

Gene Therapy Turns 30 Years Old

An NIH First That Almost Didn't Happen

BY CHRISTOPHER WANJEK, OD

WHEN STEVEN ROSENBERG REVIEWED A draft email-blast message advertising his upcoming keynote address at a May 9, 2019, meeting at the University of Pennsylvania, he was struck by the final paragraph: “This symposium comes at a historic time. Thirty years ago this May, Dr. Rosenberg and colleagues shepherded in the era of gene therapy when they removed, genetically altered, and returned cells to a patient with malignant melanoma.”

“This is not the kind of thing I keep track of, these historic events,” said Rosenberg, who as long-serving chief of the National Cancer Institute (NCI) Surgery Branch was the first to insert foreign genes into a human. “I’m too busy keeping track of today’s events.”

Nevertheless, he pulled out a set of handwritten notes in faded pencil and ink, circa 1990, listing the dates of the unprecedented 16 reviews needed to perform the world’s first gene-therapy experiment on a human. Next came a copy of the 1990 paper in the *New England Journal of Medicine* (*NEJM* **323**:570–578, 1990) describing the 1989 experiments, along with Rosenberg’s own printed list of historic NIH “firsts” around this period.

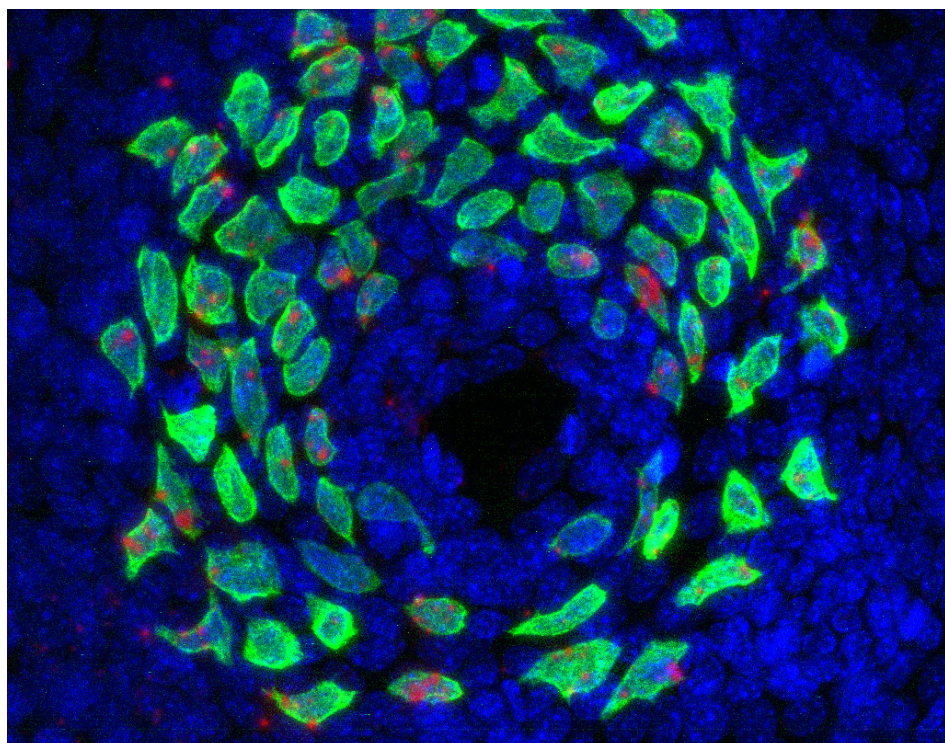
Then he rattled off names of colleagues and descriptions of patient volunteers as if the historic events transpired yesterday.

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The Dermatology Branch at NIH

Research, Colleagues, and a Shift from NCI to NIAMS

BY MOHOR SENGUPTA, NEI, AND LAURA STEPHENSON CARTER, OD



ISAAC BROWNELL AND LINGLING MIAO, NIAMS

Merkel cells (green) are clustered in touch-sensitive areas called touch domes. Shown: Neonatal mouse touch dome.

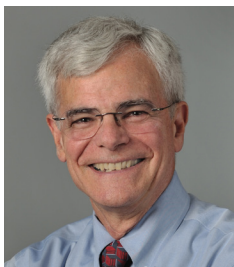
IN SPRING 1975, DESPERATE PARENTS BROUGHT THEIR SIX-YEAR-OLD DAUGHTER TO the NIH Dermatology Branch to be treated for a rare, chronic skin disease—coupled with arthritis—that had plagued her for more than four years and was making her miserable. Her doctors “were at the end of the line in terms of what to do,” said **Stephen Katz** in a 2018 oral-history interview. He was a senior investigator in 1975 and had joined the Dermatology Branch, which was then part of the National Cancer Institute (NCI), only the year before. “She had been treated with everything.” He biopsied some of the affected

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Equity and Diversity in the NIH Intramural Research Program

BY MICHAEL GOTTESMAN, DDIR, AND GISELA STORZ, CHAIR, NIH EQUITY COMMITTEE



HOW CAN EQUITY AND DIVERSITY in the NIH intramural research program (IRP) continue to be improved? The NIH Equity Committee (NEC) was established in November 2017 to help address this question. Modeled on the Central Tenure Committee, the NEC comprises 20 members—18 senior scientists and two scientific directors (SDs)—representing almost all institutes and centers (ICs). As its first task, the committee has been meeting with the SDs from each IC to learn about the demographics and resource distribution in their intramural programs.

In advance of each meeting, the SD—often with the help of the clinical director (CD) for that IC—provides de-identified information about the IC's tenure-track scientists, tenured scientists, senior scientists, and senior clinicians. The SD also provides an organizational chart showing the demographics of the IRP leadership and a written summary that comments on the data and addresses the hiring procedures, review practices, and selection process for ad hoc Board of Scientific Counselors (BSC) members. [The Deputy Director for Intramural Research (DDIR) and NIH Committee Management approve the members of the main BSC and ensure diversity; the ad hoc members are chosen by the ICs]. The summary also specifies how discretionary funding is awarded to investigators and includes proposed corrections to the

investigator-selection process that would ensure diversity; equity and inclusion goals; and recommendations for how the NEC and the Chief Officer for Scientific Workforce Diversity can help the IC achieve those goals.

At the meeting with the NEC, the SD gives a presentation about the information provided. Two committee members serve as primary reviewers and prepare a

One striking trend is the under-representation of certain groups in biomedical research . . . in leadership positions.

report that the NEC chair presents at a joint meeting of the SDs and CDs. The reports are constructed to share each IC's best practices as well as identify areas that need attention. To date, the NEC has evaluated the intramural programs of 12 ICs. The SDs have indicated that reviewing these data and getting feedback from the NEC has been a valuable experience.

The presentations have been highlighting trends across the IRP. One striking trend is the under-representation of certain groups in biomedical research—women, Asian Americans, and others—in leadership positions. The presentations also highlight extremely long tenures for some lab and branch chiefs (or their equivalents).

Given that a dynamic organization thrives on diversity and new ideas, in

October 2018 the NEC submitted a document to the DDIR with four main recommendations:

1. Each IC must clearly define the duties and expectations of lab and branch chiefs (or their equivalents).

2. The effectiveness of all lab and branch chiefs (or their equivalents) must be evaluated every four years by the BSCs. (Although the BSCs now evaluate the quality of intramural research at least every four years, they don't always evaluate the leadership effectiveness of the lab and branch chiefs.)

3. Lab and branch chiefs should remain in their positions for no more than three four-year BSC review cycles (plus time prior to the initial review and up to two years after the third cycle of positive reviews), except in extraordinary circumstances. This recommendation assumes that the BSC reviews are positive; if any of the reviews are negative, it's anticipated that the turnover of lab and branch chiefs would happen more quickly.

4. Leadership appointments must occur through open and transparent processes.

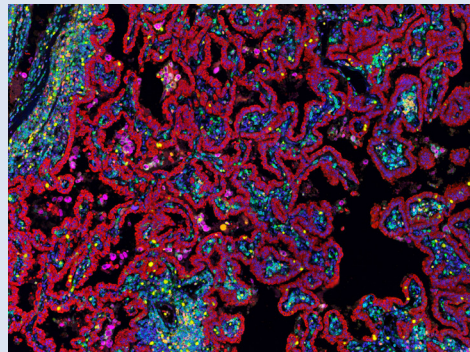
The NEC's recommendations—with input from the SDs, CDs, and NIH senior leadership—have now been converted into policy. Discussions are still ongoing about how this policy will be implemented. For example, one new policy will be that current lab and branch

chiefs whose service exceeds the three cycles of BSC review will be expected to step down within two years after the next BSC review of their lab or branch. Each IC is expected to have a completed plan by January 2020. Each SD will present their implementation plans to both the DDIR and NEC in the coming year.

Other trends are also being noted by the NEC. As a result of the frequent comment that many potential tenure-track candidates are not even aware of the tremendous benefits of working in the IRP, the NEC recommended that a “Rising Stars” seminar program be developed: Extramural junior scientists who are doing exciting research will be invited to give seminars at NIH. This recognition will allow IC investigators to become familiar with the work of the Rising Stars, who will in turn learn about the IRP. The NEC was encouraged by the very large response to the first call for nominations. Look for “Rising Star” talks in the coming months.

Much still remains to be done, however, to improve equity and diversity across the IRP. The NEC is very interested in any ideas you might have. Please send us your ideas: storzg@mail.nih.gov or gottesmm@mail.nih.gov. ●

Gisela Storz is an NIH Distinguished Investigator in the Eunice Kennedy Shriver National Institute of Child Health and Human Development. For more information on the way that BSCs work, go to <https://oir.nih.gov/sourcebook/processes-reviewing-nih-intramural-science/boards-scientific-counselors>.



HOUSSEIN A. SATER, NCI

A multiplex spectrally unmixed immunofluorescence image of a lung-cancer tissue stained with seven biomarkers.

