

Lasker Clinical Research Scholars

Compassionate Physicians with an Eye for Research

BY LAURA STEPHENSON CARTER

CONGRATULATIONS TO THE FOUR newest NIH Lasker Clinical Research Scholars: cancer researchers Christine Alewine, Jung-Min Lee, and Frank Lin and sickle-cell disease researcher Courtney Fitzhugh. They join 10 others in the Lasker program.

Christine Alewine (National Cancer Institute, NCI) is conducting clinical trials to test the effectiveness of a recombinant immunotoxin in combination with standard-of-care chemotherapy in patients who have advanced pancreatic cancer.

Jung-Min Lee (NCI) is conducting clinical and translational research to study the clinical activity and biomarkers of new immune-based DNA injury combination therapies in women who have recurrent ovarian cancer.

Frank Lin (NCI) is using targeted radionuclide therapy (tRNT) to treat cancer. Unlike conventional external-beam radiation therapy, tRNT is able to target and treat cancer cells throughout the entire body and has the potential to deliver lethal radiation doses to even micro-metastases.

Courtney Fitzhugh (National Heart, Lung, and Blood Institute) is seeking to improve—and develop new—treatment options to achieve a cure for sickle-cell disease.

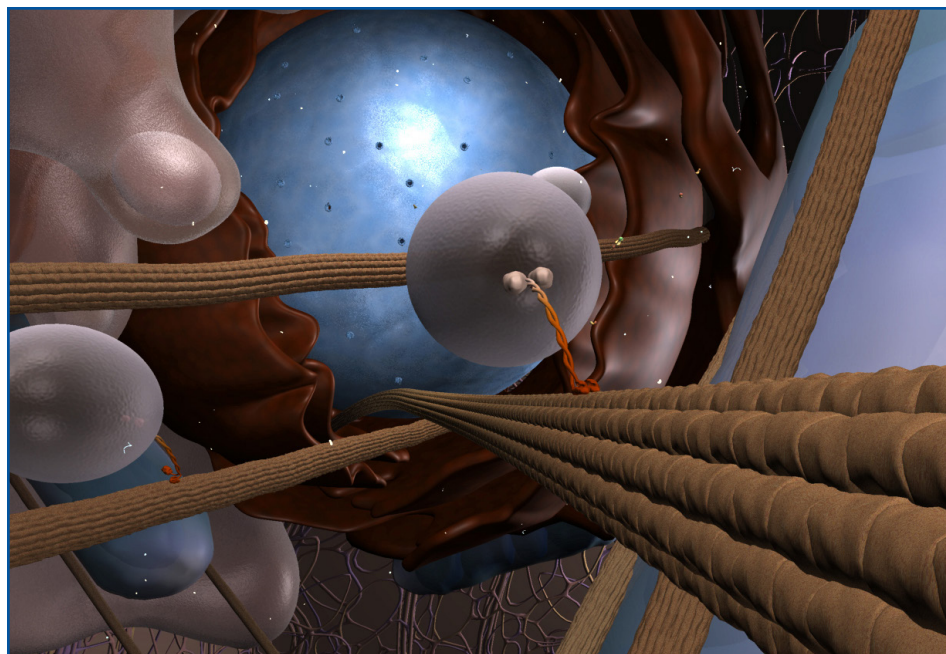
The Lasker Clinical Research Scholars Program is an “intramural–extramural” NIH program in partnership with the

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Harnessing the Power of RNA Molecules

Studying the Function of Genes, One at a Time

FROM THE NIH IMAGE GALLERY



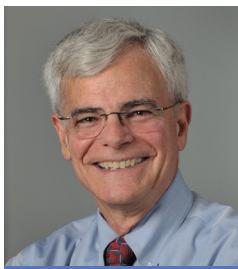
NCATS

NO, THOSE SPHERES AREN'T THE NEW PLANETS RECENTLY DISCOVERED BY NASA. They are illustrations of RNA-interference (RNAi) molecules magnified thousands of times. Scientists have harnessed the power of RNAi to study the function of many individual genes by silencing them. In genome-wide RNAi screens, robots introduce small-interfering RNAs—which have a complementary sequence to that of a targeted gene—into human cells to block the activity of each gene, one at a time. Researchers then look for changes in cell function to learn about what the gene normally does and determine its role in biological functions or diseases, an invaluable step in identifying potential drug targets.

