MINORITY Health and Health Disparities (NIMHD) announced the appointment of **Anna María Nápoles** as the scientific director (SD) of its Division of Intramural Research, making her the first Latina named to an SD position at NIH. Before coming to NIH, Nápoles was a professor and behavioral epidemiologist in the Division of General Internal Medicine, Department of Medicine, at the University of California at San Francisco (San Francisco), where she worked from 2001 until her move to NIH.

NIMHD supports intramural and extramural research on minority health and health disparities. One of the greatest challenges is reducing the profound disparity in the health status of the country's racial and ethnic minority, rural, low-income, and other underserved populations. Through the NIMHD's leadership, over the past decade,

health disparities research has become a recognized scientific field of study.

Nápoles has been at the forefront of developing methods for an underserved community to be engaged in translational research to improve its own health. Her work involves building the capacity for the community to deliver culturally suitable, evidence-based, behavioral interventions. She brings more than 25 years of experience in research on patient-clinician communication, cancer-control health disparities, psycho-oncology, and community-based models of research in racially, ethnically, and socioeconomically diverse populations. She has served as a scientific advisor to many NIH- and non-NIH-funded research projects, advising on the use of advanced qualitative and quantitative methods for studying complex sociobehavioral processes that affect the health of underserved populations. After NIH conducted an extensive national search for this appointment, Nápoles began her appointment on November 13, 2017.

"Her breadth of knowledge and notable scientific contributions are exactly what NIMHD needs to meet the challenges of the ever-evolving health-disparities environment for all racial and ethnic minorities," said NIMHD Director **Eliseo J. Pérez-Stable**. "Anna is the embodiment of one of the NIMHD intramural research program's major objectives, which is to add to the diversity of individuals and research disciplines in the NIH intramural program."

In her new role, Nápoles is using the robust basic-science environment at NIH to focus on population health with an emphasis on social, behavioral, and clinical research. She will also oversee the executive direction and scientific leadership for the entire intramural research program

at NIMHD. In addition, she will continue her own research—using lay health workers and mobile health applications—on the effectiveness of stress management and physical activity interventions for underserved cancer patients.

Nápoles holds a bachelor's degree in psychology from Pomona College (Claremont, California) and a master's in public health and a Ph.D. in epidemiology from the University of California at Berkeley (Berkeley, California). In 2003 and 2005, she received the Rising Star in Cancer Research Award from the Redes En Acción Network, and she is a 2016 Susan G. Komen Scholar. ●

IRP WEBPAGE

Highlights of what you'll find on the Intramural Research Program (IRP) webpage (<https://irp.nih.gov>)

- Research resources: <https://irp.nih.gov/our-research/research-resources>
- Principal Investigators: <https://irp.nih.gov/our-research/principal-investigators>
- Accomplishments: <https://irp.nih.gov/accomplishments>
- Research in Action: <https://irp.nih.gov/our-research/research-in-action>
- Hot Papers: <https://irp.nih.gov/news-and-events/hot-papers>
- "I Am Intramural" Blog: <https://irp.nih.gov/blog>
- Careers: <https://irp.nih.gov/careers>
- Research Training: <https://irp.nih.gov/research-training>
- And much more

From the Fellows Committee

NIH Does Fitness

BY CRAIG MYRUM, NIA

BEING A TRAINEE CAN BE TOUGH AT times. We need to be able to balance an overwhelming number of tasks including lab meetings, research, writing, keeping up to date with the literature, mentoring, teaching, and attending conferences. While we know that time for fitness and wellbeing should be prioritized, they are often the first to fall by the wayside when time is limited. To help you with that, the NIH “takes its own best advice” by turning to a fitness and wellbeing program to promote and cultivate health, happiness, and productivity across its campuses.

Fitness and wellbeing can be many things to different people, so you should choose activities that work for you. “You should always make sure your fitness activities are fun!” said **Shuntrice Holloman**, program specialist for the NIH Fitness and Wellbeing Program. “You can do fun activities like taking a dance class, hiking, [or] bowling. If you’re not enjoying your physical activity, it is likely you will be inconsistent.”

For busy individuals looking for an opportunity to participate in fitness activities at NIH, the Recreation and Welfare (R&W) Fitness Center offers free “Fitness for You” classes monthly. The Fitness Center can bring customized fitness classes to your organization based on what would be a good fit for your office. In addition, the Fitness and Wellbeing Program partners with institutes and centers to promote other wellness and fitness activities. For example, in September, The Fitness and Wellbeing Program partnered with the National Center for Complementary and Integrative Health (NCCIH) to observe “National Yoga Month” through lectures and yoga sessions.

Besides physical wellbeing,



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opportunities also exist at the NIH to cultivate a more holistic view of wellness. For example, the Office of Intramural Training and Education’s Mindfulness Meditation Group offers two hour-long weekly drop-in sessions for novices and experts alike to slow down and connect with yourself (https://www.training.nih.gov/mindfulness_meditation_group). These sessions are gaining in popularity.

At the NIH campus in Baltimore, postbaccalaureate fellow **Kevin Stieger** recently established a mindfulness meditation group. Like many of us, Stieger felt anxious and overwhelmed in college. “I didn’t really know what mindful meditation was, but I thought I wanted to try it out,” he said. “Through meditation, I’ve since gotten better at recognizing negative emotions like anxiety and stress. Instead of reacting and letting them take over, I can experience them as a feeling and let them pass. My goal is for people to come by and learn the basic principles of mindfulness meditation so that they too can start their own practice and have a group to discuss their experiences.”

Make your fitness goals S.M.A.R.T.! S.M.A.R.T. means your fitness goals should be specific, measurable, attainable, relevant, and timely.

- **Specific:** Your goals should be clear and easy to understand. A common goal is to “get healthy” such as starting an exercise program, stopping smoking and losing weight.

- **Measurable:** A goal to “lose weight” is not enough. How you track your weight loss is measurable such as losing one pound per week.

- **Attainable:** Goals should be set high, but they must also be realistic. For example, if you are new to running, having a goal to run a marathon in two months will set you up for failure and pain.

- **Relevant:** Set goals that are important to where you are currently. Do not set a goal that someone else is pressuring you attain.

- **Time-bound:** Make sure each goal has a specific time frame for completion. This allows you to easily determine if your goal has been achieved.

“Fellows may not be aware of the wide range of fitness and wellbeing activities we offer to NIH staff,” said Holloman. “It is one of our goals to bring more awareness to our program and services.”

Be creative this New Year! Try a free “Fitness for You” class or any other wellbeing activities offered at NIH. Remember fitness and wellbeing should be tailored and relevant to your goals. ●

For more information, visit <https://wellnessatnih.nih.gov/Pages/default.aspx>. To join the NIH Wellness LISTSERV and get updates on upcoming activities and fitness tips, go to <https://list.nih.gov/cgi-bin/wa.exe?AO=wellnessnih>.

Special to the Training Page

Getting the Best of Both Worlds with Data Journalism

BY HUSSAIN ATHER, NIDDK

IVARY/THINKSTOCK.COM



IT'S GREAT WHEN YOU FIND AN opportunity that provides the best of both worlds. As a postbaccalaureate researcher at NIH, I work with big data. I'm also a writer in my spare time. Last fall, I attended the 2017 World Conference of Science Journalists in San Francisco and discovered the perfect way to explore both of my interests: data journalism. It involves the finding, collecting, and analyzing of data to create compelling news stories.

At the conference, I attended a workshop on "Data Journalism in R" (R is a programming language), which was led by science writer and *BuzzFeed News* reporter Peter Aldhous. He also teaches journalism courses at the University of California, Santa Cruz (Santa Cruz, California) and the University of California, Berkeley (Berkeley, California) and his work has included machine learning, mapping, data visualization, and processing geographic data.

Aldous described how he has used the popular open-access programming language, R, to analyze data for his stories. For example, in his 2010 *New Scientist* article on a pharmaceutical company's payments to censured doctors, he used R to match doctors in four

states—California, Texas, New York, and Florida—against the company's records of payments to doctors and medical researchers. For another article, R helped him illustrate the pervasiveness of infectious diseases in lower-income countries. R has also been used to create graphics to visualize life expectancy at birth and gross domestic product per capita to understand disparities among countries or regions of the world.

He taught us about analyzing different file types, installing software packages, making graphics, and exporting files. He explained the technical specifics and jargon of the computer-science world in a way anyone could understand. Aldhous also talked about using data to create maps to visualize the damage done by Hurricane Harvey, the path of the August 2017 solar eclipse, and nationwide access to health care.

We even practiced using R and constructing graphs to visualize trends. With my experience in programming, I found the workshop projects relatively easy to complete. When I realized the similarities between the work of data journalists and that of data scientists, I was surprised at how much my scientific skill set of programming could translate into another field such as journalism.

The workshop gave me a new appreciation for science writing. The way writers like Aldhous can take advantage of statistics, network analyses, and other resources helped me realize how science writers can take advantage of whatever they have available to them in crafting stories. From the nuance of each graph to the overall idea of each story, data journalists understand how to get their messages across. ●

DEMYSTIFYING MEDICINE

Tuesdays, Jan. 9–May 8, 2018, 4:00–6:00 p.m.
Conf. Rm. 1227, Building 50 (unless noted otherwise)

Videocast live and archived online at <https://videocast.nih.gov/default.asp>.