New SIG: Multiplex Immunofluorescence

INTRAMURAL AND EXTRAMURAL SCIENTISTS who are using multiplex immunohistochemistry and immunofluorescence technologies to study complex tissue structures (such as tumor microenvironments) can share their knowledge via the Multiplex Immunofluorescence (MxIF) SIG. These technologies are used to identify the presence of multiple biological markers in a single tissue sample or different samples. The methodology can be an invaluable tool for tumor-tissue immune-profiling and as a way to identify multiple treatment targets in the same tissue section. This approach requires critical thinking and bioinformatic tools for effective segmentation, algorithm building, and advanced spatial analysis. This SIG aims to disseminate information about these technologies and foster new research collaborations across the NIH campus and around the world. The MxIF SIG welcomes pathologists, clinicians, postdocs, computer scientists, bioinformaticians, and others who have an interest in or are helping to move this field forward. The group meets monthly to discuss topics that include, but are not limited to, technical difficulties with staining, optimization, and validation. The MxIF SIG will host a seminar series featuring NIH and outside experts in the field (times will be determined later). The long-term premise of this new community

is to generate innovative approaches in the field of digital pathology through artificial-intelligence tools. For more information about the MxIF SIG and instructions for how to join the LISTSERV mailing list, contact the group chair and advisor: **Houssein A. Sater** (houssein.abdulsater@nih.gov).

New SIG: Epilepsy

THE EPILEPSY SCIENTIFIC INTEREST Group (SIG) brings together investigators, clinicians, and researchers who are interested in epilepsy and in understanding its pathophysiology and the effects of treatment on neural function and connectivity. Epilepsy studies at NIH take place in several institutes including NINDS, NIMH, and NICHD. NIH intramural researchers are using structural and functional imaging before and after surgical resection; investigating how surgical resection on regions of the human cortex affect neural plasticity and cognitive function; exploring intraoperative and long-term recordings of neural activity that are routinely acquired in the course of treatment; and evaluating human brain tissue samples to understand the physiology and molecular and genetic pathways in both normal and diseased brains. The Epilepsy SIG provides a forum for facilitating interactions among clinicians and researchers, and for sharing progress in ongoing studies and investigations across institutes and centers. The SIG holds meetings approximately every two months; each meeting provides an opportunity for investigators and clinicians inside or outside NIH to present their work. For more information about the Epilepsy SIG and how to join the LISTSERV mailing list, contact one of the chairs: **Kareem Zaghloul** (kareem.zaghloul@nih.gov) or **Sara Inati** (sara.inati@nih.gov). ●

From the Fellows Committee

Do-It-Yourself Training

BY AUTUMN HULLINGS, NCI



JILLIAN H. KLUSS, NIA

Ruth Chia (left) and Adamantios Mamais, who worked together to start a training program in which fellows teach fellows, welcomed attendees at a recent seminar. Chia and Mamais are pleased that many fellows, once they've been to a seminar, volunteer to teach.

FELLOWS CAN NOW GET PEER-TO-PEER training on the latest scientific topics and techniques. Since 2017, **Ruth Chia** (then a research fellow and now a staff scientist) and **Adamantios Mamais** (visiting fellow) at the National Institute on Aging (NIA) have been organizing seminars in which fellows teach fellows topics ranging from managing big data to conducting machine learning in genetics. The pair hopes to create more opportunities for fellows to feel comfortable teaching and learning from each other.

Mamais and Chia, who are both in NIA's Laboratory of Neurogenetics (LNG), came up with the idea of running a seminar on big data and cell-morphology analysis as a way to integrate and share their skills with other trainees. Their seminar was well-attended and received with great enthusiasm. During an LNG retreat, the lab's fellows expressed an interest in having more training and teaching opportunities, and their enthusiasm grew for a seminar

series that emphasized peer-to-peer training.

Chia and Mamais then organized a program that allowed postdocs to not only teach new knowledge but also demonstrate skills for conducting science in a real-life setting. Each seminar is about two hours long and includes a lecture and hands-on training, Mamais explained.

Without this demonstration portion, "the details between A [and] Z [of the science] are left out," said Chia. These seminars "highlight the nitty-gritty tips of how to do a scientific [technique] that you can't learn from a textbook."

Although seminars are organized by NIA fellows, trainees from other institutes and centers (ICs) are welcome to attend. Typically, 20 to 30 people attend each seminar, and fellows from more than a dozen ICs have participated.

Chia and Mamais have also developed assessment tools to evaluate the seminars. Feedback has been positive and encouraging so far. Past seminars

received an "excellent" or "very good" rating and appear to have increased the fellows' scientific knowledge and skills. On average, only 10 percent of the attendees rated themselves as having a "very good" or "excellent" knowledge or skill in the subject matter before each seminar. Afterward, about 70 percent reported their knowledge had improved.

Chia and Mamais are pleased that many fellows, once they've been to an LNG seminar, volunteer to teach. Thinking ahead, Chia and Mamais plan to work as a team and recruit other organizers on a rolling basis. They have even thought about forming a committee of fellows to run the series. Their success comes in part from the support they've received from their PIs, including the chief of the LNG, **Andrew Singleton**. The seminars "are a great example of junior folks taking control," he said. "They've taken care of everything—the agenda, [determining] what's of interest, and [figuring out] ways to self-assess. It's a great training opportunity on several levels."

NIH fellows have many exciting new workshops to look forward to in 2019 including "Tracing Tools for Neuronal Circuit Mapping" and "Python for Data Analysis." Don't worry if these topics are completely new to you. Fellows are encouraged to "just come," said Chia. "You don't need any background."

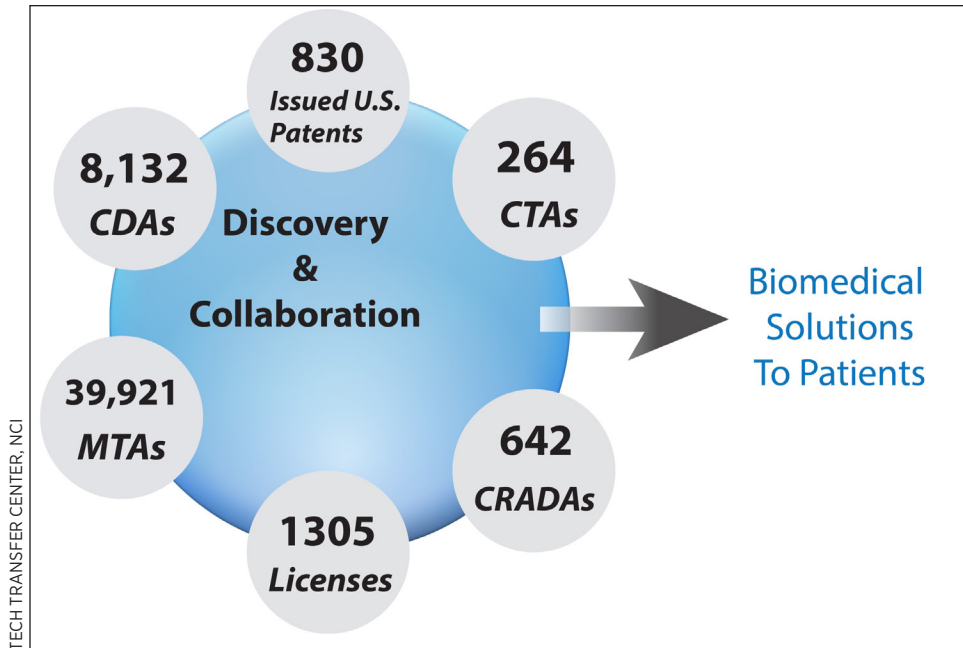
Chia and Mamais hope these seminars will break barriers to learning, provide teaching opportunities, and ultimately create a support network among fellows. ●

The 2019 seminars are held in Building 35, Room GG 607, from 10:00 a.m. to noon. For more information and a schedule, contact Adamantios Mamais (adamantios.mamais@nih.gov) or Ruth Chia (ruth.chia@nih.gov).

Technology Transfer:

Matching Researchers with Industry to Help Get NIH Inventions to Patients

BY ALLISON CROSS, NCI



NCI Tech Transfer Center (TTC) metrics for FY2007-2018. The NCI TTC handles technology transfer for NCI research labs as well as for labs from nine other NIH institutes and centers. Key: CDA (confidential disclosure agreement); CRADA (cooperative research and development agreement); CTA, (clinical trial agreement); MTA (material transfer agreement).

IN SEPTEMBER 2016, M WAS DIAGNOSED with metastatic Merkel-cell carcinoma (MCC), a rare and aggressive form of skin cancer. At the time of his diagnosis, patients with MCC were usually offered standard treatments that included surgery, radiation therapy, and/or chemotherapy. But M's doctors recommended that he participate in a clinical trial for the immunotherapy drug avelumab. M is now in remission and in March 2017, due in part to the success of that clinical trial, avelumab became the first FDA-approved treatment for MCC.

That drug was brought to market thanks to collaborations between NIH investigators and industry partners. Avelumab, an antibody that targets programmed death-ligand 1, was developed for clinical use by EMD Serono Inc. The company collaborated with National Cancer Institute (NCI) scientists, who performed the preclinical

studies and first-in-human clinical trials (conducted at the NIH Clinical Center). The preclinical research showed that avelumab allows T cells to efficiently kill a variety of tumor cells including MCC. The team's multicenter clinical phase 2 trial—funded by NCI, Merck KGaA of Darmstadt, Germany, and Pfizer—established safety and pharmacokinetic data on the drug and successfully demonstrated the use of avelumab in people with MCC. It is one of three drugs that received FDA approval in the past two years as a result of successful collaborations between investigators in the NCI Center for Cancer Research (NCI-CCR) and commercial partners.

Axicabtagene ciloleucel, another FDA-approved immunotherapy drug that resulted from a successful NIH-industry collaboration, is used to treat adults with relapsed or treatment-resistant large B-cell lymphomas. A team led by NCI-CCR's

Steven Rosenberg developed a technology that led to the drug, which is a CD19-targeted CAR T-cell immunotherapy. After promising early-phase clinical trials conducted at NCI, the drug was licensed to Kite Pharmaceuticals for further development and commercialization and received FDA approval in October 2017.

And, in September 2018, the FDA approved moxetumomab pasudotox, a bacterial toxin-based drug, for the treatment of some patients with hairy cell leukemia (HCL). The antibody moxetumomab was originally generated by **Ira Pastan** and colleagues at NCI and later licensed to MedImmune/AstraZeneca for clinical development. The FDA approval makes moxetumomab, marketed as Lumoxiti, the first treatment approved for patients with HCL who have already undergone at least two lines of standard treatments.