The National Center for Advancing Translational Sciences (NCATS) runs a state-of-the-art RNAi screening facility that is open to NIH investigators. To find out how to collaborate with the NCATS RNAi program, go to <https://ncats.nih.gov/rnai#learn-more>. ●

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Ensuring Gender Equity at the NIH

BY MICHAEL GOTTESMAN, DDIR, AND
HANNAH VALANTINE, CHIEF OFFICER FOR SCIENTIFIC WORKFORCE DIVERSITY



WE HAVE HAD THE HONOR AND privilege of co-chairing a task force whose goal is to make recommendations to ensure that women and men have equal opportunities to contribute to the creative and innovative science done at NIH in the intramural research program. This goal means that women should be on an equal footing with men with respect to recruitment to faculty (tenure-track and tenured) positions at the NIH, to career advancement through the tenure process, and—once tenured as senior investigators—to have equivalent resources and hold leadership roles at rates equivalent to men. The current situation at NIH is comparable to that at many academic institutions, with women occupying only 23 percent of our senior investigator positions and 38 percent of our tenure-track positions. What can we do to work toward true parity of men and women at the NIH?

The task force considered recommendations in two domains: (1) the institutional responsibility to ensure equal access, equal resources, equal pay, and equal advancement; and (2) steps to provide individual help for women and men at the NIH to ensure that they benefit from institutional support. For institutional advances, it is essential to have buy-in from leadership at all levels but especially from those responsible for making hiring decisions, setting salaries, allotting resource, and implementing our review processes. This effort requires

transparency of demographic information in each institute and center (IC) and accountability to ensure equity. Individual support, appropriate mentoring, coaching, and advocacy are essential for both women and men.

Although detailed implementation plans are yet to be worked out, there are several recommendations that can be emphasized. Hiring, resource allocation,

Diversity will increase our scientific progress and productivity and ensure a healthy future for the NIH.

and reviews should be free of all gender bias. Currently, our scientific directors, lab and branch chiefs, and members of our boards of scientific counselors are receiving implicit-bias training to reduce such bias. Accurate information about the size of the applicant pool and representation of men and women for all faculty positions will be made available to each IC. At the time of hiring, central advice in negotiating resources will be provided to help our new recruits. If inequities in resource allocation or salary are detected, they will be corrected. We will continue to monitor the perception of our tenure-track investigators about gender inequality.

For individual-focused recommendations, we will create a cohort of tenure-track investigators who will be networked with each other and receive mentoring, coaching, and sponsorship from their own ICs and from the Office of Intramural Research and the Office of Scientific Workforce Diversity. We are delighted that **Carl Hashimoto**, a cell biologist and a former diversity dean at Yale University (New Haven, Connecticut), will join us to oversee this cohort. In addition to receiving what we hope is good advice, this cohort will also provide feedback to NIH leadership on progress being made at their home ICs.

It has not escaped our attention that this focus on institutional and individual support of all of our faculty will improve circumstances not only for women at the NIH but also for men as well as for other groups that are under-represented in biomedical research. The principle of institutional and individual commitment to fairness applies equally to our larger scientific community including trainees, fellows, and staff scientists.

Diversity will increase our scientific progress and productivity and ensure a healthy future for the NIH. These approaches cannot succeed, however, without the enthusiastic support of everyone at the NIH. We invite all of you to join us in this noble endeavor and, as always, welcome your input as we work to implement these recommendations. ●



HHS Secretary's First Official Visit to NIH



CHRISTOPHER SMITH, HHS

NEW HEALTH AND HUMAN SERVICES SECRETARY **TOM PRICE** PAID A VISIT TO NIH ON February 21, 2017, and toured the Clinical Center. NIH Director **Francis Collins** (left) and Clinical Center CEO **James Gilman** (right) are pointing out features of the Clinical Center on the scale model. ●

New Mobile Germ-Free Facility

YOU CAN'T STOP MEDICAL PROGRESS. THE suspension of activities in the Clinical Center Pharmaceutical Development Section in June 2015 curtailed NIH's ability to make sterile products and cell-based therapies. As a result, NIH has had difficulty meeting the demands of intramural investigators who need an adequate supply of these products. Through it all, the Clinical Center Department of Transfusion Medicine (DTM) has remained "open for business" producing high-quality transfusion products, including important new chimeric antigen receptors to support immunotherapy protocols pioneered at the NIH. The DTM is working at its limit, though.

NIH will benefit greatly when the DTM can expand into its new space in the 2J area of Building 10, where it will have seven manufacturing suites. This space may be completed as

early as fall 2017. However, this facility won't be enough to meet the demands brought on by NIH's recent successes in cell-based therapies.

So NIH is embarking on an interim solution that may have permanent, positive manifestations: portable sterile-products facilities. If you enter the Clinical Center from the northwest side, where emergency vehicles receive or bring patients, you will notice a compact white trailer with an NIH logo. This state-of-the-art facility will be used to support NCI-immunotherapy studies.