To sign up and for more information, go to <https://demystifyingmedicine.od.nih.gov>.

Partial schedule:

January 9: "New Viral Diseases, Universal Vaccines, and Removing Agents from the Blood Supply" (Anthony S. Fauci, MD, NIAID; Robert Allison, MD, MPH, CC)

January 16: "Is Leukemia Curable?" (Terry Frey, MD, NCI; Nirali Shah, MD, NCI)

January 23: "Sexually Transmitted Diseases: Situation Getting Worse...and Also Better" (Thomas Quinn, MD, NIAID/Johns Hopkins Bloomberg School of Public Health; Douglas Lowy, MD, NCI)

January 30: "Why Is HIV Still a Biologic and Epidemiologic Challenge Worldwide?" (John Coffin, PhD, Tufts/NCI; John Mellors, MD, University of Pittsburgh)

February 6: "The New Frontier: Immunotherapy of Cancer" (James Gulley, MD, PhD, NCI; James Hodges, PhD, MBA, NCI) *Lecture will be held in Building 1, Wilson Hall

February 13: "Does Inflammation Cause Cardiovascular Disease? If So, How?" (Alan Remaley, MD, PhD, NHLBI; Nehal Mehta, MD, NHLBI)

February 20: "The Microbiome in Man, Animals, and Disease: Where Do We Stand?" (Yasmine Belkaid, PhD, NIAID; Barbara Rehermann, MD, NIDDK)

February 27: "The Great Neglected Diseases" (Alan Sher, PhD, NIAID; Thomas Nutman, MD, NIAID)

March 6: "Diabetes and Artificial Sweeteners" (Phillip Gorden, MD, NIDDK; Kristina Rother, MD, NIDDK)

March 13: "Brave New World: Imaging from the Cosmos to the Molecule" (John Mather, PhD, NASA; Jennifer Lippincott-Schwartz, PhD, MS, HHMI, Janelia Research Campus)



NIH Develops Toolkit for Enhancing Scientific Workforce Diversity

BY ALISON DAVIS, OD

WORKFORCE DIVERSITY IS IMPORTANT for many reasons, one of which is to engage diverse perspectives in creating practical solutions, without which we can encounter serious problems.

For example, when YouTube's almost entirely right-handed developer team built an iOS app without considering how left-handed people would use it, as many as 10 percent of videos were uploaded upside down!

Diversity promotes increased scrutiny of a problem, opening the door to a multitude of solutions made possible by a heterogeneity of experiences.

Workforce diversity contributes directly to problem solving by inviting varied thoughts, experiences, and abilities. Research shows that such cognitive diversity may not only reflect racial, ethnic, and gender diversity but also differences in geographic and life

experiences and in scientific interest.

Yet the country's scientific workforce and NIH still lack diversity, especially at the level of faculty, thus limiting our potential for innovation and relevance. Fortunately—according to the National Science Foundation survey of earned doctorates—the pool of scientists from diverse backgrounds has grown substantially over the past few decades: The number of biomedicine-relevant Ph.D.s earned by individuals from underrepresented groups has increased by about 60 percent since 1996.

The NIH Scientific Workforce Diversity (SWD) office has created an integrative strategy for enhancing scientific workforce diversity that will help NIH institutes and centers to identify, recruit, and advance scientists from underrepresented groups ready to pursue today's biomedical challenges.

NIH staff can learn about this strategy by using a free, downloadable interactive toolkit. Through text-based information, informative weblinks, video, and an extensive citation library, the toolkit provides users with evidence-based interrelated activities developed and implemented by SWD. These include methods to expand diversity of candidate pools, proactive outreach approaches, strategies for mitigating bias in search processes, and tips on developing and sustaining mentoring relationships.

The toolkit details a search recruitment protocol developed by SWD in concert with the NIH library. This protocol guides users through readily available online search techniques and proactive outreach approaches that broaden and deepen candidate pools. Also central to enhancing diversity is understanding, and mitigating, the impact of implicit bias throughout the process of identifying and hiring scientific talent. The SWD toolkit describes multiple ways to approach this sociocultural issue that is common across sectors and not limited to science and medicine.

Finally, toward addressing inclusion—a key factor for retaining talent—the toolkit presents an up-to-date view of the value of fostering mentoring relationships. Strategies and resources presented go beyond the traditional mentor-mentee dyad and have been proven to enhance career satisfaction and productivity. ●

For more information and to download the toolkit, visit <https://diversity.nih.gov>, or contact SWDToolkit@od.nih.gov.

Fabricators Move from ORS to ORF

BY ERIC BOCK, OD (ADAPTED FROM AN ARTICLE IN THE DECEMBER 1, 2017 *NIH RECORD*)

WHERE DO NIH SCIENTISTS GO WHEN they need custom instrumentation, equipment design, fabrication, or modification services? For the past 35 years, the Mechanical Instrumentation Design and Fabrication Branch in the Office of Research Services' (ORS) Division of Scientific Equipment and Instrumentation Services (DSEIS) has provided these services to campus researchers.

On October 1, 2017, the design and fabrication services moved from ORS to the Office of Research Facilities (ORF). DSEIS, however, will continue to provide equipment sales, rental, maintenance, and repair services.

The fabricators are “experts at their craft,” said former supervisor **Jerry Tyus**. Everything they make is a one-of-a-kind piece to help scientists conduct experiments and contribute to innovative research.

One of the fabricators, **Howard Metger**, has worked there since 2004. Before that, he was with the Department of Defense and the National Institute of Standards and Technology (NIST). At NIST, he and his

co-worker **Robert Clary** (now at NIH) helped design and build the display cases for the Declaration of Independence, the Constitution, and the Bill of Rights at the National Archives in Washington, D.C.

These days, Metger and his co-workers help researchers, scientists, and surgeons design or modify metal and plastic devices. Often, customers come in and describe a problem to him and he finds a solution. Recently, the branch built devices that house animals, separate blood, and support a knee.

The branch regularly saves researchers money. In one instance, a scientist needed a replacement screw for a microscope. She came to Metger after she learned the device's manufacturer didn't have any replacements. The researcher would have had to buy another microscope. Metger looked at the screw and started working. “In 10 minutes, we saved NIH \$20,000,” he explained.

NIHers can procure fabrication services by completing a maintenance service request online or by phone. For more information, visit <https://www.orf.od.nih.gov/Property-Management/MaintenanceServiceRequests/Pages/default.aspx>. ●

BTRIS

BY MANJU BHASKAR, NINDS

BTRIS — THE BIOMEDICAL Translational Research Information System—is a resource available to the NIH intramural community that brings together clinical research data from the Clinical Center and other NIH institutes and centers. BTRIS provides clinical investigators with access to identifiable data for subjects on their own active protocols. It also gives all NIH investigators access to data without personal identifiers across all protocols. Data are available from 1976 to the present and includes laboratory results, vital signs, radiologic reports (with links to radiographic images), medication-administration data, and clinical documents. BTRIS provides users with advanced search, filtering, and aggregation methods to create datasets to support ongoing studies and to stimulate ideas for new research. Also, many types of reports can be easily produced with a user-friendly series of prompts.

Under the leadership of **Jose Galvez**, who has been chief of BTRIS since July 2016, BTRIS is getting even better. He intends to provide access to data analysis using various tools such as programming languages R and Python in a more-secure environment. As BTRIS continues to develop, new report features data from new sources and will be added.

“Our primary objective is to make BTRIS a more user-friendly interface,” said Galvez. “In the near future we will be upgrading the server to include data-analysis tools to help researchers obtain the data in desired and usable forms.” ●

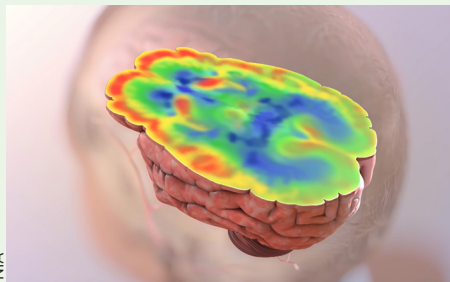
For more information and how-to videos, visit <https://btris.nih.gov>. Galvez plans to revive the BTRIS Scientific Interest Group soon, too.



ERNIE BRANSON

Howard Metger is one of the fabricators who designs and customizes scientific equipment and devices.

Intramural Research Briefs



NIA

NIA: Scientists found potential connections between problems with how the brain processes glucose and Alzheimer disease: glucose processed normally (red); glucose processed poorly (blue) so there's excess in some areas of the brain.

NIA: HIGHER BRAIN GLUCOSE LEVELS MAY MEAN MORE-SEVERE ALZHEIMER DISEASE

For the first time, scientists have found a connection between abnormalities in how the brain breaks down glucose and the severity of the signature amyloid plaques and tangles in the brain, as well as the onset of eventual outward symptoms, of Alzheimer disease. The study, led by NIA researchers, involved looking at brain tissue samples at autopsy from participants in the Baltimore Longitudinal Study of Aging (BLSA), one of the world's longest-running scientific studies of human aging.