Commercial Partners

"If you look through the success stories [of] the products that have come out of the intramural program, most if not all of them involve a commercial partner," said **Tom Misteli**, the scientific director of NCI-CCR.

NIH does not perform product development or commercialization. And unlike their counterparts at universities, NIH investigators cannot spin out a company around an invention. So it's essential that there be a way for intramural ideas and technology to be transferred to industry partners.

Working with Tech Transfer

Tech-transfer coordinators and offices throughout NIH facilitate these collaborations by helping researchers choose from an assortment of

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NINDS Welcomes Lorna Role as New Scientific Director

Plans to Expand Mentorship and Training Opportunities

BY EMILY PETRUS, NINDS

THE FIRST EMAIL FROM LORNA ROLE to the scientists and staff of the National Institute of Neurological Disorders and Stroke (NINDS) read “TALK TO ME.” And, as the new NINDS scientific director (SD), that’s exactly what she wants people to do. Role hopes to “serve the faculty and do everything I can to make the environment as positive and productive as possible,” she said.

The first order of business was to assemble an executive advisory council, composed of NINDS principal investigators (PIs) and scientific staff, to provide her with valuable input and feedback on program planning. The committee members were selected based on differences in their experiences and expertise as well as with an eye toward gender and seniority balance. Role has already found the diverse opinions expressed helpful in considering potential organizational changes.

Among many important areas of focus, one of great interest to Role is mentoring and training. Role hopes to create more training opportunities, especially for NINDS junior scientists. She will also expand mentorship opportunities for junior scientists; formalize mentoring committees so that each includes three or more mentors; and require documented annual meetings.

In addition to her role as the NINDS SD, Role will also have her own lab—the Circuits, Synapses and Molecular Signaling Section—where her research will focus on the brain’s cholinergic system over the lifespan. Cholinergic signaling, which is essential for attention, cognitive processing, and memory, is compromised in neurological disorders including Alzheimer disease and Parkinson disease. Role’s work in these domains has focused primarily on physiological approaches to circuits and



Lorna Role, new SD for NINDS.

neural systems in genetically modified mice, but has recently expanded to include human studies with a novel cholinergic positron-emission-tomography tracer. She has been the principal investigator on numerous NIH-funded grants, supported continuously since 1982, and has received many awards.

Before coming to the NIH, Role was a full professor at Columbia University College of Physicians and Surgeons and then a State University of New York (SUNY) Distinguished Professor and Chair of the Department of Neurobiology and Behavior at SUNY Stony Brook. She was also co-director of SUNY Stony Brook’s Neurosciences Institute.

Role has brought with her **Simon Halegoua**, who served as her vice-chair and continues as a professor at SUNY Stony Brook in the Department of Neurobiology and Behavior. Halegoua is an NINDS senior advisor to the NINDS Office of the Scientific Director. Role enjoys working with Halegoua, she said, because he “always sees issues from a completely different

perspective” than she does.

As a department chair, Role doubled the size of the department at SUNY Stony Brook and increased the number of female faculty from one to six. Her commitment to increasing the representation of women in science will continue at NINDS.

Role obtained an A.B. in applied mathematics from Harvard University (Cambridge, Massachusetts) and a Ph.D. in physiology from Harvard Medical School (Boston). She did her postdoctoral training in pharmacology at Harvard Medical School and at Washington University School of Medicine (St. Louis) with **Gerald Fischbach**, who later served as the director of NINDS (1998–2001).

Role raised two daughters—Lindsay and Masha (short for Marussia)—as a single mother in the city of New York. Today, Lindsay is a psychiatrist at Johns Hopkins University (Baltimore) and Masha is a clinical psychologist at Tufts University (Boston). Role is excited to be geographically closer to Lindsay, who has a 14-month-old son, Role’s first grandchild. Although it can be harrowing to have two daughters in the field of mental health, who now roll their eyes at their mother’s antics “with authority,” Role is exceptionally proud of their accomplishments.

Beyond spending time with family and her husband **David Talmage** (a molecular geneticist at the National Institute of Mental Health), Role enjoys doing and looking at “ahht” (that’s “art” with a Boston accent) and listening to jazz. She and her husband are keeping their New York apartment, which was previously occupied by jazz legend Thelonious Monk. ●

[Read more about Lorna Role in the “Recently Tenured” section, which begins on page 16.](#)



Former NINDS SD, Alan Koretsky

Stepping Forward (Not Back!) to the Lab

BY EMILY PETRUS, NINDS



RITA DEVINE, NINDS

Former NINDS SD Alan Koretsky (front row, center) was given a wonderful thank you from the 2019 NINDS summer interns.

DURING ALAN KORETSKY'S 12 YEARS AS the scientific director (SD) of NINDS, widespread changes occurred to make the institute larger and more cohesive while maintaining it at the frontiers of neuroscience research. Milestones met during Koretsky's tenure include the completion of the John Edward Porter Neuroscience Research Center (Building 35), modernization of the clinical program, enhancement of core facilities for neuroscientists, and the recruitment of an outstanding—and increasingly diverse—group of PIs.

Some of the most satisfying experiences Koretsky encountered during his time as SD came from mentoring staff at all career levels.

“Alan has had immeasurable influence on my career,” said NINDS senior investigator **Daniel Reich**. “He’s been a tremendously supportive scientific director, striking what I think is a delicate and often difficult balance between providing opportunities to individual PIs while remaining fair to everyone. His vision for the NINDS [IRP] has made it a unique place in the world of neuroscience, spanning a far greater range of expertise and research interests than any other place I know.”

Koretsky is probably best known for

pioneering magnetic-resonance-imaging (MRI) technology such as arterial spin labeling, which is used in functional MRI to measure blood flow. His group also pushes MRI-resolution capabilities to detect single cells as they migrate throughout the brain; uses novel contrast agents to identify synaptic connections; and is developing sensors that are capable of detecting changes in physiology. Koretsky said he is excited to return to this research full time even though he is proud of the accomplishments of NINDS under his leadership.

Outside of the lab, Koretsky enjoys spending time with his family, including his wife **Tracy Koretsky** (who's in the office of scientific review in the National Institute of General Medical Sciences) and their three children. Evan is a senior studying chemistry at the University of California at Berkeley (Berkeley, California); after graduation he plans to do a brief stint in the pharmaceutical industry and then go on to medical school. Mathew is at the University of Vermont (Burlington, Vermont) studying data science, statistics, and skiing. Anna is a senior at Walt Whitman High School (Bethesda, Maryland) and plans to attend college in the fall to study physics and math. ●

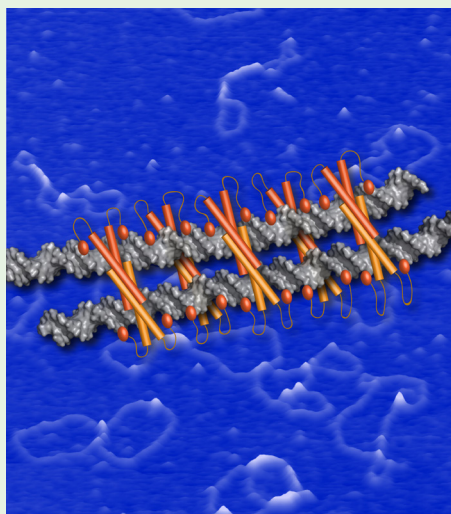
NIH ABBREVIATIONS

- CBER:** Center for Biologics Evaluation and Research, FDA
- 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
- FNIH:** Foundation for the NIH
- 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
- NHGR:** 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
- NIHGS:** 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
- OD:** Office of the Director
- 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



Intramural Research Briefs

SARA ANDRES AND SCOTT WILLIAMS, NIEHS



NIEHS: A model for the Ctp1-DNA bridging filament is depicted as orange Ctp1 protein tetramers bound to silver DNA strands, shown on a blue background of atomic-force imaging.

NIEHS: PROTEIN USES FILAMENTS TO BRIDGE BROKEN DNA

A protein called Ctp1 mediates the repair of DNA double-strand breaks by forming filaments that bridge two DNA strands, according to a study in yeast by NIEHS researchers and their colleagues. The findings could provide insight into a defect in DNA repair that causes Seckel and Jawad syndromes in humans.

In what is the first molecular snapshot of the Ctp1 protein bound to DNA, the researchers used atomic-force-microscopy imaging to observe how Ctp1 interacted with DNA. They discovered that while it was bound to double-stranded DNA, Ctp1 clustered into tetramers, each with an average length of approximately 15 base pairs. These Ctp1 tetramers formed filaments that each spanned approximately 180 base pairs and bridged two double-stranded DNA molecules. To mediate zipping the DNA, multiple Ctp1 tetramers lined up next to one another. Mutations that prevented Ctp1 from forming multiunit complexes severely impaired DNA bridging. Moreover, mutations that changed the DNA bridging made cells especially sensitive to radiation and chemicals that produce double-strand breaks. The findings could provide insight into the DNA-repair defect that causes Seckel syndrome

and Jawad syndrome, which are rare genetic diseases characterized by facial, skin, and finger abnormalities; developmental delays; and microcephaly. (NIH Authors: S.N. Andres, and R.S. Williams, *J Biol Chem* 294:3312–3320, 2019; DOI: 10.1074/jbc.RA118.006759.)

[BY JANELLE WEAVER, NIEHS]

NCI-DCEG: CONTROLLING CERVICAL CANCER

Scientists in NCI-DCEG are among the leaders of a growing global effort to greatly reduce the number of deaths each year from cervical cancer. They are building upon a legacy of research advances for this malignancy, that resulted from decades of investment in natural-history studies. By leveraging support from the Cancer Moonshot, partnerships with non-profit organizations, integrated health-care systems, pharmaceutical and medical-research companies, and others, NCI-DCEG investigators have launched a multi-faceted, highly-integrated research program to improve both primary and secondary prevention for a malignancy that affects more than half a million women each year and causes over 300,000 deaths worldwide. Read more at <http://bit.ly/2GUQoDs>.