A second germ-free trailer, next to the first, will also serve this function. Given the difficulty of renovating space for clinical Good Manufacturing Practices (cGMP) facilities in the 65-year-old Clinical Center, coupled with the limited open real estate on the Bethesda campus, these relatively affordable trailers connected into module cGMP facilities could serve as a long-term solution. ●

New NIH Child-Care Facility to Open by Summer

MANY NEW PARENTS FIND THEMSELVES stuck between a rock and a hard place, attempting to establish their careers on a modest salary while providing their children with quality care during working hours. Indeed, the shortage of affordable, reliable, and convenient child care is a national concern.

The NIH will soon open the Northwest Child Care Center (NWCCC), a facility on the NIH Bethesda campus kitty-corner from the Clinical Center, between the Children's Inn and the NIH Fire Department. The new center will have room for 170 children between the ages of six weeks and six years of age and will replace the Infant and Toddler Child Care Center in Building T-46, which had a capacity of only 33 children.

While spacious, the NWCCC still falls short of meeting the demand for onsite child care...as the growing wait list clearly indicates (999 and counting). NIH could use several more such facilities. The NWCCC is scheduled to open in May 2017. ●

Learn more about child- and family-care options at <https://www.ors.od.nih.gov/pes/dats/childcare/centers/Pages/centers.aspx>.



ERIC COLE, CC

New NIH Northwest Child Care Center under construction.



FROM THE OFFICE OF INTRAMURAL TRAINING AND EDUCATION

Making the Most of Your NIH Experience

ADAPTED FROM [HTTPS://WWW.TRAINING.NIH.GOV/TRAINees](https://www.training.nih.gov/trainees)

IN THE 21ST CENTURY, SUCCESSFUL scientists need strong communication skills. You must be able to teach in the research environment and perhaps in the classroom; you must collaborate effectively; and you must function well both as a manager and as a leader. Furthermore, you must understand the career-exploration process, the importance of networking, and effective job-search strategies. These core competencies are at the heart of a successful research career and also represent the transferrable skills needed to make transitions to the non-bench careers that are critical to the success of the entire scientific enterprise.

Your NIH training should focus on the development of science, professional, and career skills. You should take the time to assess your strengths and weaknesses, the activities you enjoy most, and the values that underlie your actions. There are many ways to contribute to the scientific enterprise, and only you know the career paths that are right for you. The NIH offers a wide array of career-development opportunities for you to use as you develop your own specific strategies for success.

Whether you are a summer intern, a postbac, a graduate student, or a postdoctoral fellow, make the most of your NIH experience. You must plan your time wisely and begin almost immediately to develop the skills and expertise that you will need to succeed during the next phase of your career.

The NIH Office of Intramural Training and Education (OITE) encourages you to focus your energies on three major areas: Doing outstanding science; attending to your career and professional development; and exploring and contributing to the community around you.

Career and professional development begins with knowing yourself. Consider completing the Myers–Briggs Type Indicator, an assessment tool that will help you to understand your psychological makeup in terms of how you take in information about the world around you, how you make decisions, and where you get your energy. You can also make an appointment with an OITE career counselor for help with self-reflection and increasing your self-awareness. Making solid career decisions depends on understanding what skills you possess, what interests excite you, and what values add meaning to your life.

If you are not already firmly committed to a particular career path (or perhaps even if you are), the next step in career and professional development is career exploration. What options are out there? What are various careers really like, and how does one prepare for them?

It is important to recognize that you are likely to change career directions many times, and each transition will require that you return to these activities.

Core competencies provide an excellent way to look at career and professional development. Core competencies are primarily blends of skills and experience that future employers and/or educational institutions will be seeking. You should aim to build competence in career exploration and job-search skills; communication; writing; speaking; grant writing; communicating in English (if you are not a native English speaker); teaching and mentoring; and leadership and management. OITE offers programming in each of these areas.

Make a plan if you don't yet have defined career goals, to explore career options before beginning to work on developing

skills. One effective approach is to create an individual development plan (IDP). Here are two resources: myIDP (<http://myidp.sciencecareers.org>); and a model IDP at <http://www.faseb.org/portals/0/pdfs/opa/idp.pdf>.

You may want to talk with your PI or supervisor about your short-term and long-term personal goals, and about scientific and career goals. A goal can be as simple as presenting a poster at Postbac Poster Day or as complex as developing a teaching portfolio. Write down both your specific goals and a timeline for achieving them. Then revisit your IDP periodically, perhaps every six months, to ensure you are making appropriate progress and to revise your IDP as needed.