Researchers measured glucose concentrations in different brain regions, some of them vulnerable to Alzheimer-disease pathology, such as the frontal and temporal cortex, and some that are resistant, such as the cerebellum. They analyzed three groups of BLSA participants: those with Alzheimer symptoms during life and confirmed at death; healthy controls; and individuals without symptoms but with Alzheimer pathology found post mortem. The researchers found distinct abnormalities in glycolysis: Lower rates of glycolysis and higher brain glucose concentrations correlated to more-severe plaques and tangles found in the brains of people with the disease. (NIA authors: Y. An, V.R. Varma, C.W. Chia, J.M. Egan, L. Ferrucci, and M. Thambisetty, *Alzheimers Dement* DOI:<https://doi.org/10.1016/j.jalz.2017.09.011>)

NIAID: INFECTIOUS PRION PROTEIN FOUND IN SKIN OF CJD PATIENTS

NIAID scientists and collaborators at Case Western Reserve University School of Medicine (Cleveland) have detected abnormal prion protein in the skin of nearly two dozen people who died from Creutzfeldt-Jakob disease (CJD). The scientists also exposed a dozen healthy mice to skin extracts from two of the CJD patients, and all developed prion disease. The study results raise questions about the possible transmissibility of prion diseases via medical procedures involving skin and about whether skin samples might be used to detect prion disease. The researchers stressed that the prion-seeding potential found in skin tissue is significantly less than what they have found in studies using brain tissue. (NIAID authors: C.D. Orrú, B.R. Groveman, and B. Caughey, *Sci Transl Med* 9:eaam7785, 2017; DOI:10.1126/scitranslmed.aam7785)

NINDS, NCATS: HIBERNATING GROUND SQUIRRELS PROVIDE CLUES TO NEW STROKE TREATMENTS

Like people suffering from ischemic strokes, ground squirrels experience dramatically reduced blood flow to their brains when they hibernate, depriving cells of life-sustaining oxygen and glucose. Yet the squirrels awaken with no ill effects because they rev up a neuroprotective pathway called SUMOylation during their extended naps. A team of NINDS researchers and NIH-funded scientists has recently identified a potential drug—ebselen—that could grant the same resilience to the brains of ischemic-stroke patients by mimicking the cellular changes that protect the brains of the squirrels. (NINDS authors: J.D. Bernstock, D.Ye, Y.-J. Lee, and J.M. Hallenbeck; NCATS authors: A. Yasgar, J. Kouznetsova, A. Jadhav, W. Zheng, and A. Simeonov, *FASEB J* DOI:10.1096/fj.201700711R)

[BY BRANDON LEVY, NINDS]

NIDA: SAFE FOR MOTHERS TO BREASTFEED WHILE BEING TREATED FOR OPIOID ADDICTION

Scientists at NIDA investigated the safety of breastfeeding when new mothers are taking buprenorphine, a medication used to treat opioid addiction. Although there are many known benefits of breastfeeding for women and infants, there was little evidence about the concentration and activity of buprenorphine in human breast milk. Using liquid chromatography–mass spectrometry, researchers measured the concentrations of buprenorphine and its metabolites in human breast milk and maternal plasma in 10 buprenorphine-managed mothers. In addition, plasma samples were taken from nine infants when they were 14 days old. The results indicated that buprenorphine concentrations are low in the breast milk and blood of the mothers and low or undetectable in the breastfed infants. The study's findings support the recommendation that it is safe for women to breastfeed while maintaining buprenorphine treatments. Further study is needed, however. (NIH authors: M.J. Swortwood, A.J. Barnes, and K.B. Scheidweiler, *J Hum Lact* 32:675–681, 2016; DOI:10.1177/0890334416663198)

[BY CLAIRE MCCARTHY, NCI]

NIEHS: PUTTING THE BRAKES ON PROTEIN PRODUCTION

New research from NIEHS scientists suggests that intragenic enhancers, which occur within genes rather than outside genes, act like brakes to slow transcription of the gene. The scientists showed that deletion of intragenic enhancers increases the expression of the host gene and can alter cell fate, with important implications. Enhancer mutations are associated with many types of cancer; the research is aimed at determining whether any cancers involve the activation of a cancer-causing gene due to the loss of the enhancer-mediated suppression function. Alternatively, if

the protein in question prevents tumor growth, then having less of it may increase the risk of developing cancer. According to the researchers, the discovery of an unanticipated role for enhancers will break new ground in the field of transcription and alter the conventional view of enhancers as transcriptional activators. (NIEHS authors: S. Cinghu, P. Yang, J.P. Kosak, A.E. Conway, D. Kumar, A.J. Oldfield, K. Adelman, and R. Jothi, *Mol Cell* 68:104–117.e6, 2017)

[BY ROBIN ARNETTE, NIEHS]

NICHD: EXPOSURE TO AIR POLLUTION IN EARLY PREGNANCY MAY BE LINKED TO MISCARRIAGE

Exposure to common air pollutants, such as ozone and fine particles, may increase the risk of early pregnancy loss, according to a study by NICHD scientists. Researchers followed 501 couples attempting to conceive between 2005 and 2009 in Michigan and Texas. The investigators estimated the couples' exposures to ozone based on pollution concentrations in their residential communities. Of the 343 couples who achieved pregnancy, 97 (28 percent) experienced an early pregnancy loss—all before 18 weeks.

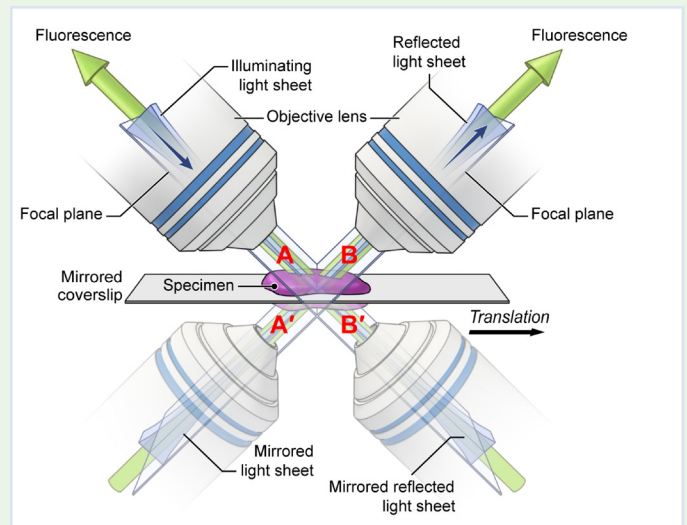
Couples with higher exposure to ozone were 12 percent more likely to experience an early pregnancy loss, whereas couples exposed to particulate matter (small particles and droplets in the air) were 13 percent more likely to experience a loss. The researchers do not know why exposure to air pollutants might cause pregnancy loss, but it could be related to increased inflammation of the placenta and oxidative stress, which can impair fetal development. More research is needed to confirm this association. (NICHD authors: S. Ha, R. Sundaram, G.M. Buck Louis, C. Nobles, I. Seeni, and P. Mendola, *Fertil Steril* DOI:10.1016/j.fertnstert.2017.09.037)

NIBIB: RESEARCHERS CREATE HIGHER-QUALITY PICTURES OF BIOSPECIMENS

Researchers from NIBIB and the University of Chicago improved the speed, resolution, and light efficiency of an optical microscope by switching from a conventional glass coverslip to a reflective,

mirrored coverslip and applying new computer algorithms to process the data. The team has spent the past few years developing optical microscopes that produce high-resolution images at very high speed.

After the lab develops each new microscope, it releases the plans and software for free, so any researcher can replicate the advances made at NIH. In 2013, the team developed the dual-view inverted selective-plane illumination microscope equipped with two lenses so it obtains two views of the sample instead of just one. In 2016, the team added a third lens and showed that this additional view can further improve light efficiency and resolution in 3-D imaging. But once three lenses were incorporated, it became increasingly difficult to add more. The researchers' solution was conceptually simple and relatively low-cost. Instead of trying to find ways to stuff in more lenses, they use mirrored coverslips. One complication is that both the conventional and the reflected views contain an unwanted background generated by the light source. To deal with this problem, the NIH researchers collaborated with University of Chicago researchers, who helped create computer-processing software to identify and remove the unwanted background and clarify the image. The researchers hope that in the future this technique may be adapted to other forms of microscopy.



NIBIB: In this diagram, the mirrored coverslip allows for four simultaneous views.

(NIBIB authors: Y. Wu, A. Kumar, E. Ardiel, P. Chandris, R. Christensen, I.N. Rey-Suarez, M. Guo, H.D. Vishwasrao, J. Chen, and H. Shroff, *Nat Commun* 8:article number 1452, 2017, DOI:10.1038/s41467-017-01250-8) ●

Read longer versions of these briefs online and more at <https://irp.nih.gov/catalyst/v26i1/research-briefs>:

- NIAID: Gene-Based Zika Vaccine Is Safe and Immunogenic in Healthy Adults
- NIAID: Cases of Unexplained Anaphylaxis Linked to Red-Meat Allergy
- NIEHS, NIAID: Allergens Widespread in Largest Study of U.S. Homes
- NIDA: Brain Pathway Involved in Drug Relapse
- NIDA: Brain Networks Predict Drug Relapse with Cocaine
- NIDA: Opioid-Treatment Drugs Have Similar Outcomes Once Patients Initiate Treatment
- NICHD, NCI: Obesity During Pregnancy May Lead Directly to Fetal Overgrowth
- NIAID: Cellphone-based Microscope Can Treat River Blindness

Rosenberg

CONTINUED FROM PAGE 1

treatment was tried, there was no sign that it worked and all of these patients died of progressive cancer. Then in 1984, Rosenberg treated his 67th patient with a new regimen of high-dose IL-2 and this patient experienced a complete cancer regression that is ongoing 33 years later. These studies of IL-2 administration led to the first FDA approval of a cancer immunotherapy in patients with renal cancer in 1992 and in metastatic melanoma in 1998.