NIDA: THE GENIUS OF CHEMOGENETICS

NIDA scientists and others funded by the institute have published findings showing the development of a new, groundbreaking chemogenetics technology for modulating brain function in a remote, precise, and ultra-sensitive manner in living subjects. These findings describe new chemogenetic ion channels for neuron activation and silencing that are controlled by very low doses of the anti-smoking medication varenicline. This drug is an especially attractive molecule for chemogenetic applications in part because it is well-tolerated by patients, effectively penetrates the brain, and has long-lasting effects. This technique for modulating neuronal function, reported in laboratory animals, has potential for use in

humans and may pave the way for new treatments for addiction, pain, depression, and other conditions. Ongoing experiments at NIDA are already applying this technology to study malfunctioning brain circuits and their relevance to development of drug addiction. (NIDA authors: J. Bonaventura, J.L. Gomez, and M. Michaelides, *Science* 364:eaav5282, 2019; DOI: 10.1126/science.aav5282)

NINDS: WANT TO LEARN A NEW SKILL? TAKE SOME SHORT BREAKS

In a study of healthy volunteers, NINDS researchers found that our brains may solidify the memories of new skills we just practiced a few seconds earlier by taking a short rest. The results highlight the critically important role rest may play in learning. (NINDS authors: M. Bonstrup, R. Thompson, G. Cruciani, and L.G. Cohen, *Current Biology* 29:1346–1351, 2019; DOI:<https://doi.org/10.1016/j.cub.2019.02.049>)

NIAID: EPSTEIN-BARR VIRUS VACCINE

A research team led by NIAID scientists has determined how several antibodies induced by Epstein-Barr virus (EBV), a herpesvirus that causes infectious mononucleosis and is associated with certain cancers, block infection of cells grown in the laboratory. They used this information to develop novel vaccine candidates that, in animals, elicited potent anti-EBV antibody responses that blocked infection of cell types involved in EBV-associated cancers. [NIAID authors: W. Bu, M.G. Joyce, H. Nguyen, D.V. Banh, F. Aguilar, Z. Tariq, R.A. Gillespie, S.F. Andrews, S.R. Narpala, A.B. McDermott, G.J. Nabel, M. Kanekiyo, and J.I. Cohen, *Immunity* pii:S1074-7613(19)30127-X, 2019; DOI: 10.1016/j.immuni.2019.03.010]

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<https://irp.nih.gov/catalyst/v27i3/research-briefs>

From Deep Sea Vents to Our Own Stomachs

Demystifying How Bacteria Thrive in Extreme Environments

BY MEGAN ROEGNER, NIDDK

WHAT COULD MICROORGANISMS THAT exist in extreme environments such as hot springs in the crushing depths of our oceans have to do with bacteria that reside in our own bodies? This is the question that the “Demystifying Medicine” lecture series attempted to answer on February 5, 2019. Bridging a huge gap, from 2,500 meters under the sea to inside our own intestines, Stefan Sievert and **John Dekker** (National Institute of Allergy and Infectious Diseases) explained how intricately connected these two worlds are and how new genomic technologies can help us understand the evolution of these microorganisms.

Sievert is a microbial ecologist at the Woods Hole Oceanographic Institution in Falmouth, Massachusetts. His primary interest is the microbes that live in deep-sea hot springs or hydrothermal vents. Temperatures around the vents vary from 41 to 662 degrees Fahrenheit. The warm temperature gradients coupled with chemical compounds from the vent fluids create a chance for life to thrive even in the dark and food-starved deep sea.

Instead of getting energy from light, as plants do in photosynthesis, these microbes use chemical energy in a process called chemosynthesis. The microbes form the base of the food chain at these highly productive ecosystems that were only discovered about 40 years ago. The microbes use chemical compounds such as hydrogen sulfide and hydrogen rising out of the vents, along with oxygen and nitrate from the deep-ocean water, to create the biological compounds needed for life from carbon dioxide.

As Sievert showed images of deep-sea vents and otherworldly creatures drifting by a deep-ocean submersible vehicle, it was hard

to imagine the connection to human health. Yet many of these bacteria are closely related to those that live, and cause disease, in our own bodies. Relatives of *Campylobacter* (which causes food poisoning), *Helicobacter* (which causes ulcers), and *Arcobacter* (a *Campylobacter*-like organism that can tolerate oxygen) are all found along the deep-sea vents.

While not genetically identical to their land-locked relatives, these bacteria do have some similar traits including a glycosylation pathway that aids in interactions with any host species. The bacteria also tend to be highly adaptive, for example by having highly plastic genomes due to a lack of DNA-repair mechanisms, perhaps giving them the unique ability to exist in extreme environments such as the deep oceans and the human intestinal system.

Did the sea and terrestrial bacteria evolve together or did the evolution take place later? New genomic techniques introduced by the next speaker, John Dekker, may hold the secret to unlocking this mystery.

Although Dekker did not talk about the same bacteria as Sievert, he reviewed recent advances from labs around the world involving the application of genomic techniques to identify other human pathogens—such as *Leptospira* (which is passed from animals to humans), astrovirus (a major cause of acute diarrhea in children), and Ebola virus.

Dekker takes specimens from infected patients and applies high-throughput sequencing to generate a huge number of short “reads” of the DNA base-pair sequences which are then analyzed computationally. All the human reads are filtered out, and the remaining reads are cross-referenced against databases of bacterial, viral, and fungal pathogens.



STEFAN SIEVERT, WOODS HOLE

Microorganisms that exist in deep-sea hydrothermal vents like this one have a lot in common with the microorganisms that live inside our bodies. Relatives of *Campylobacter* (which causes food poisoning), *Helicobacter* (which causes ulcers), and *Arcobacter* (a *Campylobacter*-like organism that can tolerate oxygen) are all found along the deep-sea vents.

These techniques have been used to diagnose rare diseases and to track the evolution of Ebola outbreaks in West Africa. An even newer technology, nanopore sequencing with a pocket-sized sequencing device, allows this analysis to be completed faster and with greater accuracy. During the 2015 Ebola outbreak, on-site use of nanopore sequencing allowed researchers to track the evolution of the virus in real time. Dekker also presented work from his own lab in which it used rapid nanopore sequencing to identify antibiotic resistance mechanisms in bacteria.

The application of genomic techniques helps researchers understand how bacteria evolved to develop resistance to antibiotics and adapt to new environments. Perhaps these same techniques applied to disease outbreaks can answer the question of how deep-sea bacteria came to play a part in our day-to-day lives. ●

Read more online at

<https://irp.nih.gov/catalyst/v27i3/from-deep-sea-vents-to-our-own-stomachs/>

To see a videocast of the whole lecture:

<https://videocast.nih.gov/launch.asp?27302>

Gene Therapy Turns 30 Years Old

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NCI

Thirty years ago this May, Steven Rosenberg and colleagues shepherded in the era of gene therapy when they removed, genetically altered, and returned cells to a patient with malignant melanoma.

Rosenberg's surprise over the 30th anniversary perhaps was more of a *tempus fugit* feeling. Time flies when you're pioneering the development of effective immunotherapies and gene therapies for patients with advanced cancers.

As far as classic clinical studies go, the set of gene-therapy experiments in 1989 was akin to the NIH face that launched a thousand research ships. Gene therapy is now performed worldwide, with several gene-therapy drugs approved by the FDA, including one that Rosenberg helped develop (axicabtagene ciloleucel, trade name Yescarta, for the treatment of adult patients with relapsed or treatment-resistant large B-cell lymphoma).

Thirty years ago, Rosenberg and his team were building on the pathbreaking experimentation by **French Anderson** (National Heart, Lung, and Blood Institute, NHLBI), **Michael Blaese** (National Human Genome Research Institute), and others at the NIH who in 1985 used a retrovirus to carry a correct human gene for adenosine deaminase (ADA) into patient cells in a tissue culture.

In 1988, NIH researchers switched from bone marrow to white blood cells as the cell of choice to “infect” with the retrovirus, which dramatically increased the number of correct genes taken up by the cells in animal experiments. This result set the stage for Rosenberg's group, who in 1988 were the first to use non-genetically modified tumor-infiltrating lymphocytes (TIL) cells to successfully mediate tumor regression.

On May 22, 1989, Rosenberg and his team attempted a retroviral-mediated gene transduction to introduce the gene coding for resistance to neomycin into human TIL cells before their infusion into patients; the goal was to help determine the traffic of the infused cells in the body. The results of this proof-of-concept experiment with marked TIL cells, first performed on a 52-year-old truck driver from Indiana, demonstrated that the engineered virus can be used safely in humans and also elucidated the prolonged survival of the transferred cells in the patient.

The initial experiments on the truck driver and four other patients were a success, with no signs of toxicity or ill effects of the procedure, although all the patients ultimately died of their cancer.

The preceding year, however, had been filled with trouble and angst. In mid-1988, Rosenberg sought permission from the NCI and NHLBI institutional review boards to conduct his experiment. It was so novel that more and more reviews were needed. On October 3, 1988, the Recombinant DNA Advisory Committee (RAC) approved the Rosenberg-led experiment by a margin of 16 to 5. That approval should have been the green light.

However, given the controversy of gene therapy—with some members of the public opposed to scientists “playing God” and tinkering with the human genome—the NIH Director at the time, **James Wyngaarden**, mandated that the

experiment could only move forward with a unanimous vote from the RAC. Perhaps miraculously, Rosenberg got just that—a 13 to 0 RAC vote—on December 9, 1988. And that unanimous approval again should have been the green light.

However, upon Wyngaarden's approval, American economic and social theorist Jeremy Rifkin, representing the Foundation on Economic Trends, filed suit against the NIH. Rifkin, well known as an activist against certain biotechnology trends, argued that the RAC approval was not at a public meeting and violated NIH guidelines. This matter took several more months to resolve.

With the success of the initial gene-therapy experiments, Anderson, working with Blaese and Rosenberg at the NIH, stepped up the game in 1990 with the therapeutic use of a virus to deliver the correct gene to two girls, ages 4 and 9 years old, with ADA deficiency. The results also were successful, albeit limited.