Take advantage of all available resources at the NIH and in the broader scientific community. A partial list includes: Training Office in your IC; NIH Scientific Interest Groups (<https://www.nih.gov/research-training/scientific-interest-groups>); videocasts of prior OITE workshops; the OITE Careers Blog; career-development activities in your professional societies; informational interviewing; and the NIH Career Symposium.

Exploring and contributing to the community is often a large part of feeling comfortable here. The NIH is home to many organized communities (https://www.training.nih.gov/you_are_not_alone). And, if you are also a parent, take a look at resources for parents at https://www.training.nih.gov/parenting_resources_at_the_nih. ●

For more information, visit the OITE website at <https://www.training.nih.gov/home>.

Go with the Flow

Highlights from the Flow Cytometry Interest Group Winter Meeting

BY JACQUELINE MINEHART, NEI

THESE ARE INNOVATIVE TIMES IN FLOW cytometry, a technology that simultaneously analyzes multiple characteristics of thousands of cells as they move through fluid and are excited by a light source. On February 14, 2017, the Flow Cytometry Interest Group (FCIG) invited nine experts to its winter meeting at NIH to talk about the latest research in the field. More than 100 people gathered for presentations and discussions on clever solutions to some of flow cytometry's challenges. Cytometrists are using magnetics, light behavior, and high-dimensional imaging to analyze populations of rare cells, eliminate cell labeling, and capture tissue physiology.

Elke Bergmann-Leitner, head of the flow cytometry center at the Walter Reed Army Institute of Research (Silver Spring, Maryland), described how when traditional flow cytometry limited the analysis of rare-cell populations, she used a technique called magnetic-enrichment columns instead.

Electrical engineer Charles Camp of the National Institute of Standards and Technology (Gaithersburg, Maryland) explained how he uses a technique called Raman-scattering detection, which exploits light-matter interactions to analyze cell samples without the use of expensive fluorescent antibodies.

Dragan Maric, manager of the Flow and Imaging Cytometry Core in the National Institute of Neurological Disorders and Stroke, contributed high-dimensional imaging and analysis to the presentation roster. With his *in situ* cytometry techniques, he analyzes mouse and rat brain cross-sections to understand the effects of stroke on several types of cells that mediate neuroinflammation, neuroplasticity, neurogenesis, gliogenesis and angiogenesis.

The meeting also featured a talk by **Sapna Gangaputra** (National Eye Institute), who uses flow cytometry to track changes in patient immune-cell populations to assess the efficacy of a novel ocular inflammation treatment. **Stephen Perfetto**, chief of the Vaccine Research Center Flow Cytometry Facility (National Institute of Allergy and Infectious Diseases), showed the advancements in procedures for instrument calibration and standardization using the quantiFlash LED pulser.

Katherine McKinnon, head of the National Cancer Institute's (NCI) Vaccine Branch Flow Cytometry Core, showcased the benefits of using high-dimensional flow cytometry, which in some cases reduces the need for large volumes of patient blood. Also from NCI, **Gregoire Altan-Bonnet** focused on using cytometric data to analyze the cell-to-cell variability of leukocytes in their response to tumors and pathogenic infections.

Highlighting industry advances, Jin Akagi of On-Chip Biotechnologies (San Diego) pitched his company's newest invention for ultragentle on-chip cell sorting, and Katherine Drake of Cytobank, Inc. (Mountain View, California) described a technique for high-dimensional data processing.

"The talks were great," said **William Telford**, manager of the NCI cytometry core and one of the moderators of the Flow Cytometry Interest Group. "We had not just flow cytometry, but also a lot of imaging talks as well. They are doing very high-dimensional work." ●

All biomedical researchers with an interest in cytometry regardless of institutional affiliation are welcome to join FCIG. Visit <https://sigs.nih.gov/fcig> to learn more about this group.

NEW SIGS:

PSYCHONEUROENDOCRINOLOGY

The new Psychoneuroendocrinology Scientific Interest Group (PSIG) provides a forum for scientists and clinicians across multiple institutes and centers (ICs) at the NIH to present their latest scientific findings related to psychoneuroendocrinology and discuss their implications for future translational and clinical research as well as for clinical practice. Psychoneuroendocrinology is the branch of science that studies the relationships among the endocrine system, the nervous system, and psychology. The PSIG will meet every three months. To join the LISTSERV, go to <https://list.nih.gov/cgi-bin/wa.exe?AO=psychoneuroendocrinology-l>. For more information, contact the PSIG chairs, **Lorenzo Leggio** (lorenzo.leggio@nih.gov) and **Wendy A. Henderson** (hendersw@mail.nih.gov). The first meeting will be on Wednesday, April 26, 2:00–3:30 p.m., in FAES classrooms 1 and 2 (Building 10).