“There is a possibility that an experimental therapy is never going to work,” said Rosenberg. “But when it works once then you know it’s possible.”

To understand the mechanism underlying the ability of IL-2 to cause the regression of cancer in patients with metastatic melanoma, Rosenberg identified immune cells found in cancer tumors called tumor infiltrating lymphocytes (TILs) that had cancer-fighting properties. In a series of clinical trials, Rosenberg and his group were the first to show that the administration of these TILs extracted from a tumor and grown in the laboratory to large numbers could mediate tumor regression in patients with advanced melanoma.

The second big break for immunotherapy was Rosenberg’s discovery that T cells could be *genetically* modified to detect and destroy cancer in patients. One type of these gene-engineered cells are named chimeric antigen receptor (CAR) T cells, and they were featured on the Discovery Channel’s three-part documentary series *First in Human* in August 2017. For CAR T-cell therapy to work, the T cells need to be harvested from the patient and outfitted with receptors that recognize surface proteins on the cancer cells. Hematological cancers such as lymphoma and melanoma reside in B cells, which express the cluster of differentiation 19 (CD19) protein. When



RHODA BAER

Dr. Steven Rosenberg, chief of Surgery in the National Cancer Institute, pioneered the development of the first effective immunotherapies for patients with advanced cancer.

T cells are modified to be able to identify and destroy B cells expressing CD19, the cancer is destroyed, but so is the normal B-cell population. Luckily, people can live without B cells as long as they get regular infusions of immunoglobulins.

The final piece of the puzzle includes wiping out the patient’s original immune system with chemotherapy, which creates an environment in which the modified T cells can be multiplied within the patient’s body and get to work. In 2009, Rosenberg’s group was the first to successfully treat a lymphoma patient with CAR T-cell therapy, and that patient remains cancer free to this day.

Rosenberg’s clinic can only treat about six patients per month. To help more people, he needed to collaborate with an industry that could mass produce the therapy. So, in 2012, NCI signed a Cooperative Research and Development Agreement (CRADA) with Kite Pharma, a pharmaceutical company founded by Rosenberg’s former NCI trainee **Arie Beldegrun** and recently

purchased by Gilead Sciences. The company can produce enough CAR T cells to treat 4,000 to 5,000 hospital patients per year.

Kite replicated Rosenberg’s findings in 101 patients from 22 institutions, with more than 40 percent of refractory lymphoma patients experiencing complete responses—meaning all signs of cancer disappeared.

“The institutions would obtain the patient’s blood cells, send them to Kite Pharma, [which] would introduce the *anti-CD19 CAR* gene, and then send it back to the hospital’s pharmacy and [the CAR T cells] would get dispensed to patients,” said Rosenberg. It sounds simple, but “behind every discovery that reaches a person there’s a long history of success and failures.” After the replication study, Kite submitted an Investigational New Drug (IND) application to the FDA in 2014, and its protocol was approved in October 2017 thus enabling the treatment to be applied throughout the United States. Rosenberg’s and NCI’s goal is to wipe out cancer. Getting the treatment to the



maximum number of patients is the best way to make that happen.

As for the future of cancer research, Rosenberg said, “We are working on approaches now that are really exciting: cell-transfer immunotherapy for patients with any type of cancer.” Current FDA-approved immunotherapies produced by companies like Kite/Gilead are successful in treating only specific types of hematological cancer such as acute lymphoblastic leukemia and lymphoma because the CAR T cells can recognize molecular targets expressed on a certain type of cell’s surface, such as CD19 on B cells. But in the grand scheme of things, epithelial solid cancers such as esophageal, colon, and ovarian cancers account for about 90 percent of cancer fatalities.

With advances in genetic sequencing, scientists and clinicians can now appreciate how complicated cancer really is. Almost every cancer in every patient has a different genetic blueprint, with unique mutations recognized by the immune system. These differences explain why cancer vaccinations and other therapies to target common mutations in patients have failed: There’s no one-size-fits-all treatment.

What Rosenberg’s group is doing now fits the definition of personalized medicine: Target the T cells to the mutations specific to the cancer in each individual. A patient’s tumor is run through genomic sequencing to detect all the mutations in the cancer and identify the TIL that recognize these mutations. These TILs are expanded in culture and reinfused into the patient. “We can find a way to attack the unique patient’s mutations that caused the cancer,” said Rosenberg. “It’s ironic that the mutations that caused the cancer may turn out to be the cancer’s Achilles’ heel and enable successful treatments.”

On the way to Rosenberg’s sizeable

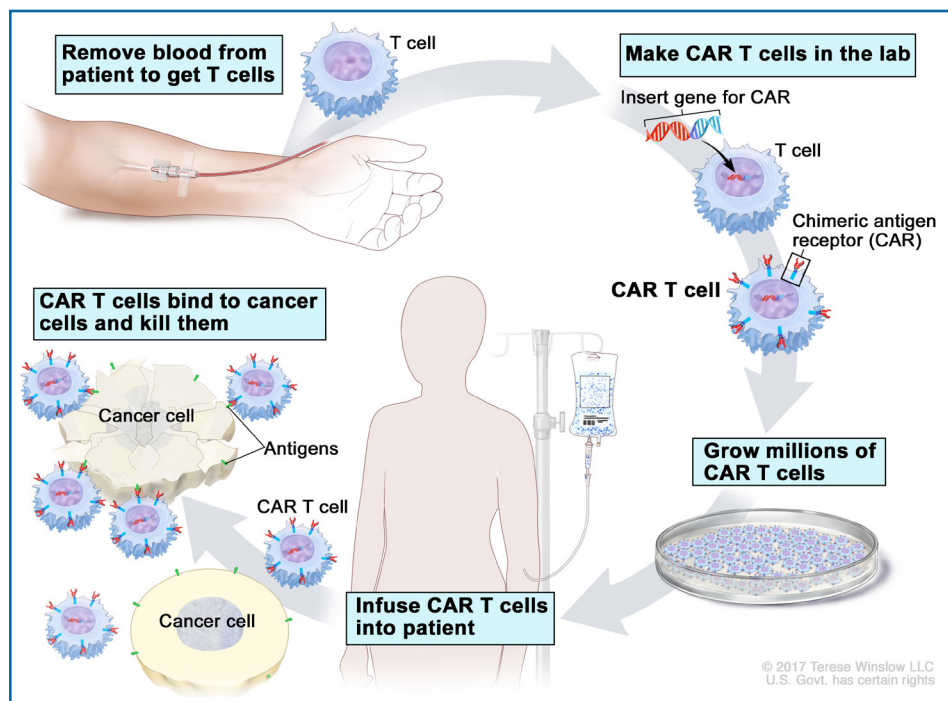
corner of the NIH Clinical Center, there is a long hallway with framed portraits of the fellows he has trained over his long and productive career. Each portrait is signed and contains a sentence or two. This wall serves as a reminder that Rosenberg isn’t curing cancer by himself but is leading a battalion of cancer warriors within and beyond the walls of NIH.

What does it take to lead the NCI’s fight against cancer, or for anybody to make substantial progress in a complicated field? Rosenberg recommends passion, but a more precise label might be obsession.

“You have to be living what you’re doing, thinking of the problem in the shower or when stopped at a red light; immerse yourself in the knowledge of a field,” he said. You also have “to define the problem you’re trying to solve in just one sentence, and pursue it with a laser-like focus.” ●

Rosenberg presented “Cells as Anti-cancer Drugs Entering Mainstream Oncology” at the 12th Annual Philip S. Chen Jr. Distinguished Lecture on Innovation and Technology Transfer in Masur Auditorium (Building 10) on November 17, 2017. Chen spent his career at NIH pioneering ways to deliver ideas discovered at NIH to the outside world. He is credited with forming the NIH Office of Technology Transfer and the CRADA. The recorded videocast can be viewed at <https://videocast.nih.gov/launch.asp?23596>.

Read more about Steven Rosenberg online at <https://irp.nih.gov/catalyst/v26i1/steven-a-rosenberg-md-phd>



CAR T-Cell Therapy (clockwise from top left): Blood is removed from a vein to get T cells; a special receptor called a chimeric antigen receptor (CAR) is made in the laboratory; the gene for CAR is inserted into the T cells; millions of CAR T cells are grown; CAR T cells are infused into the patient; and the CAR T cells bind to cancer cells and kill them.