Progress in gene therapy has since exploded, with more than 2,000 clinical trials worldwide, according to the Gene Therapy Clinical Trials Worldwide Database. These trials include dozens of clinical trials at the NIH testing immunotherapy for cancers and other cell-based therapies for diseases such as sickle cell. To facilitate even more experimentation, the NCI has invested in a 6,000-square-foot facility with sterile cell-processing units to create naturally occurring and genetically modified lymphocytes for patient therapy. This facility is under construction between Buildings 10 and 30 on the NIH Bethesda, Maryland, campus.

The impact will be huge, and it all started right here 30 years ago. ●

To read a profile of Steven Rosenberg that appeared in the January-February 2018 issue of the *NIH Catalyst*, go to <https://irp.nih.gov/catalyst/v26i1/steven-a-rosenberg-md-phd>.

My Room, Your Room

Room 212, The Cloister

BY LAURA STEPHENSON CARTER, OD

NIH MEDICAL RESEARCH SCHOLAR

Nicole Dalal knew she was living in a historic building once occupied by nuns. But what she didn't know was that her residence—Room 212 in the Cloister (Building 60), built in 1923 and taken over by NIH in 1984—had its own special history: Former National Cancer Institute (NCI) Director—now Acting Commissioner of the FDA—**Ned Sharpless** had lived there in the early 1990s. He was a medical research scholar when the program was run as a partnership between NIH and the Howard Hughes Medical Institute (HHMI).

The Medical Research Scholars Program (MRSP) provides a year of intensive training for medical, dental, and veterinary students—typically between their third and fourth years of professional school—at the NIH campus in Bethesda, Maryland. The program is a successor program to the NIH-HHMI Research Scholars Program that ran from 1985 to 2012.

“I thought it was pretty cool [that Ned Sharpless] lived in the same room as me,” said Dalal.

Sharpless, who visited his old room and met Dalal in January, was pleased that the room—which is really a small one-bedroom apartment—looked pretty much as he remembered it. One difference was that in the 1990s, the shelves were filled with textbooks and reprints of journal articles; Dalal's shelves are nearly bare. Nowadays, medical students often use online materials, so there's little need to have physical books and printouts around.

Suddenly, Sharpless noticed the Duke University banner hanging on the wall and gasped in mock disbelief. Dalal is a student at Duke University School of Medicine (Durham, North Carolina), home to the

Blue Devils. Sharpless was a medical student at Duke's arch rival school—the University of North Carolina (UNC) School of Medicine (Chapel Hill, North Carolina), home of the Tarheels. The two engaged in some good-natured teasing.

When Sharpless was an NIH-HHMI program participant, he did research on HIV with the late **Monique Dubois-Dalcq**, who was the chief of the Laboratory of Viral and Molecular Pathogenesis in the National Institute of Neurological Disorders and Stroke. After graduating from medical school and completing his residency in internal medicine and a hematology-oncology fellowship, he spent two years on the Harvard Medical School (Boston) faculty. In 2002, he accepted an appointment at the UNC School of Medicine later becoming the Wellcome Professor of Cancer Research and director of UNC-Chapel Hill's Lineberger Comprehensive Cancer Center. In 2017, he was sworn in as the 15th director of NCI, and on April 5, 2019, he went on leave from that position to become the Acting Commissioner of the FDA.

Sharpless still conducts research, too. His current work is on understanding the biology of the aging process that promotes the conversion of normal self-renewing cells into dysfunctional cancer cells. He has made seminal contributions to the understanding of the relationship between aging and cancer and in the preclinical development of novel therapeutics for melanoma, lung cancer, and breast cancer.

Dalal, who hopes to become an oncologist one day, is doing cancer epidemiology research with **Lindsay Morton**, a senior investigator in the NCI's Radiation Epidemiology Branch. Using the Surveillance, Epidemiology, and End Results database, which provides detailed population-based statistics on cancer, Dalal is trying to determine the causes of death of people who survived their cancers. “With better treatments, patients are surviving their cancers but may be dying of other causes,

such as infections and heart disease, at a rate that is different from the general U.S. population,” she said. Such information is important for oncologists to understand so they know how to appropriately monitor and treat their patients' unique disease risks.

Population-based research “allows scientists to study so many more patients—in different socioeconomic groups and geographic locations—than can be conventionally studied in clinical trials,” she said.

But past and present MRSP scholars do more than spend time in the lab. Sharpless and Dalal enjoyed being so close to Washington, D.C., cooking pizza, and playing sports. Sharpless played tennis and basketball and loved running in Rock Creek Park. Dalal enjoys running, too, and recently ran in the “Rock ‘n’ Roll Marathon” in Washington, D.C., along with two other Cloister residents. ●

For more information about the MRSP, go to <https://cc.nih.gov/training/mrsp/index.html>.



ERIN BRANSON

Medical Research Scholar Nicole Dalal (right) was delighted to meet Acting FDA Commissioner Ned Sharpless who had lived in her room in the Cloister (Building 60) when he was part of the NIH-HHMI Research Scholars Program in the 1990s. Dalal, who attends Duke University School of Medicine (notice the banner in the background), teased Sharpless about having attended medical school at Duke's arch rival—the University of North Carolina at Chapel Hill.

Dermatology Branch

CONTINUED FROM PAGE 1



NIAMS

NIAMS Director Stephen Katz, who died on December 20, 2018, was a leader in the study of skin-based immunology and trained more than 45 people who have gone on to play significant roles in dermatology.

areas of her skin and scheduled her to return in July for a follow-up visit.

After analyzing the biopsied tissue and conferring with his brother, who was also a dermatologist, Katz determined that the child had a rare disease called erythema elevatum diutinum. It's characterized by painful, necrotizing vasculitis that causes thick red, purple, brown, and yellow patches on knees, elbows, hands, and other areas of the body. He had even come up with a plan for how to treat it. "I knew that this rare disease responded to a drug that wasn't usually included when one says, 'She was treated with everything,'" said Katz. "This is a drug called dapsone, which was otherwise used [for] treatment of leprosy." Colleagues laughed in disbelief when Katz told them what he had in mind.

But when the girl returned for her follow-up visit on the July 4 weekend, Katz did treat her with dapsone and within a couple of days, she was 98 percent better, he said. "She's been on that drug for 40-some years because if she stops, the disease comes back." To this day, dapsone is the first line of treatment for this rare disease.

Katz, who died in December 2018, became the chief of NCI's Dermatology Branch in 1980 and served in that capacity

until 2001 even after being made Director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) in 1995. During his tenure as chief, the branch grew into a formidable force and trained dozens of scientists who went on to assume leadership positions in dermatology departments throughout the world—including Germany, Austria, England, Hungary, Belgium, Switzerland, Japan, Korea, Taiwan, and the United States. He's also largely responsible for building an awareness that the skin is an important part of the body's immune system and that abnormalities in the immune system are associated with many skin diseases.

Under Katz's guidance, Dermatology Branch scientists have made many discoveries including the:

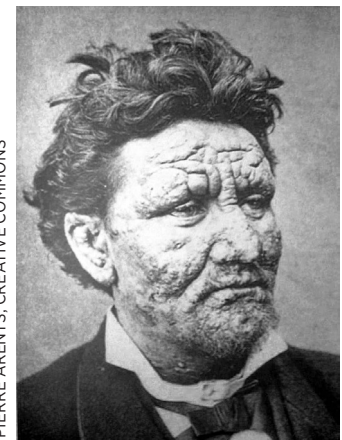
- Pathogenesis of xeroderma pigmentosum (XP), a genetic disease that makes cancer more likely and is associated with developmental abnormalities and cellular hypersensitivity to ultraviolet radiation
- Use of synthetic retinoids to treat severe disfiguring acne and as chemoprevention agents
- Composition and function of the skin immune system with special emphasis on Langerhans cells
- Cytokines and chemokines that mediate cutaneous inflammation
- Structure of adhesive junctions that mediate the attachment of keratinocytes to each other and to underlying basement membranes
- Characterization of patient autoantibodies that react with adhesive structures and that cause skin-blistering diseases
- Characterization of dendritic-cell HIV interactions; identification of mechanisms that regulate leukocyte and cancer-cell localization
- Characterization of normal tissue and cancer stem cells

Early Dermatology Research

Dermatology research was being conducted at NIH as far back as the 1930s, before NIH was divided into institutes and centers (ICs). The Division of Industrial Hygiene, for example, investigated the health of workers in different industries. In 1939, the division's scientists described industrial dermatitis (redness, itchiness, cracking, and blistering of the skin caused by tar and other substances) and melanosis (a form of hyperpigmentation caused by increased melanin). The research led to procedures for protecting workers' skin. The Occupational Safety and Health Administration, and then the National Institute for Occupational Safety and Health (part of CDC) and the Environmental Protection Agency, have taken over much of what the division used to do.

NIH's Division of Infectious Diseases, led by **Rolla E. Dyer**, focused on a wide range of diseases caused by bacteria, viruses, and fungi. In 1934, **Chester Emmons**, an expert on fungi as a cause of disease, established the current classification system of dermatophytes (fungi that infect the hair, skin, and nails, causing ringworm).

The Division also studied leprosy (today, Hansen disease), a contagious disease caused by a Mycobacterium species that affects the skin, nerves, and eyes. In Hawaii, the



PIERRE ARENTS, CREATIVE COMMONS

Early dermatology research at NIH included studies of leprosy. Shown: Twenty-four year old man from Norway, suffering from leprosy (circa 1886).

division's Leprosy Investigation Station invented orthopedic devices to correct deformities caused by nerve damage and found that malnourishment (particularly deficiencies in vitamin B1 and calcium) increased susceptibility to leprosy. It was not until the late 1940s that the causative organism was found and an antibiotic treatment for leprosy was developed.

Beginning in 1937, NCI (which had been established by Congress as a separate entity within the Public Health Service and became a division of NIH in 1944) funded a Public Health Methods study on the number and characteristics of cancer deaths in the United States using records dating back to 1900. Among the findings were that although more people in the northeast *died* of cancer, more people in the South *had* cancer. The scientists thought the difference was because of the greater prevalence of skin cancer in the South.

Branch Founded in the 1960s

There wasn't a formal Dermatology Branch at NCI until 1961, when **Eugene Van Scott** became its first chief. He left NIH in the late 1960s to head Temple University's (Philadelphia) dermatology department and later founded a company that became a major skin-care corporation. His work on psoriasis led to the development of methotrexate, which is to this day a first-line systemic drug for its treatment. He also won a Lasker Award in 1972 "for his outstanding contribution to the concept of topical chemotherapy in the treatment of mycosis fungoides" (the most common form of the skin-cancer cutaneous T-cell lymphoma).