DEEP LEARNING IN MEDICAL IMAGING AND BEHAVIOR

The goal of the Deep Learning in Medical Imaging and Behavior (DLMIB) interest group is to engage investigators who are using or interested in using graphics-processing unit-accelerated computing and deep-learning software to develop new analytics, diagnostics, and treatments for diseases such as stroke, cancer, and epilepsy. Investigators in DLMIB are located across NIH ICs and use deep neural networks to extract features from medical-imaging data, signal time-series data, or behavioral data. This work may also provide insights into brain function and novel treatments. The DLMIB group meets once a month. For more information, contact **Sunbin Song** (songss@ninds.nih.gov).



Building a Partnership

Rwandan Physician Will Bring Home Lessons Learned at NIH

BY LESLEY EARL, NCI



Rwandan physician Jean Utumatwishima (right) is spending a one-year fellowship at NIH with NIDDK senior investigator Anne Sumner to learn how to conduct clinical research. He plans to use what he learns to help people in his home country.

A PHYSICIAN FROM THE REPUBLIC OF Rwanda is spending a one-year fellowship at the NIH learning how to conduct clinical research and studying the epidemiology of diabetes and heart disease in African immigrant populations. He plans to use what he learns to help people in his home country.

“I’ve found here a very good place for learning, a very good place for science,” said **Jean Utumatwishima**, who was the director of the Kinyihira Provincial Hospital, a rural hospital in the Northern Province of Rwanda. “It’s encouraging for me to go back and try to bring these lessons back home.”

Utumatwishima’s fellowship is a unique inter-institute and international partnership involving the Rwanda Ministry of Health, the National Institute on Minority Health and Health Disparities (NIMHD), and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

The idea for this fellowship was born after a visit to the NIH by then-Rwandan Minister of Health, Agnes Binagwaho, to deliver the 2015 Barmes Lecture for Global Health. Binagwaho

spoke about her country’s recovery from the 1994 genocide, the value of research and capacity building to make a health system resilient, and the importance of training and empowering Rwanda’s own researchers. Inspired by Binagwaho’s lecture, **Anne E. Sumner**, chief of NIDDK’s Section on Ethnicity and Health, reached out to the Fogarty International Center to arrange contact with Binagwaho. Sumner’s research focuses on identifying biomarkers that can be highly predictive of prediabetes and cardiovascular disease in people of African descent including both African-Americans and African immigrants.

“One conversation led to another,” said Sumner, “and that led to the recruitment of a Rwandan physician to come to work with me at NIH.” With the support of NIDDK’s Scientific Director **Michael Krause** and NIMHD’s Director **Eliseo J. Pérez-Stable**, Sumner arranged for a one-year inter-institute, international fellowship to train and mentor a Rwandan physician in clinical research. Utumatwishima, the first physician chosen, arrived at the NIH in July 2016.

In Sumner’s lab, Utumatwishima studies both how stress affects cardiometabolic disease in African immigrants and how NIH conducts clinical research. He’s also taking courses in endocrinology and statistics. Most of all, he likes how treating patients is entwined with research. “In Rwanda, if you are in research or in public health administration, you rarely go back to the patients,” he said. But NIH’s “principle of bench to bedside and then back—from bedside to bench” has inspired him. “I think this [practice] is something I need to bring back home.”

After Utumatwishima completes his training at NIH, Sumner plans two

more years of collaboration and mentorship while he launches his own clinical research in Rwanda.

When he gets back to Rwanda, he knows he will “work both in a teaching hospital and in a university.” His goal, he said, is to find better ways to prevent and “detect cardiometabolic diseases in Rwandans now living in Rwanda.” The challenge is that usual biomarkers for prediabetes and cardiometabolic diseases—such as hemoglobin A1c and triglycerides—are not terribly predictive in patients of African descent.

“We’ve engaged in an amazingly positive and enthusiastic collaboration where we’re building on our work about the effect of stress on cardiometabolic disease and diabetes,” said Sumner. “Rwanda has a special history [that] we want to explore more, [focusing on] how to prevent disease in the high-risk population, even moving into studies such as the effect of post-traumatic stress disorder on silent [cardiovascular] disease.”