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Nobel Laureate Roderick MacKinnon: How Ion Channels Work

Wednesday Afternoon Lecture Series Presentation in September 2017

BY ANNE DAVIDSON, NICHD

LISTENING TO NOBEL LAUREATE Roderick MacKinnon describe how ion channels function is like having Microsoft co-founder Bill Gates explain binary code. MacKinnon was the opening act for the 2017-2018 season of the NIH Director's Wednesday Afternoon Lecture Series (WALS), held on September 27, 2017, in Masur Auditorium (Building 10).

MacKinnon, a John D. Rockefeller Jr. Professor and Howard Hughes Medical Investigator at The Rockefeller University (New York), received the 1999 Albert Lasker Basic Medical Research Award (with Clay Armstrong and Bertil Hille) for "his elucidation of the structure and function of potassium channels [providing] the first molecular description of an ion selective channel" and the 2003 Nobel Prize in chemistry (with Peter Agre) "for structural and mechanistic studies of ion channels."

"The love of his life [is] how ion channels work," said **Anirban Banerjee** during his introduction of MacKinnon at the lecture. Banerjee was MacKinnon's postdoc at The Rockefeller University in New York (2006-2012) and is now a principal investigator in the National Institute of Child Health and Human Development.

Ion channels are pivotal in many biological processes, such as controlling the pace of the heart, regulating the secretion of hormones, and generating electrical impulses in the nervous system. Dysfunctions in the channels are linked to physiological, neuronal, and other disorders.

Banerjee recalled lively lab meetings at Rockefeller among MacKinnon's graduate students and postdocs. MacKinnon would listen patiently and then would break in with a remarkably insightful soliloquy. Such insights were pivotal when Banerjee and MacKinnon successfully used a

pore-blocking toxin to show the first co-crystal structure of a potassium channel.

But MacKinnon's path to Rockefeller was not an easy one. He wanted to be able to visualize his love—the potassium ion channel; however, when he started working on channel proteins at Harvard Medical School (Boston), the structure had not been solved. The prevailing view in the field at the time (1990s) and among MacKinnon's own colleagues was that a structure of ion channels was impossible to determine because 1) they are membrane proteins; only a few, naturally abundant membrane proteins had been characterized at that time; and 2) they exist in a mixture of states.

So despite a lack of faith among his colleagues, MacKinnon left Harvard for Rockefeller, where he set up a lab that used X-ray crystallography to determine the structures of ion channels. The move was a challenge: MacKinnon, who was trained in electrophysiology, had to transition to structural biology and learn crystallography. "Rod was just stubborn and so driven by the question," Banerjee explained.

The question driving MacKinnon's early research was how the membrane channels select for potassium ions over other ions. Using monoclonal antibodies for getting crystals that would offer a higher-resolution picture, he discovered the structure of the selectivity filter.

There are some 80 potassium channels in humans. Different channels have evolved to sense different environmental stimuli: chemical, mechanical, and electrical, MacKinnon said. The channels are diverse, but "what makes them a common family is that they all have...the selectivity filter."

One channel MacKinnon discussed in the WALS lecture was the G protein coupled inwardly rectifying potassium



DALE LEWIS, NCI

Nobel laureate Roderick MacKinnon presented a WALS lecture on the biophysics and biology of potassium channels.

(GIRK) channel, which suppresses electrical activity and is activated by the G protein. G proteins (guanine nucleotide-binding proteins) act as molecular switches and are involved in transmitting signals from a variety of stimuli outside a cell to its interior. MacKinnon's lab did GIRK reconstitution in a synthetic lipid membrane and found that four highly cooperative beta-gamma subunits are needed to open the channel.

Recently, MacKinnon has begun delving into single-particle cryoelectron microscopy. This technique has allowed his lab to visualize the protein Slo2, a sodium-dependent potassium channel, which is activated under different sodium concentrations. ●

To watch a videocast of MacKinnon's WALS talk, "Biophysics and Biology of K⁺ Channels," held on September 27, 2017, go to <https://videocast.nih.gov/launch.asp?23487>.

Free Radical Interest Group

Celebration of the 30th Anniversary of the Oxygen Club

BY CLAIRE MCCARTHY, NCI

NIH'S FREE RADICAL INTEREST GROUP and the interagency and university consortium the Oxygen Club of Greater Washington, D.C., bring together a wide range of individuals who are interested in understanding the roles that free radicals and other reactive oxygen and nitrogen species play in basic physiology, disease mechanisms, and treatment strategies. The Oxygen Club, founded in 1987 by **Daniel L. Gilbert** (1925–2000), was the first group organized to study and discuss free radicals and what is now called “oxidative stress,” in which pathogenic imbalances in the body’s use of oxygen occurs. On October 3, 2017, the Oxygen Club celebrated its 30th anniversary with a symposium in Lipsett Amphitheater (Building 10).

Gilbert was a pioneer in the field of reduction-oxygen reaction (redox) biology. In 1957, when he was a graduate student at the University of Rochester (Rochester, New York), he and Rebeca Gerschman were the first to describe “oxygen poisoning” and link the existence of oxygen-free radicals with damaging effects on biological systems (*Science* **119**:623–626, 1954). Later, as an intramural researcher at the National Institute of Neurological Disorders and Stroke, Gilbert discovered that free radicals impair communication between nerve cells, promote neuroinflammation, and contribute to Alzheimer disease and other disorders. His groundbreaking work on oxygen toxicity laid the foundation for many current extramural and intramural scientific studies.

At the symposium, several people gave talks that emphasized the importance of oxygen and free radicals in biological processes. Gerald Shadel (Yale University,

New Haven, Connecticut), who gave the Daniel Gilbert Memorial Lecture, described how mitochondrial reactive oxidative species (ROS) play a role in aging and maternally inherited deafness. He presented new studies that indicate how mitochondrial stress can activate innate antiviral signaling pathways that upregulate DNA damage-resistance genes. He hypothesized that this mechanism acts as a protective signal to prevent ROS-induced damage to the nuclear genome.

Sonia Franco (Johns Hopkins University School of Medicine, Baltimore), who is doing similar research, described how early, innate immune activation from DNA damage is the “canary in the coal mine” that warns the cell of genotoxic danger.

Other presentations highlighted the important role that oxygen plays in cell death. Valerian E. Kagan (University of Pittsburgh, Pittsburgh) explained how oxidized lipids trigger programmed cell death through interactions with metabolic enzymes. And Juliann G. Kiang (Armed Forces Radiobiology Research Institute, Bethesda, Maryland) reported that blood loss (which results in hypoxia) from a wound after radiation injury causes more cell death and damage than blood loss or radiation alone.

Another important aspect of redox biology is the development of tools to measure oxygen in tissue. **Murali Krishna Cherukuri**, head of the Biophysical Section in NCI’s Radiation Biology Branch, described how his lab is developing noninvasive imaging techniques based on electron paramagnetic resonance (EPR) to measure oxygen concentration in tumors. (Cancer patients with hypoxic tumors are resistant to radiation therapy.) The research

findings indicate that EPR imaging could potentially be used to develop effective cancer treatments based on oxygen concentrations in cancerous tissue.

Daniel Gilbert’s spirit of collegial scientific curiosity lives on as the researchers interact with each other—via the interest group and Oxygen Club—and continue to explore the many unanswered questions about oxygen and free radicals. ●

The interdisciplinary nature of the NIH Free Radical Interest Group and the Oxygen Club of Greater Washington, D.C., provides attendees with the opportunity to both learn and network. Members enjoy a spirit of informality during seminar discussions; many productive collaborations that transcend chemistry, biology, and medicine have begun through these interactions. To receive event announcements and/or to learn more, contact **Michael Espey (NCI)** at o2club@nih.gov or visit <https://oir.nih.gov/sigs/free-radical-interest-group>.

Scientific Interest Groups

NIH Scientific Interest Groups (SIGs) are assemblies of scientists with common research interests. These groups engage with their members via a listserv; sponsor symposia, poster sessions and lectures; offer mentoring and career guidance for junior scientists; help researchers share the latest techniques and information; act as informal advisors to the Deputy Director for Intramural Research (DDIR); provide advice for the annual NIH Research Festival; and serve as hosts for the Wednesday Afternoon Lecture Series. Most of these groups welcome interested non-NIH scientists. To learn more and see a list of the SIGs, go to <https://oir.nih.gov/sigs>.



Recently Tenured



LUCY R. FORREST, NINDS

LAURA BEANE FREEMAN,
NCI-DCEG

MICHAEL S. LIONAKIS, NIAID

ANTONINA ROLL-MECAK,
NINDS

JUSTIN W. TARASKA, NHLBI

LUCY R. FORREST, PH.D., NINDS

Senior Investigator and Section Chief, Computational Structural Biology Section, National Institute of Neurological Disorders and Stroke

Education: University of Surrey, Guildford, England (B.Sc. in computer-aided chemistry); University of Oxford, Oxford, England (D.Phil. in biochemistry)

Training: Postdoctoral training, Department of Physiology, the Johns Hopkins University School of Medicine (Baltimore); postdoctoral training, Medical Research Council Dunn Human Nutrition Unit (Cambridge, England); postdoctoral training, Center for Computational Biology and Bioinformatics, Columbia University (New York)

Before coming to NIH: Max Planck research group leader, Computational Structural Biology Group, Max Planck Institute for Biophysics (Frankfurt, Germany)

Came to NIH: In 2013 as a tenure-track investigator

Selected professional activities: Reviewing editor, *eLife*; editorial advisory board, *Journal of General Physiology*; Faculty of 1000 member in structural biology

Outside interests: Hiking; sailing

Website: <https://irp.nih.gov/pi/lucy-forrest>

Research interests: Membrane-embedded proteins are essential components of cellular organisms. The proteins allow cells to

communicate with their surroundings by providing bridges through the lipid-membrane barrier.