Marvin Lutzner became branch chief next. He and two French dermatologists discovered Lutzner cells, a mutated form of T lymphocytes. Lutzner cells can cause cutaneous T-cell lymphoma, a type of non-Hodgkin lymphoma that starts as skin

lesions and may eventually spread to other parts of the body. During his tenure, he collaborated on XP research with other NCI scientists, including **Kenneth Kraemer**, who was a postdoc in the Dermatology Branch in the early 1970s and is now a senior investigator in NCI's Laboratory of Cancer Biology and Genetics.

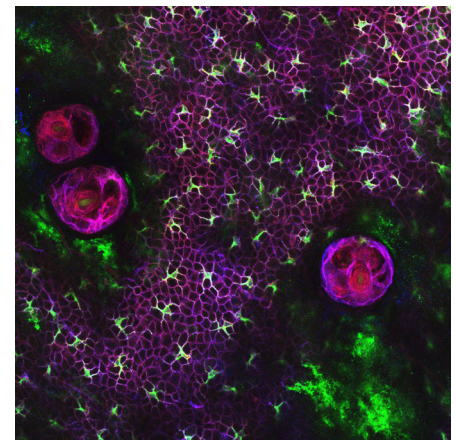
In 1969, Lutzner recruited **Gary Peck**, who studied how retinoids could change epidermal differentiation from keratin-producing to mucus-producing. He collaborated with **Peter Elias** (currently a world-renowned skin biologist at the University of California at San Francisco) and **John DiGiovanna** on research that led to the widespread use of retinoids in patients who were at high risk for multiple skin cancers. Peck, who left NIH in the 1990s to become the founding director of the Melanoma Center in the Washington Cancer Institute (Washington, D.C.), later won several awards in recognition of his discovery of isotretinoin (Accutane) for the treatment of severe, recalcitrant nodulocystic acne and other applications, including the prevention of basal-cell carcinomas.

Peter Steinert, an international expert in the structural biology of the skin, came to NCI's Dermatology Branch in 1973. In 1990 he started the Laboratory of Skin Biology in NIAMS. He died in 2003.

DiGiovanna went on to become the head of the Dermatology Clinical Research Unit in NIAMS in 1994. His group discovered the genes underlying several severe skin disorders. Currently a senior research physician in NCI, he continues to work with Kraemer on the clinical, basic, and translational studies of DNA-repair disorders.

Steve Katz as Chief (1980–2001)

Katz, who had come to NIH in 1974 and had started his own laboratory with **Ken Hertz** and a technician, became Acting



CHRIS NAGAO, NIAMS

Former Dermatology Branch Chiefs Steve Katz and Mark Udey, as well as others in the branch, made important discoveries concerning Langerhans cells, which are dendritic cells of the skin and present in all layers of the epidermis. Shown: Langerhans cells (green) visualized in whole-mount skin. The purple circles are hair follicles.

Branch Chief in 1977 and permanent chief in 1980. Under Katz's leadership, the branch started having a greater focus on the skin as an immunological organ. There was an increasing interest in skin immunology worldwide at the time, and Katz was considered a pioneer in the field.

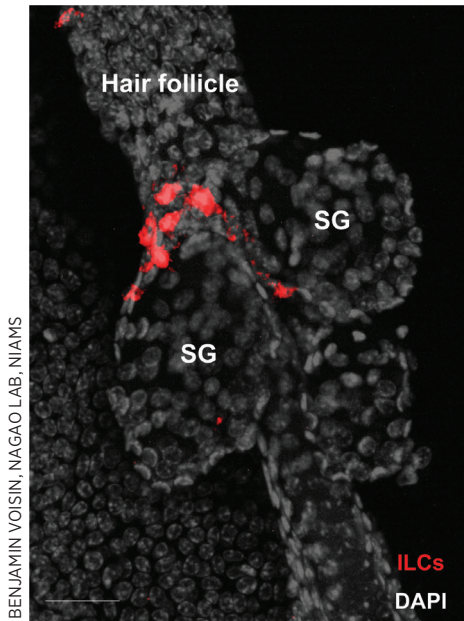
Katz's "research showed that skin is an important component of the immune system both in its normal function and as a target in immunologically mediated disease," wrote Benjamin Barkin in a 2016 article in *The Dermatologist*. In addition, "Dr. Katz and his colleagues have added considerable new knowledge about inherited and acquired blistering skin diseases." Katz discovered an antigen that is associated with pemphigus vulgaris, an antibody-mediated autoimmune skin disease that results in blisters (*J Clin Invest* **70**:281–288, 1982).

In addition, Katz did landmark studies on Langerhans cells, which are dendritic cells of the skin and present in all layers of the epidermis. His first stint with the cells was when he and **Georg Stingl**, then a postdoctoral fellow from Vienna (he later became professor and chair of dermatology at

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Dermatology Branch

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BENJAMIN VOISIN, NAGAO LAB, NIAMS

Hair follicles are the epicenter of immune cells in the skin. Shown: Innate lymphoid cells (ILC) that have been guided to the upper hair follicles where they control sebaceous gland (SG) function to tune the microbial balance on skin surface.

the Medical University of Vienna in Vienna), investigated the immunological functions of surface markers of Langerhans cells. These studies, done in collaboration with **David Sachs** (now a professor emeritus at Harvard Medical School in Boston), led to the new discovery that Langerhans cells could originate from a mobile pool of cells in the bone marrow and likely play an important role in allogeneic graft rejection. (*Nature* 282:324–326, 1979).

In his long association with the Dermatology Branch, Katz supervised dozens of trainees, many of whom went on to become notable leaders in dermatology around the world.

In 1995, he became the director of NIAMS, but he remained the Dermatology Branch Chief until 2001, when **Mark Udey** took over. Katz also continued his own dermatology research until his death in 2018.

“I don’t know anyone who’s had as broad an impact as Steve Katz,” said Udey. “He trained over 45 people” who have gone on to play significant roles in dermatology.

Mark Udey as Chief (2001–2017)

Udey, who had been an assistant professor of medicine (dermatology) at Washington University School of Medicine (Saint Louis), was drawn to NIH in 1989 because it was doing research in areas that interested him: skin immunology and Langerhans cells. He became internationally recognized for his work on cutaneous immunophysiology and for his seminal research on the biology of Langerhans cells including the role of epithelial cadherin (which plays a role in cell migration and adhesion) and transforming-growth-factor-beta (which controls cell growth, proliferation, and differentiation) in the cells’ development and localization.

Udey rose from the position of investigator to senior investigator in 1996 and to branch chief in 2001. Under his leadership, the branch expanded its clinical-research program and broadened its range of research to include studies of graft-versus-host disease (GVHD) and Merkel cells. The branch also continued to be a training ground for dermatologists. Udey considers one of his major accomplishments to be the recruitment and mentoring of **Ed Cowen**, **Heidi Kong**, **Isaac Brownell**, and **Chris Nagao**, who are all leaders in NIH’s Dermatology Branch now.

Udey left NIH in 2017 to become a professor in the Department of Medicine (Dermatology) at the Washington University School of Medicine. He has also been the editor of the *Journal of Investigative Dermatology* since 2017.



Mark Udey

Today’s Dermatology Branch

In 2017, soon after Udey’s departure, the Dermatology Branch moved from NCI to NIAMS. The move made sense, according to NIAMS Scientific Director **John O’Shea**, because the institute studies skin diseases as well as arthritis and musculoskeletal diseases. Despite the administrative shift, branch scientists didn’t even have to move their labs because they were already adjacent to NIAMS labs in the NIH Clinical Center (Building 10).

Today, the Dermatology Branch is headed by Acting Chief **Edward Cowen** and continues to conduct clinical and basic investigations of skin biology and researches the etiology, diagnosis, and treatment of skin disease. Research areas of interest include the skin as an immunological organ and the role of tissue-leukocyte-microbiota cross-talk in mediating immunological and structural homeostasis; inflammatory skin diseases in patients and in mouse models; the human microbiome in healthy individuals as well as in patients with atopic dermatitis and primary immunodeficiencies; long-term clinical and laboratory studies and investigator-initiated therapeutic trials in chronic GVHD, neurofibromatosis, and autoinflammatory skin disease; skin stem cells; and cutaneous malignancies including Merkel-cell carcinoma.

On the facing page are highlights of the Dermatology Branch current activities.

Read more online including comments about Stephen Katz from his former trainees and a description of other dermatology research happening at NIH: <https://irp.nih.gov/catalyst/v27i3/the-dermatology-branch-at-nih/>

Dermatology Branch at NIAMS

Dermatology Consultation Service

Head: Senior Clinician Edward Cowen, M.D., M.H.Sc.

The Dermatology Consultation Service evaluates patients with a variety of rare diseases that have cutaneous manifestation as well as patients who experience adverse reactions to experimental therapeutic agents or develop unrelated skin conditions while at the NIH. Dermatology Branch clinical fellows, fellows from other NIH ICs, and visiting dermatology residents from around the country receive training on the service.

Cowen is one of a very few dermatologists in the United States studying cutaneous GVHD. He discovered that total-body radiation during conditioning before hematopoietic-cell transplantation poses a risk for the development of a debilitating form of skin thickening caused by GVHD. He also found that adverse reactions to the antifungal agent voriconazole can cause immunosuppressed patients, including patients with GVHD, to develop squamous-cell carcinoma.

Assistant Research Physician **Dominique Pichard** studies patients with rare diseases such as chronic GVHD and neurofibromatosis 1 (NF1). She is conducting clinical trials to test the efficacy of the topical Janus kinase inhibitor ruxolitinib as a treatment for epidermal chronic GVHD and to test the efficacy of a systemic mitogen-activated-protein-kinase-kinase (MEK) inhibitor in NF1 cutaneous neurofibromas.

Read more about the NIH Dermatology Branch and its training programs at <https://irp.nih.gov/catalyst/v27i3/the-dermatology-branch-at-nih/>

Cutaneous Development and Carcinogenesis Section

Head: Investigator Isaac Brownell, M.D., Ph.D.