Sumner’s hope is “to build a whole community of physicians in Rwanda who have this research orientation so that when Jean goes back he’s not by himself in terms of trying to bring a research agenda forward,” she said. “And that’s why we’re recruiting a second Rwandan physician to come join us, so we can create a whole cadre.” That second physician is scheduled to come to the NIH in summer 2017.

Utumatwishima is grateful that NIH has “opened [the] gate” for training opportunities so physicians and researchers like him can help people in their home countries. ●

More photos at <https://irp.nih.gov/catalyst/v25i2/building-a-partnership>.

Ambition, and Lots of Fruit Flies

Mihaela “Ela” Serpe Explores Cell Signaling

BY EMILY PETRUS, NINDS

MIHAELA “ELA” SERPE CREDITS NOBEL laureate George Emil Palade for inspiring her in the 1990s when she was a research associate at the Institute of Cellular Biology and Pathology (Bucharest, Romania). Palade, who had discovered the ribosome, shared the 1974 Nobel Prize for Physiology or Medicine with two others “for their discoveries concerning the structural and functional organization of the cell.”

Serpe attended a seminar Palade gave and was impressed by his insistence that although the discovery of cell structures was important, what really deserved recognition was the discovery that phosphorylation (the addition of phosphate groups to molecules) is critical for many cellular processes. It changes the activity and subcellular distribution of proteins, an entry point to understanding how cells talk to each other.

And that’s what Serpe has been trying to figure out ever since. Now a senior investigator at the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), she is elucidating molecular mechanisms that regulate cell-to-cell communication. In particular, she is studying how synapses form and optimize their function via extracellular signals. Those molecular messengers accumulate at high concentrations at the synapse but are only deployed at very specific times and places.

This specificity means that “all the extracellular communication is guarded” very carefully, Serpe said. She has devoted her career to investigating how all those signaling molecules get organized and concentrated at specialized cell-cell interaction zones, including glutamatergic synapses. She uses *Drosophila melanogaster* neuromuscular junctions (NMJ) as a model because the glutamatergic synapses of the fruit fly and human are highly similar. And

fruit flies are more readily manipulated genetically so scientists can identify and characterize key components of the nervous system.

Discovery

After coming to NIH in 2008, Serpe discovered something big: a novel modulator of trans-synaptic signaling called Neto, which stands for Neuropilin and Tolloid-like—critically involved in synaptic development. The significance of the discovery was not immediately apparent because fly embryos that lack the *neto* gene initially develop just fine due to the maternal supply of mRNAs and proteins to the egg. It’s only after the supply of the Neto protein runs out at the end of embryogenesis that the synapses fail to form and paralysis sets in. Serpe and colleagues demonstrated that Neto is required for the initial clustering and normal functioning of glutamate receptors on the postsynaptic side of the NMJ.

Beginnings

Serpe got a Ph.D. in biochemistry at the State University of New York at Buffalo (Buffalo, New York) and did her postdoctoral training in developmental biology and neurobiology at the University of Minnesota and the Howard Hughes Medical Institute (Minneapolis), where she entered the world of intercellular signaling and development.

Since her arrival at NICHD in 2008, she has built her lab from two summer students, who generated the first *neto*-null mutants, to her current full-fledged lab comprising



Ela Serpe (center) and members of her lab enjoy a light moment posing in front of the Santiago Ramón y Cajal exhibit in the Porter Neuroscience Building. Pictured, from left: (standing) Peter Nguyen, Lindsey Friend, Serpe, Qi Wang, Shelby Newsad; (front) Rosario Vicidomini, Tae Hee Han.

HUU THO NGUYEN, NICHD

a mix of electrophysiologists, geneticists, molecular and cell biologists, and imaging experts. The breadth of research strategies she uses to answer scientific questions is a product of her broad background and hard-won collaborations.

Mentorship

Mentorship is a common theme that runs through Serpe’s experience. “Nobody clipped my wings,” she said. “I was never limited in what I was trying to learn.” So she isn’t about to limit her trainees. She personally trains all the researchers in her lab, ensuring that her high standards are met and that she stays engaged in the fun of doing research.

Dedication, collaboration, and mentorship are three qualities that make for an excellent scientist. Serpe brings all three to her lab every day. ●

To watch a January 27, 2017, Director’s Seminar Series lecture by Serpe, go to <https://videocast.nih.gov/launch.asp?21101>.

Read more online at <https://irp.nih.gov/catalyst/v25i2/ambition-and-lots-of-fruit-flies>.



Intramural Research Briefs



NINR researchers have found that measuring concentrations of tau in the blood may provide an unbiased way to determine when it's safe for athletes to return to play after a concussion.