My group is using computational and theoretical approaches to understand the mechanisms of membrane proteins. Of particular interest are transporter proteins, which capture the chemical potential energy of ionic gradients (across the membrane) to facilitate the movement of essential chemicals, or unwelcome toxic compounds, into and out of the cell. A fundamental question is how transporters achieve the required degree of specificity for a given chemical or substrate and how the protein-substrate interaction is coupled to transport ions such as sodium. A further puzzle is how the transporter changes shape to allow access of the substrate binding sites to either side of the membrane, while also preventing leakage.

An essential characteristic of our work is that our hypotheses and interpretations are connected with experimental evidence from biochemical, biophysical, or structural studies. For example, we have long-standing collaborators at Yale University (New Haven, Conn.) with whom we have studied

If you have been recently tenured, *The NIH Catalyst* will be in touch with you soon to do an article about you on these pages.

the transport of neurotransmitters such as serotonin, which is crucial to the function of the nervous system. We also collaborate with researchers at several other institutions.

We look for simple rules that underlie very complex biological phenomena. At the same time, to understand these processes at atomic detail, we apply a range of computational tools such as protein-structure prediction and molecular-dynamics simulations. More recently, we have been developing databases to capture the diversity of beautiful, and functionally important, patterns of symmetry that abound in membrane-protein structures.

LAURA BEANE FREEMAN, M.S., PH.D., NCI-DCEG

Senior Investigator, Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute

Education: Iowa State University, Ames, Iowa (B.S. in biology); University of Iowa, Iowa City, Iowa (M.S. in preventive medicine; Ph.D. in epidemiology)

Training: Cancer Prevention Fellow, Division of Cancer Prevention and Occupational and Environmental Epidemiology Branch, NCI-DCEG; Research fellow in same branch (2006–2009); became tenure-track investigator in 2009



Came to NIH: In 2003 for training

Selected professional activities: Elected member, EPICOH Management Group; member, Cross-Sector Steering Council for Chronic Diseases and external co-chair for Cancer Agenda, National Occupational Research Agenda (NORA), National Institute for Occupational Safety and Health; Cancer Sub-Group chair, AGRICOH (an international consortium of agricultural cohort studies)

Outside interests: Reading; traveling; cooking

Website: <https://irp.nih.gov/pi/laura-beane-freeman>

Research interests: I conduct research on several occupational and environmental exposures including pesticides and other agricultural agents; drinking-water contaminants, such as disinfection byproducts; and formaldehyde and other industrial chemicals.

In the agricultural realm, studies around the world have found that farmers and other agricultural workers are at elevated risk of several specific cancers including Hodgkin lymphoma, non-Hodgkin lymphoma, leukemia, multiple myeloma, and cancers of the brain, skin, lip, stomach, and prostate. Work-related exposures suspected of contributing to the excesses include pesticides, viruses, mycotoxins, and well-water contaminants.

I am the NCI principal investigator of the Agricultural Health Study (AHS)—a collaboration of the NCI, the National Institute of Environmental Health Sciences, the National Institute for Occupational Safety and Health, and the Environmental Protection Agency. The AHS is a prospective cohort study of approximately 90,000 participants. The participants include licensed private pesticide applicators and their spouses in Iowa and North Carolina, and commercial applicators in Iowa. We are investigating how agricultural exposures including

pesticides, but also exposure to livestock and poultry, diesel exhaust, endotoxins and other bioaerosols, influence cancer risk. There is increasing evidence that early-life exposures may influence disease risk in adulthood. Therefore, I have initiated a study of offspring of the AHS participants to investigate how their childhood farm exposures may affect their health in later life.

In the drinking-water contaminants realm, previous studies have shown that exposure to disinfection byproducts (DBPs) increases the risk of bladder cancer. However, DBPs are a complex mixture of chemicals, so questions remain about the etiologic agents responsible for the associations. Recent results from a case-control study suggest that in addition to ingestion, exposure through showering and bathing may contribute to risk. In a large case-control study in the United States, we investigated exposure from multiple routes and found evidence that brominated DBPs may be of particular concern.

My research with formaldehyde has involved assessing whether occupational exposure to formaldehyde increases the risk of cancer at several sites, specifically the respiratory tract, and whether it induces lymphohematopoietic malignancies. We are also evaluating the biologic plausibility of formaldehyde carcinogenicity, particularly at sites distant from the respiratory tract. The NCI Cohort of Workers in Formaldehyde Industries is the largest study of occupationally exposed workers and includes more than 25,000 participants who have a median follow-up time of over 40 years.

Our most recent follow-up on this study offered further insight into the temporality of potential associations between formaldehyde and leukemia and other lymphohematopoietic malignancies.

MICHAEL S. LIONAKIS, M.D., SC.D., NIAID

Senior Investigator and Chief, Fungal Pathogenesis Section, Laboratory of Clinical Microbiology and Immunology, National Institute of Allergy and Infectious Diseases

Education: University of Crete Medical School, Heraklion, Greece (M.D.); University of Crete, Heraklion (Sc.D.)

Training: Rural service physician, Greek Ministry of Health and Welfare (Katerini, Greece); postdoctoral research fellow, Department of Infectious Diseases, Infection Control and Employee Health, University of Texas M. D. Anderson Cancer Center (Houston); internal medicine resident, Department of Internal Medicine, Baylor College of Medicine (Houston); infectious diseases clinical fellow, NIAID

Came to NIH: In 2007 for training; became assistant clinical investigator in 2010, clinical tenure-track investigator in 2012

Selected professional activities: Member of several editorial boards including *JCI Insight* and *Journal of Infectious Diseases*; associate editor, *Frontiers in Cellular and Infection Microbiology*; faculty member, Faculty of 1000—Immunology, Immunity to Infections

Outside interests: swimming; music; dancing; traveling

Website: <https://irp.nih.gov/pi/michail-lionakis>

Research interests: Since the 1990s, fungal infections have emerged as a major cause of morbidity and mortality in immunosuppressed and critically ill patients. The yeast genus *Candida* is the most common human fungal pathogen, and the mold genus *Aspergillus* is the leading cause of infectious mortality in transplant recipients.

My laboratory research focuses on 1) the cellular and molecular factors that regulate the immune response against mucosal and invasive candidiasis and invasive



Recently Tenured

CONTINUED FROM PAGE 15

aspergillosis in clinically relevant animal models; 2) a better understanding of the genetic and immune defects that underlie enhanced susceptibility to mucocutaneous and invasive fungal infections in humans.

Our goal is to develop a detailed mechanistic understanding of the molecular and cellular basis of innate and adaptive immune responses against *Candida* and *Aspergillus*. We aim to devise novel strategies to improve the diagnosis of fungal infections and augment or supplement the current antifungal drug treatment. To study host-fungal interactions, we are using in vitro cell-culture systems and clinically relevant mouse models of mucosal and systemic *Candida* and *Aspergillus* infections. Our research techniques include a variety of immunological, biological, and imaging approaches.

The molecular factors that mediate the immune response to candidiasis and aspergillosis are poorly defined. So my lab is investigating the molecular cues that mediate trafficking and effector function of specific resident and recruited immune cells in antifungal host defense in vivo. We are also interested in delineating the host factors that govern fungus-specific resistance versus susceptibility at different anatomical sites.

In our clinical-research program, we are investigating the mechanisms of fungal susceptibility in inherited immunodeficiencies that lead to invasive pulmonary and brain fungal infections or to chronic mucocutaneous candidiasis. We have enrolled the world's largest cohort of patients with genetic immune disorders—deficiency of caspase recruitment-domain-containing protein 9 and deficiency of autoimmune regulator—that make them susceptible to fungal infections. By using corresponding gene-deficient mice and patients with susceptibility to severe or

recurrent fungal disease, we hope to discover novel genetic variants associated with this susceptibility and to develop mechanism-based therapies for people affected by fungal infections.

ANTONINA ROLL-MECAK, PH.D., NINDS

Senior Investigator and Chief, Cell Biology and Biophysics Unit, National Institute of Neurological Disorders and Stroke

Education: Albert E. Nerken School of Engineering, The Cooper Union for the Advancement of Science and Art, New York (B.E. in chemical engineering); The Rockefeller University, New York (Ph.D. in molecular biophysics)

Training: Postdoctoral fellow, Department of Cellular and Molecular Pharmacology, University of California, San Francisco (San Francisco)

Came to NIH: In 2010

Selected professional activities: Referee for several journals including *Journal of Cell Biology*, *Cell*, *Nature*, and *Science*; faculty member, Faculty of 1000 Cell Signaling and Trafficking Structures Section

Outside interests: Loves classical music so she tries to squeeze in a concert whenever she can; also enjoys the great museums in Washington, D.C.