This section studies the regulation of cutaneous stem cells and the molecular pathogenesis of skin cancer, especially Merkel cells and Merkel-cell carcinoma.

Brownell oversaw a clinical trial that led to the 2017 FDA approval of avelumab to treat Merkel-cell carcinoma. His team collaborates with the National Center for Advancing Translational Science to do drug-discovery studies for this disease and plans to test one of the drugs in a clinical trial in collaboration with the NCI Rare Tumors Initiative and AstraZeneca, which manufactures a nanoparticle version of this drug.

Cutaneous Microbiome and Inflammation Section

Head: Investigator Heidi H. Kong, M.D., M.H.Sc.

The section studies the skin microbiome—in both healthy individuals and patients with skin diseases—with the goal of expanding the understanding of host-microbe interactions. The Kong group has examined the role of microbes in atopic dermatitis and other eczematous skin diseases. Current work has expanded to include investigations into human-skin fungi and viruses.

Kong is collaborating with NCI investigators to look at the skin microbiome of cancer patients who are undergoing treatment with immunotherapies. She also works closely with intramural researchers from other ICs to study and care for patients with dedicator of cytokinesis 8 (DOCK8) immunodeficiency who are undergoing stem-cell transplants. The syndrome is a rare immune disorder that causes immune cells to malfunction; patients suffer from

recurrent viral infections of the skin and respiratory system and typically have allergies, asthma, and an increased risk for some types of cancer.

Since 2007, Kong has partnered with **Julie Segre** (National Human Genome Institute) to perform many large-scale DNA-sequencing skin-microbiome studies. Their analyses have shown that human microbiota varies by specific regions of the skin surface and among individuals.

Cutaneous Leucocyte Biology

Head: Stadtman Investigator Keisuke (Chris) Nagao, M.D., Ph.D.

The section is exploring the mutual cross-talk that occurs among the skin epithelium, the microbiota, and the immune cells that are involved in maintaining immunological and microbial homeostasis in skin. In particular, Nagao's group has identified hair follicles as the control towers of skin immunity; the follicles guide the localization of skin-resident immune cells and enhance their survival by producing chemokines and cytokines. In turn, the immune cells help shape the function of the skin barrier. The group has established that such cross-talk is crucial in regulating the balance of the skin microbiota during homeostasis and that imbalance, or dysbiosis, of the microbiota drives inflammation in atopic dermatitis.

Nagao collaborates with Kong and investigators in NIAID to understand the human-disease pathology that underlies inflammation and susceptibilities to certain microbial agents. In particular, Nagao focuses on patients with severe drug hypersensitivities and monogenic diseases that manifest as atopic skin inflammation. He receives cross-support for his work from other ICs in the form of collaborations with investigators in the NCI, NIAID, the National Heart, Lung, and Blood Institute, and the National Institute on Aging.

Recently Tenured



LORENZO LEGGIO, NIAAA and
NIDA



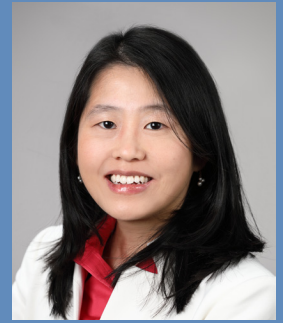
FRANK MALDARELLI, NCI-CCR



ALEKSANDRA URSZULA NITA-
LAZAR, NIAID



LORNA ROLE, NINDS



EDWINA H. YEUNG, NICHD

LORENZO LEGGIO, M.D., PH.D., M.Sc., NIAAA AND NIDA

Senior Investigator and Chief, Section on Clinical Psychoneuroendocrinology and Neuropsychopharmacology (CPN), a joint National Institute on Alcohol Abuse and Alcoholism (NIAAA) and National Institute on Drug Abuse (NIDA) laboratory; Associate Director for Clinical Research, Medication Development Program, NIDA

Education: Catholic University of Rome, Rome (M.D.; Ph.D. in physiopathology of nutrition and metabolism); Department of Clinical Physiopathology, University of Florence, Florence, Italy (M.Sc.)

Training: Residency in internal medicine, Agostino Gemelli University Polyclinic, Catholic University of Rome, Rome; postdoctoral fellowship in psychiatry and human behavior, Brown University (Providence, Rhode Island)

Before coming to NIH: Assistant professor, Warren Alpert Medical School and Public Health Program, Brown University

Came to NIH: In 2012 as a tenure-track clinical investigator

Selected professional activities: Professor (adjunct), Department of Behavioral and Social Sciences, Brown University; member, American College of Neuropsychopharmacology; member of several editorial boards of scientific journals; member of several advisory boards

Outside interests: Listening to music; watching movies; going to the opera

Website: <https://irp.nih.gov/pi/lorenzo-leggio>

Research interests: My laboratory conducts clinical and translational inpatient and outpatient studies to identify possible novel medications for addiction. My group uses a combination of state-of-the-art, innovative biobehavioral and pharmacological procedures performed under well-controlled laboratory conditions. Brain-imaging techniques, such as functional magnetic-resonance imaging, are also used. We are particularly interested in the role of the gut-liver-brain axis in alcohol- and drug-seeking behaviors.

Specifically, we are currently investigating the potential role of feeding-related pathways—such as those for the hormones ghrelin, leptin, oxytocin, and glucagon-like peptide 1—as possible new neuropharmacological targets for the treatment of alcohol- and substance-use disorders. We are also investigating other neuroendocrine pathways such as the aldosterone-mineralocorticoid receptor pathway.

We have recently expanded our research to look at the role of the gut microbiome in heavy drinkers of alcohol. Our special emphasis is on the relationships

between alcohol-related seeking behaviors and the microbiome-gut-brain axis. Future research includes work on the effects of bariatric surgery on alcohol-related seeking behaviors.

Our preclinical work—in collaboration with other laboratories—and human studies in our lab aim to shed light on the possible role of these pathways in alcohol- and substance-use disorders.

FRANK MALDARELLI, M.D., PH.D., NCI-CCR

Senior Investigator and Head, Clinical Retrovirology Section, HIV Drug Resistance Program Host-Virus Interaction Branch, Center for Cancer Research, National Cancer Institute

Education: Johns Hopkins University, Baltimore (B.A. in biology); City University of New York, New York (Ph.D. in biomedical sciences); Mount Sinai School of Medicine, New York (M.D.)

Training: Residency in internal medicine, The Presbyterian Hospital (New York); medical staff fellow and senior staff fellow, Laboratory of Molecular Microbiology, National Institute of Allergy and Infectious Diseases (NIAID)

Came to NIH: In 1988 for training; became a clinical associate in NIAID in 1996; became clinical associate in NCI in 1998; became staff physician in 1999; in 2012, became



head of Clinical Retrovirology Section, HIV Dynamics and Replication Program

Selected professional activities: Attending physician in NIAID and in the HIV Service in the NIH Clinical Center's Critical Care Medicine Department

Website: <https://irp.nih.gov/pi/frank-maldarelli>

Research interests: HIV infection can be controlled, but not cured, by current combination antiretroviral therapy (cART); a large reservoir of HIV-infected cells that persists during cART prevents HIV eradication and contributes to long-term morbidity and mortality. My laboratory is conducting clinical studies at the NIH Clinical Center to investigate mechanisms underlying HIV persistence during cART. We are also studying the long-term effects of HIV persistence including the emergence of resistance to HIV drugs in individuals undergoing cART and the spread of HIV within individuals in populations.

One of the most critical challenges limiting the development of curative strategies for HIV is the lack of understanding of the precise mechanisms underlying HIV persistence during cART. We and others have demonstrated that HIV-infected cells may persist for many years during cART and undergo clonal expansion. In new studies at the NIH Clinical Center, we are investigating the origin and persistence of long-lived clonal populations of infected cells. In most cases, we have found that clonal expansion is not driven by the integrated provirus but is the result of normal T-cell behavior. We are determining the distribution of these infected cell clones within T-cell subsets and in anatomic compartments within infected individuals. In clinical studies, we are investigating whether clinical events, such as co-infections, drive clonal expansion and HIV persistence. In new

studies, we will be determining the roles of these clonal populations in reactivation of HIV after antiretroviral therapy is interrupted.

In a second research project, we are investigating the genetic structure of HIV populations in infected individuals. The goal of this study is to understand the nature of the forces (mutation, selection, drift, and recombination) that mold the genetic diversity of virus populations before and after cART is introduced. We are determining the roles of HIV population size, genetic drift, selection, and recombination in shaping HIV populations and in the emergence of drug resistance during cART.

We have also adapted these genetic approaches to investigate the spread of HIV, including drug-resistant variants, in populations. In studies with investigators in NIAID and NCI, as well as with collaborators at Georgetown University and George Washington University (both in Washington, D.C.), we are characterizing the origin and spread of the HIV epidemic in Washington, D.C., which has the highest prevalence of HIV in the United States. Our studies will be an important part of the effort to control and eliminate this epidemic.

ALEKSANDRA URSZULA NITA-LAZAR, PH.D., NIAID

Senior Investigator and Chief, Cellular Networks Proteomics Section, Laboratory of Immune System Biology, National Institute of Allergy and Infectious Diseases

Education: University of Warsaw, Warsaw, Poland (M.S. in molecular biology); University of Basel, Basel, Switzerland (Ph.D. in biochemistry)

Training: Postdoctoral fellow, Stony Brook University (Stony Brook, New York); post-

doctoral associate, Massachusetts Institute of Technology (Cambridge, Massachusetts)

Came to NIH: In 2009

Selected professional activities: Executive editor, *Journal of Proteomics*; member of Human Proteome Organization Council

Outside interests: Taking every opportunity to actively spend time outside with her son and her husband; reading; knitting; running and coaching running at the county running club; doing and teaching yoga.

Website: <https://irp.nih.gov/pi/aleksandra-nita-lazar>

Research interests: My research focuses on understanding the changes that occur in the cell proteome in response to exogenous factors such as pathogen-derived molecules, cytokines, and chemokines. These factors alter the differentiation state of cells in the immune system or characterize specific disease states. My group is especially interested in large-scale absolute-quantitative measurements of immune-cell signaling cascade components and in the characterization of post-translational modification (PTM) dynamics on a global scale. We use the resulting large datasets to create predictive models of molecular interactions by use of the Simmune software generated by NIAID's Computational Biology Section. The predictions of these models will in turn be employed to elucidate biological responses to stimuli at multiple scales of biological organization including the cell, tissue, and, eventually, the whole organism.