NINR: BIOMARKER IN BLOOD MAY HELP PREDICT RECOVERY TIME FOR SPORTS CONCUSSIONS

Despite the millions of sports-related concussions that occur annually in the United States, there is no reliable blood-based test to predict recovery and an athlete's readiness to return to play. A new study by NINR researchers and others, however, shows that measuring concentrations of a protein called tau in the brain could potentially provide an unbiased tool to help prevent athletes from returning to action too soon and risking further neurological injury. Tau is also connected to the development of Alzheimer and Parkinson diseases and is a marker of neuronal injury after severe traumatic brain injuries.

A group of 632 soccer, football, basketball, hockey, and lacrosse athletes from the University of Rochester (Rochester, New York) first underwent preseason blood-plasma sampling and cognitive testing to establish a baseline. They were then followed during the season for any diagnosis of concussion, with 43 of them developing concussions during the study. For comparison, a control group of 37 teammate athletes without concussions was also included in the study as well as a group of 21 healthy non-athletes. After a sports-related concussion, blood was sampled from both the concussed and control athletes at six hours, 24 hours, 72 hours, and seven days post-concussion.

Concussed athletes who needed a longer recovery time before returning to play (more than 10 days post-concussion) had higher tau concentrations overall at six, 24, and 72 hours post-concussion compared with athletes who were able to return to play in 10 days or fewer. These observed changes in tau levels occurred in both male and female athletes, as well as across the various sports studied. Further research will test additional protein biomarkers and examine other post-concussion outcomes. (NIH authors: J. Gill and W. Livingston, *Neurology* DOI:<http://dx.doi.org/10.1212/WNL.0000000000003587>)

NIMH, NIAAA, NICHD: SEX HORMONE-SENSITIVE GENE COMPLEX LINKED TO PREMENSTRUAL MOOD DISORDER

NIH researchers have discovered molecular mechanisms that may underlie a woman's susceptibility to disabling irritability, sadness, and anxiety in the days leading up to her menstrual period. Such premenstrual dysphoric disorder (PMDD) affects two to five percent of women of reproductive age, whereas less-severe premenstrual syndrome is much more common. The researchers found dysregulated expression in the *ESC/E(Z)* gene complex, which regulates epigenetic mechanisms that govern the transcription of genes into proteins in response to the environment—including sex hormones and stressors. (NIH authors: N. Dubey, J.F. Hoffman, K. Schuebel, Q. Yuan, P.E. Martinez, L.K. Nieman, P.J. Schmidt, and D. Goldman, *Mol/ Psychiatry* DOI:10.1038/mp.2016.229)

NICHD: PARENTAL OBESITY MAY BE LINKED TO DELAYS IN CHILD DEVELOPMENT

Children of obese parents may be at risk for developmental delays, according to an NICHD study. The investigators found that compared with children of normal-weight mothers, children of obese mothers were 70 percent more likely to fail tests of fine motor skills. Children of obese fathers were 75 percent more likely to fail measures of social competence, and those

born to extremely obese couples were nearly three times as likely to fail tests of problem-solving ability. In the study, authors reviewed data collected from the Upstate KIDS study, which originally sought to determine whether fertility treatments could affect child development from birth through age three. More than 5,000 women enrolled in the study roughly four months after giving birth in New York state between 2008 and 2010. To assess development, researchers asked parents to complete the Ages and Stages Questionnaire after performing a series of activities with their children.

If the link between parental obesity and developmental delays is confirmed, physicians may need to take parental weight into account when screening young children for delays and early interventional services. (NIH authors: E.H. Yeung, R. Sundaram, A. Grassabian, Y. Xie, and G. Buck Louis, *Pediatrics* 139(2):e20161459, 2017)

NIAID: INVESTIGATIONAL MALARIA VACCINE DEMONSTRATES CONSIDERABLE PROTECTION IN MALIAN ADULTS FOR DURATION OF MALARIA SEASON

An investigational malaria vaccine—known as the PfSPZ vaccine—given intravenously was well-tolerated and protected a significant proportion of healthy adults against infection with malaria caused by *Plasmodium falciparum*, a malaria-causing parasite carried by mosquitoes. The study was conducted by researchers from NIAID and the University of Science, Techniques, and Technologies of Bamako, one of NIAID's International Centers of Excellence in Malaria Research in Bamako, Republic of Mali. The study participants live in Mali, where they are naturally exposed to the parasite.

The Mali study was launched in January 2014 and enrolled 109 healthy African men and nonpregnant women ages 18 to 35 years old. Participants received either five doses of the intravenous PfSPZ vaccine or five doses of placebo (saline) over five months of the dry season at the study's clinical site in rural Mali. (NIH authors: S.A. Healy, I. Zaidi, K. Ding, S.