Website: <https://irp.nih.gov/pi/antonina-roll-mecak>

Research interests: I am interested in the morphology and dynamics of the microtubule cytoskeleton. Microtubules provide structural support to cells as well as form a complex and dynamic intracellular “highway” that delivers molecular cargo from one end of the cell to the other.

In particular, I am trying to understand how the chemical and genetic diversity of tubulin—the protein building blocks of microtubules—modulates the microtubule

network. Microtubules are involved in biological processes throughout the body such as cell division, motility, and differentiation; microtubule disturbances underlie many neurodegenerative disorders such as Alzheimer and Parkinson diseases as well as cancer.

Deceptively uniform ultrastructurally, microtubules are composed of multiple tubulin isoforms that bear a bewildering range of post-translational modifications including acetylation, detyrosination, phosphorylation, glutamylation, and glycylation. Tubulin alpha and beta heterodimers consist of a compact folded body and intrinsically disordered COOH-terminal tails. These tails form a dense lawn on the microtubule surface and serve as binding sites for molecular motors and microtubule-associated proteins. The majority of sequence variation and post-translational modifications of tubulin isoforms concentrates on these intrinsically disordered tails. Some of the modifications we study, such as glutamylation and glycylation, can add amino-acid chains that are significantly longer than the tubulin tails themselves. These modifications are thought to constitute a “tubulin code” (analogous to the histone code), which is read by cellular effectors.

To crack the code, we first need to understand how it is written: the mechanism and regulation of the enzymes that introduce tubulin-post-translational modifications.

Second, we need to elucidate how post-translational modifications and isoform variability affect the basic properties of the microtubule polymer itself. Third, we need to know how the spatial and temporal patterns of microtubule modifications are established and propagated.

Ultimately, we need to understand how tubulin isoform composition and



modifications are interpreted by the cellular effectors that regulate their recruitment or activity.

To provide a mechanistic look at the tubulin code, my laboratory has developed a biochemical platform to obtain recombinant, isotypically pure human tubulin as well as quantitatively defined, differentially modified tubulins. We use a variety of techniques to decipher the code, from structural biology and classic enzymology to single-molecule biophysics, live-cell imaging, and modeling.

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JUSTIN W. TARASKA, PH.D., NHLBI

Senior Investigator, Laboratory of Cellular Biophysics, Biochemistry and Biophysics Center, National Heart, Lung, and Blood Institute

Education: Reed College, Portland, Ore. (B.A. in biology); Vollum Institute, Oregon Health and Science University, Portland (Ph.D. in cell biology)

Training: Postdoctoral training, Department of Physiology and Biophysics, University of Washington (Seattle)

Came to NIH: In 2010

Selected professional activities: Editorial board, *Journal of General Physiology*; director, Analytical and Quantitative Light Microscopy course, Marine Biological Laboratory (Woods Hole, Mass.); recipient of Presidential Early Career Award for Scientists and Engineers (2012)

Outside interests: Spending time with family; drawing; aikido; running; gardening; surfing

Website: <https://irp.nih.gov/pi/justin-taraska>

Research interests: My lab develops and uses advanced fluorescence and electron microscopy imaging methods to investigate the molecular organization of proteins that regulate exocytosis and endocytosis in human cells.

Cells communicate with each other and the body by releasing proteins, peptides, and chemicals through a highly regulated process called exocytosis, in which cytoplasmic cargo-loaded vesicles fuse with the cell's plasma membrane and release their contents. Cells go to great lengths to ensure that exocytosis occurs at precisely the right time and location and that the correct quantity and type of materials are released. Once vesicles fuse, vesicle material is cleared from the plasma membrane through a coat-driven process called endocytosis, in which the plasma membrane folds inward to bring substances into the cell. The primary retrieval mechanism in eukaryotic cells is clathrin-mediated endocytosis (CME). In CME, dozens of proteins capture, polymerize, and bend a honeycomb-like coat around pieces of the plasma membrane to internalize material. But scientists don't yet understand how this complex ensemble of proteins is organized.

In a healthy cell, the exocytosis and endocytosis processes are carefully balanced. Disruption of either can result in deficiencies or excesses of chemical signals, leading to such disorders as Parkinson and Huntington diseases, schizophrenia, epilepsy, diabetes, and heart and lung diseases. Not surprisingly, understanding exocytosis and endocytosis has been a major goal for the biological sciences. A gap exists between understanding protein structures and their cellular contexts. We aim to fill this gap by developing and using imaging tools to determine the nanoscale structures, organization, and dynamics of molecules that are important for the biology of membrane traffic. My lab maps the fundamental architecture of molecular machines to understand how these complex assemblies function. ●

- CC:** NIH Clinical Center
- CCR:** Center for Cancer Research, NCI
- CIT:** Center for Information Technology
- DCEG:** Division of Cancer Epidemiology and Genetics, NCI
- DIPHR:** Division of Intramural Population Health Research, NICHD
- FAES:** Foundation for Advanced Education in the Sciences
- FARE:** Fellows Award for Research Excellence
- FelCom:** Fellows Committee
- FDA:** Food and Drug Administration
- FNL:** Frederick National Laboratory
- IRP:** Intramural Research Program
- HHS:** U.S. Department of Health and Human Services
- NCATS:** National Center for Advancing Translational Sciences
- NCBI:** National Center for Biotechnology Information
- NCCIH:** National Center for Complementary and Integrative Health
- NCI:** National Cancer Institute
- NEI:** National Eye Institute
- NHGRI:** National Human Genome Research Institute
- NHLBI:** National Heart, Lung, and Blood Institute
- NIA:** National Institute on Aging
- NIAAA:** National Institute on Alcohol Abuse and Alcoholism
- NIAID:** National Institute of Allergy and Infectious Diseases
- NIAMS:** National Institute of Arthritis and Musculoskeletal and Skin Diseases
- NIBIB:** National Institute of Biomedical Imaging and Bioengineering
- NICHD:** Eunice Kennedy Shriver National Institute of Child Health and Human Development
- NIDA:** National Institute on Drug Abuse
- NIDCD:** National Institute on Deafness and Other Communication Disorders
- NIDCR:** National Institute of Dental and Craniofacial Research
- NIDDK:** National Institute of Diabetes and Digestive and Kidney Diseases
- NIEHS:** National Institute of Environmental Health Sciences
- NIGMS:** National Institute of General Medical Sciences
- NIMH:** National Institute of Mental Health
- NIMHD:** National Institute on Minority Health and Health Disparities
- NINDS:** National Institute of Neurological Disorders and Stroke
- NINR:** National Institute of Nursing Research
- NLM:** National Library of Medicine
- OITE:** Office of Intramural Training and Education
- OIR:** Office of Intramural Research
- ORS:** Office of Research Services
- ORWH:** Office of Research on Women's Health
- OTT:** Office of Technology Transfer

**IN 2016 (NOT INCLUDED LAST YEAR)**

David A. Cooney (died on October 8, 2016, at 78), who was a leading scientist in the fields of pharmacology and toxicology, especially relating to various families of anticancer drugs, worked in the National Cancer Institute from 1964 until his retirement in 1998.

IN 2017

Faye Glenn Abdellah (died on February 4, 2017, at 97) was the founding dean of the Uniformed Services University of the Health Sciences Daniel K. Inouye Graduate School of Nursing and a retired rear admiral of the Public Health Service. In the mid-1960s, she worked in NIH's Division of Nursing and was the first nurse and the first woman to serve as deputy surgeon general (with U.S. Surgeon General C. Everett Koop) and was the first nurse to hold the rank of rear admiral.

Darrell Robert Abernethy (died on November 18, 2017, at 68) served on the medical faculties at several universities before joining the National Institute on Aging, where he directed a program to better understand the effects of drugs in older patients.

Calvin "Cal" Benham Baldwin Jr. (died on June 28, 2017, at 91) was a founding member—and a board member—of the NIH Alumni Association and the Children's Inn at NIH. He is survived by his wife, **Ann Baldwin Nucci**, who worked in NIH's Office of Human Resources for 31 years.

Soojay Banerjee (died on October 23, 2017, at 50), a biochemist who specialized in the purification of proteins for structural analysis, came to the National Institute of Neurological Disorders and Stroke in 2005 and later moved to the National Cancer Institute. He played key roles in the identification of the first ubiquitin kinase and in projects that further advanced the field of cryoelectron microscopy.

Michael A. Beaven (died on April 8, 2017, at 80), an expert in mast-cell biology and the roles of

mast cells in immunological processes, began working at NIH in 1962, first as a visiting fellow in the National Heart, Lung, and Blood Institute (NHLBI). He became a tenured scientist and eventually deputy chief in NHLBI's Laboratory of Molecular Immunology. After formally retiring in 2010, he became an NIH scientist emeritus and continued to work full time.

Erwin Bellack (died on July 31, 2017, at 97), a chemist with the Public Health Service's division of dental public health (1954 to 1973) was best known for his work on the fluoridation of public drinking water.