With state-of-the-art equipment and technologies available in our laboratory and at NIH, we use mass-spectrometry-based technology together with other proteomic and biochemical methods.

In one of our projects, we are investigating the protein modifications involved in cell signaling. Because dynamic PTMs such as phosphorylation,

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Recently Tenured

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ubiquitination, or glycosylation are essential for the regulation of cell signaling, it is crucial to quantitatively map the PTMs of proteins involved in signaling cascades. Examples of our interests include toll-like receptor signaling in macrophages.

In another project, we are interested in the absolute quantification of protein expression and protein-protein interactions. We have established a methodology for analyzing the lipid-induced signaling pathways in which sphingosine-1-phosphate (S1P) receptor 1 and S1P2 receptor play a role in monocyte and macrophage cell lineage-derived osteoclast precursors that control cell mobilization at bone surfaces. We are currently working on the absolute quantification of molecules in the macrophages exposed to different toll-like receptor ligands, which play a key role in the innate immune system.

LORNA ROLE, PH.D., NINDS

Senior Investigator, Circuits, Synapses and Molecular Signaling Section; Scientific Director, National Institute of Neurological Disorders and Stroke

Education: Harvard University, Cambridge, Massachusetts (A.B. in applied mathematics); Harvard Medical School, Boston (Ph.D. in physiology)

Training: Postdoctoral training with **Gerald D. Fischbach** (who later became the director of NINDS and served from 1998 to 2001) at Harvard Medical School and at Washington University School of Medicine (St. Louis)

Before coming to NIH: 2008–2018: State University of New York (SUNY) Distinguished Professor and Chair, Department of Neurobiology and Behavior, College of Arts and Sciences and the Renaissance School of Medicine, SUNY Stony Brook (Stony Brook, New York); co-director, Neurosciences Institute and co-director of SUNY

Stony Brook's Thomas Hartmann Center for Parkinson Research; 1985–2008: professor of cell biology, Department of Neurobiology and Behavior, Columbia University College of Physicians and Surgeons (New York)

Came to NIH: In February 2019

Selected professional activities: Elected Fellow of the American Association for the Advancement of Science; elected Fellow in the American College of Neuropsychopharmacology; reviewing editor for several scientific journals

Outside interests: Spending time with family; looking at and doing art (painting and sculpture); studying the history of architecture and traveling to experience it; enjoying jazz and classical music

Website: TBA

Research interests: My research focuses on the brain's cholinergic system over the lifespan. Cholinergic signaling—which is essential for attention, cognitive processing, and memory—is compromised in neurological disorders including Alzheimer disease and Parkinson disease. The lab has focused primarily on physiological approaches to cholinergic circuits and neural-systems analysis in genetically modified mice. Recently, we have expanded our research to include human studies of mild cognitive impairment. In this work, we are using a novel positron-emission tomography tracer of cholinergic neurons in the brain.

We are using new molecular genetic approaches to dissect the role of cholinergic modulation in the encoding of high-salience memories. Detecting saliency (the quality of something standing out or being noticeable) facilitates learning and survival by enabling organisms to focus their perceptual and cognitive resources on the most pertinent subset of the available sensory data.

We are also developing high-volume imaging and computational approaches

for mapping cholinergic projections, and we have been collaborating on studies of new imaging probes for the assessment of cholinergic-terminal integrity in dementia.

For more about Lorna Role, who was recently appointed scientific director of NINDS, see “NINDS Welcomes Lorna Role as New Scientific Director” on page 6.

EDWINA H. YEUNG, PH.D., NICHD

Senior Investigator, Epidemiology Branch, Eunice Kennedy Shriver National Institute of Child Health and Human Development

Education: Johns Hopkins University, Baltimore (B.A. in natural sciences area and public health studies); Johns Hopkins Bloomberg School of Public Health, Baltimore (Sc.M. in clinical epidemiology; Ph.D. in cardiovascular disease epidemiology)

Training: Postdoctoral fellow in epidemiology, NICHD

Came to NIH: In 2008 for training; became tenure-track investigator in 2011

Selected professional activities: Editorial board member, *Fertility & Sterility*

Outside interests: Cooking; fishkeeping (an aquarium hobby)

Website: <https://irp.nih.gov/pi/edwina-yeung>

Research interests: My research aims to understand the developmental origins of health and disease (DOHaD), a theory that hypothesizes that a fetus's adaptive responses to a broad range of environmental cues influence its long-term health. Specifically, I am examining the effects of infertility treatment, obesity during pregnancy, and their related comorbidities on the “programming” of different health outcomes including early childhood development and cardiometabolic risk.

Most recently, a few studies have examined the cardiometabolic health of children conceived by infertility treatment. There is some indication that



vascular alterations may have occurred in the children who were conceived by such treatments. The rationale remains unclear, but scientists hypothesize that the supraphysiological exposure to hormonal treatment may be a potential mechanism. As such, it is important to investigate not only children conceived by assisted reproductive technologies but also children conceived by ovulation-induction methods. To this end, I have overseen the completion of the first phase of the Upstate KIDS Study and continue to lead its prospective follow-up. The Upstate KIDS Study is a large exposure-matched cohort from New York state that was formed to determine whether children conceived by infertility treatments differ from their peers in growth and development.

There is increasing recognition that parental obesity may influence not only the metabolic health but also the cognitive development of the child. We hypothesize that exposure to increased inflammation in utero may be the mechanism, but causal evidence is lacking. My research has also examined whether epigenetic differences (specifically DNA methylation) exist and act as mediators of later health conditions. However, because DOHaD research has traditionally focused on mothers, I am also leading a new initiative to look at the father's contribution. In an upcoming pregnancy cohort, we will examine the effect of cardiometabolic health status of both parents on the neonatal health of their offspring.



CONTINUED FROM PAGE 5

agreements—including material-transfer agreements, collaborative agreements, licensing agreements, clinical-trial agreements, and cooperative research and development agreements (CRADAs)—and by managing licenses and patents.

The offices can also help investigators develop translational strategies and find commercial partners. For example, NCI's Technology Transfer Center (TTC) acts as an "NIH version of Match.com" by advertising NIH technologies to the extramural community and working to find the relevant industry partners to develop those ideas, explained **Michael Salgaller**, supervisor of the Invention Development and Marketing Unit in NCI's TTC.

Yet many investigators aren't aware of all that tech-transfer offices can do for them.

Every institute and center (IC) has a technology-transfer coordinator and access to a technology-transfer office. Some ICs have their own tech-transfer offices, whereas others are served by bigger ICs. For example, the National Human Genome Research Institute has its own and so does the National Institute of Allergy and Infectious Diseases. NCI's TTC, which is the largest tech-transfer center at NIH, serves nine other ICs; the National Heart, Lung, and Blood Institute serves six others.

How Partnerships Begin

Partnerships between labs at NIH and commercial entities usually begin in one of two ways. In one common scenario, a company may reach out to an investigator after reading their paper(s) or hearing a talk at a scientific meeting. For example, several companies approached NCI investigator **Mitchell Ho** after seeing posters presented by his postdocs during the 2018 American Association for Cancer Research meeting in Chicago. Ho's lab develops antibody-engineering technologies that target and validate tumor antigens in solid tumors. He

now collaborates with several commercial partners through three CRADAs and three licenses (other agreements are in the works). Thanks to these partnerships, antibodies to target two cell-surface proteins, glypican-3 (GPC3) on liver cancer cells and GPC2 on neuroblastoma cells, will likely begin in clinical trials this year.

Alternatively, an investigator may need to reach out to their tech-transfer office before talking to a company about their ideas. This is certainly the case if they develop something that may be patentable. Once something is introduced to the public, whether by talk or publication, it "starts a [patent] clock ticking," said **Mark Rohrbaugh**, NIH Special Advisor for Technology Transfer. A patent must be filed in the United States within a year, but foreign rights are lost upon publication.

Challenges and Resources


Many of the ideas and inventions that come out of NIH labs are very early in product development and sometimes too risky for a commercial partner to be interested. But tech-transfer offices can help investigators overcome this hurdle. Some ICs, such as NCI, the National Institute of Neurological Disorders and Stroke, and the National Center for Advancing Technology Sciences, have special programs to move early-stage technologies forward.

In 2018, NIH entered into 82 CRADAs, executed 298 licenses to NIH inventions, and obtained 94 newly issued U.S. patents. But NIH "would like there to be more relationships" between NIH labs and industry, said Rohrbaugh.

Investigators are encouraged to sit down with their tech-transfer coordinators and describe their ideas, said Salgaller. "That's the first step."

To find your institute's technology-development coordinator, visit the Office of Technology Transfer website at <https://www.ott.nih.gov/tdds>.

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IF YOU HAVE A PHOTO OR other graphic that reflects an aspect of life at NIH (including laboratory life) or a quotation or confession that scientists might appreciate and that would be fit to print in the space to the right, why not send it via e-mail: catalyst@nih.gov; fax: 301-402-4303; or mail: *The NIH Catalyst*, Building 1, Room 333.

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PHOTOGRAPHIC MOMENT



World's Largest Brain Scanner Delivered to NIH

THE WORLD'S MOST POWERFUL magnetic-resonance-imaging (MRI) scanner was delivered to NIH in March and installed in the NIH Clinical Center (Building 10). The 11.7-Tesla magnet, weighing 51 tons, was built in Italy, journeyed across the ocean by cargo ship to Baltimore, and then transported by tractor-trailer truck to NIH. A huge crane gently lifted the scanner and slid it via a special trolley through an opening in side of the building. Scientists hope the scanner's high resolution will help bridge the gap between scanners and microscopes and invasive electrode recording of neural activity. Clinical scanners are 1.5-Tesla and research scanners are typically 3-Tesla. NIH also has two 7-Tesla MRI scanners. But the 11.7-Tesla scanner is the strongest. ●



DINH NGUYEN, OD

For a video of the delivery, go to <https://youtu.be/BeFoeBfKKLO>.

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