Robert Lewis Berger (died on July 29, 2017, at 91) worked at the National Heart, Lung, and Blood Institute from 1962 to 1994. He studied the fast reactions of hemoglobin and its ligands in the blood, which spurred him to develop an entirely new line of instrumentation that ultimately had applications in other fields as well. He is survived by his wife, **Victoria Harden**, the former director of the Office of NIH History and the Stetten Museum at NIH.

Kristine Lynne Buchler (died on August 31, 2017, at 74) was a microbiologist at NIH.

Carlos E. Caban (died on May 1, 2017, at 75) retired from NIH in 2008 after 38 years of service. He began as a research scientist and later held administrative and program director positions in the National Cancer Institute.

Kevin John Catt (died on October 1, 2017, at 85) worked at the National Institute of Child Health and Human Development from 1970 until his retirement in 2012. He served as chief of the Endocrinology and Reproduction Research Branch, where he led an internationally recognized group working on hormone receptors, signaling, and actions.

Peter Chines (died on July 10, 2017, at 50) was a computer scientist and database programmer in **Francis Collins's** lab in the

National Human Genome Research Institute's Molecular Genetics Section (from 1997 until his death). Chines was an expert in designing and managing complex databases.

Paul Chretien (died on August 16, 2017, at 86), a pioneer of head-and-neck tumor immunology, was a National Cancer Institute (NCI) senior investigator (1966–1972) and chief of the Tumor Immunology Section in NCI's Surgery Branch (1972–1980). He was among the first to characterize deficiencies in T-lymphocyte function in patients with head-and-neck cancer and to compare impaired immune reactivity in head-and-neck cancer to other cancer types and correlated these findings with treatment outcomes.

Andrew Dwyer (died on October 26, 2017, at 70) was a staff clinician in the NIH Clinical Center's Radiology Department since 1977.

Rhea Moore Frazier (died on May 30, 2017, at 69) was a program assistant in the NIH Clinical Center's Office of Clinical Research Training and Medical Education.

Richard W. Hendler (died on August 8, 2017, at 90) was an accomplished biochemist who was part of the NIH and National Heart, Lung, and Blood Institute family for 48 years beginning in 1952. He worked on energy-driven proton pumps and developed techniques to follow the path of protons across cell membranes, which had far-reaching implications for many types of biomedical investigations. Particularly important was Hendler's development of new linear algebra-based mathematical techniques for isolating absolute visible and infrared spectra of intermediates and better defining the kinetic sequence of events. Such insight has proven to be valuable for unraveling the kinetic steps of plaque formation in Alzheimer disease, for example.

A. Everette James (died on March 14, 2017, at 78), a former visiting scientist at NCI (1991–



1992), was chair and professor of radiological sciences at Vanderbilt University School of Medicine (Nashville).

Martin Katz (died on January 12, 2017, at 89) helped to establish the field of neuropsychopharmacology and was one of the first researchers to study the action of antidepressants on mentally ill patients. He spent most of his career at the National Institute on Mental Health and was chief of its clinical research branch (1968–1978).

Amar Klar (died on March 5, 2017, at 69) was a member of the National Cancer Institute community since 1988. His seminal contributions were key in the discovery of gene silencing in budding yeast and fission yeast and the demonstration that cell-type changes can be mediated by site-specific DNA substitutions in those organisms. He was a co-discoverer of the *SIR2* gene. Most intriguing, Amar's work demonstrated that the two strands of DNA need not have identical genetic properties.

Claude Klee (died on April 3, 2017, at 85) was a pioneer in the biochemistry of calcium-binding proteins and calcium-dependent signaling. Although retired for more than a decade, she remained an active mentor and advisor at the National Cancer Institute until her death.

Lois Whidden Kochanski (died on January 12, 2017, at 93) began a 35-year career in 1970 at the Foundation for Advanced Education in the Sciences (FAES) and served for many years as its executive director until 2005.

Irwin Kopin (died on August 1, 2017, at 88), scientist emeritus and retired scientific director in the National Institute of Neurological Disorders and Stroke (NINDS), was a giant in catecholamine research at the NIH. His groundbreaking work on the characteristics and metabolism

of catecholamines—a class of chemicals that includes adrenaline, norepinephrine, and dopamine—provided the backbone for major advances in neurological and psychiatric disorders and helped bring the NIH international distinction in the 1960s.

Catherine D. Lewis (died on July 12, 2017) joined NIH in 1983 as a staff fellow at the National Institute of Diabetes and Digestive and Kidney Diseases; in 1989, she moved to the National Institute of General Medical Sciences.

Patricia Anne Martone (died on May 24, 2017, at 66) retired from the NIH as an administrative lab manager.

Charles McIntosh (died on May 20, 2017, at 79), a cardiac surgeon in the U.S. Public Health Service, spent 20 years at the NIH and attained the rank of captain. He invented—and held several patents for—implantable heart valves.

Dennis L. Murphy (died on September 23, 2017, at 80), former chief of the National Institute of Mental Health's (NIMH) Laboratory of Clinical Science, was known for his research exploring the neurobiology of mood and anxiety disorders using molecular, neurochemical, and genetic techniques. He joined NIMH as a clinical fellow in 1966 and became chief of the Clinical Neuropharmacology Branch in 1977. He is survived by his wife, **Nancy Garrick**, who is Deputy Communications Director at the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

Edward H. Oldfield (died on September 1, 2017, at 69), a neuroscientist and neurosurgeon, led research programs that changed the surgical treatment of patients with pituitary tumors in Cushing disease, with brain and spinal cord tumors in von Hippel-Lindau disease, and with spinal arteriovenous malformations. He came to NIH in 1981 as a senior staff fellow, eventually becoming chief of the National Institute of Neurological

Disorders and Stroke's Surgical Neurology Branch (1986–2007).

Mary Margaret Herman Rubinstein (died on June 9, 2017, at 81) was a neuropathology researcher at the National Institute of Mental Health (NIMH) from 1991 to 2013. She was a leader in advocating for the necessity of using human brain material for the study of psychiatric disorders and worked to successfully expand the NIMH brain collection, a forerunner of today's Human Brain Core Collection.


Emma Shelton (died on March 29, 2017, at 96) was among the first female scientific leaders at the NIH, arriving first as a cytology technician in 1942. After receiving her Ph.D. in cell biology in 1949, she became a resident biologist at the National Cancer Institute. She was one of the first women to head her own lab and conducted path-breaking research into the causes of cancer.

Jane E. Shure (died on April 8, 2017, at 71), began at NIH in 1967 as an information intern and became the communications director at the National Institute on Aging (NIA) when it was founded in 1974.

Julius Youngner (died on April 27, 2017, at 96) was a world-renowned virologist best known for his contributions to the development of the first effective polio vaccine. In the 1940s, Youngner was drafted into the Army and selected to work on the Manhattan Project, studying the effects of uranium salts on human tissue. He was serving in the U.S. Public Health Service Commissioned Corps at the National Cancer Institute when he was recruited to the University of Pittsburgh in 1949 to join Jonas Salk in the quest for an effective polio vaccine. ●

Read more online at <https://irp.nih.gov/catalyst/v26i1/obituaries-2017>.

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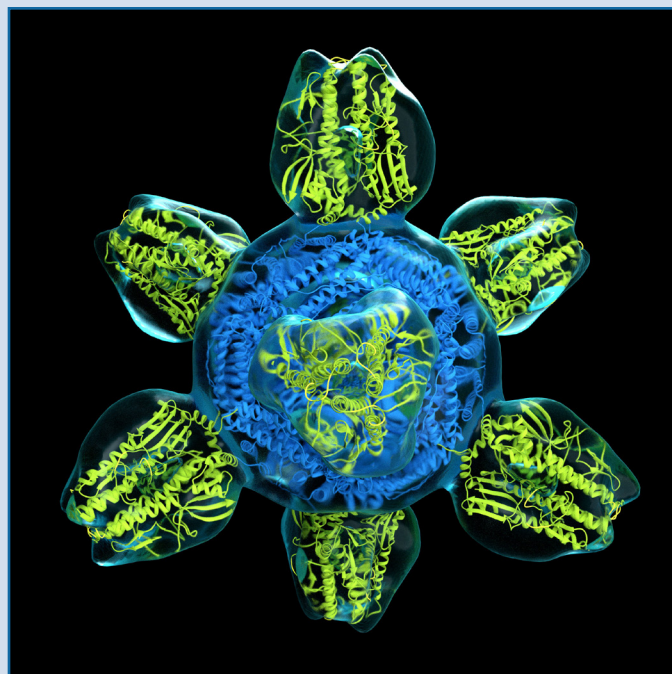
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PHOTOGRAPHIC MOMENT

Prototype for a Universal Flu Vaccine

COLORIZED STRUCTURE OF a prototype for a universal flu vaccine. This nanoparticle is a hybrid of a protein scaffold (blue) with eight influenza hemagglutinin proteins on its surface (yellow). The hemagglutinin was specifically engineered to display antibody-binding sites common to all human influenza subtypes. The particle, designed by **Jeffrey Boyington** (Vaccine Research Center, NIAID), has been shown to be an effective immunogen in mice and ferrets. The three-dimensional structure of the particle was determined by cryoelectron microscopy by **John Gallagher** and **Audray Harris** (Laboratory of Infectious Diseases, NIAID).



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