Wong-Madden, M. Walther, P.E. Duffy, E.E. Gabriel, M.P. Fay, E.M. O'Connell, and T.B. Nutman, *Lancet* DOI:[http://dx.doi.org/10.1016/S1473-3099\(17\)30104-4](http://dx.doi.org/10.1016/S1473-3099(17)30104-4)

NEI: STEM-CELL SECRETIONS MAY PROTECT AGAINST GLAUCOMA

NEI scientists found that stem-cell secretions, called exosomes, promote the survival of retinal ganglion cells in rats. The findings point to potential therapies for glaucoma, a leading cause of blindness in the United States. In a rat glaucoma model, the researchers studied the effects of exosomes isolated from bone-marrow stem cells on retinal ganglion cells. Exosomes were injected weekly into the rats' vitreous, the fluid within the center of the eye. Before injection, the exosomes were fluorescently labeled, allowing the researchers to track the delivery of the exosome cargo into the retinal ganglion cells. (NIH authors: B. Mead and S. Tomarev, *Stem Cells Transl Med* DOI:10.1002/sctm.16-0428)

NCI, NHLBI, CC: EARLY-PHASE TRIAL DEMONSTRATES SHRINKAGE IN PEDIATRIC NEURAL TUMORS

In an early-phase clinical trial of a new oral MEK inhibitor, selumetinib, children with the genetic disorder neurofibromatosis type 1 (NF1) and plexiform neurofibromas (tumors of the peripheral nerves) tolerated selumetinib and, in most cases, responded with tumor shrinkage. NF1 affects 1 in 3,000 people. The multicenter phase 1 clinical trial included 24 patients, was led by NIH investigators, and was conducted at the NIH Clinical Center and three participating sites.

NCI is currently sponsoring an ongoing phase 2 trial of the drug for adults with NF1, in which serial tissue samples are being obtained. This study should provide information about possible mechanisms of resistance to selumetinib. In addition, a larger phase 2 pediatric trial is enrolling patients and should help establish the efficacy of selumetinib treatment in children. In this trial, researchers are

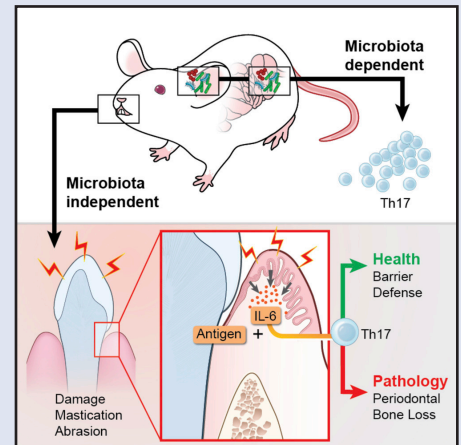
also measuring tumor volume and assessing the effect of selumetinib on plexiform neurofibroma-related disfigurement, pain, quality of life, and function. (NIH authors: E. Dombi, A. Baldwin, L.J. Marcus, E. Dombi, P. Whitcomb, S.I. Martin, R. Ershler, P. Wolters, J. Therrien, J. Glod, A. Brofferio, A.J. Starosta, A. Gillespie, A.L. Doyle, and B.C. Widemann, *N Engl J Med* 375:2550–2560, 2016)

NIDCR, NIAID, NCI: MECHANICAL DAMAGE CAUSED BY CHEWING REGULATES TH17 CELL RESPONSES IN THE MOUTH

The immune system performs a remarkable balancing act at barrier sites such as the skin, mouth, and intestines, by fighting off harmful pathogens while tolerating normal flora. Multiple immune cell types protect these sites, including T helper 17 (Th17) cells. Although Th17 cells are known to be important in immunity at barrier surfaces, exaggerated Th17 cell responses have been linked to the oral inflammatory-disease periodontitis. Understanding the tissue-specific factors that regulate immunity at the oral barrier is critical and may lead to new ways to treat this common inflammatory condition.

In a new study, NIDCR researchers and scientists from the University of Manchester (Manchester, United Kingdom) have shown that, in the mouth, mechanical damage caused by chewing controls physiologic Th17-cell responses. Mice fed a soft-food diet requiring minimal chewing accumulated fewer Th17 cells than mice fed a normal or hard-food diet. The investigators also showed that the signaling molecule interleukin 6 (IL-6) mediates the damage-induced rise in Th17 cell numbers. Unlike normal mice, mice lacking IL-6 failed to accumulate Th17 cells in response to a hardened diet or to oral mechanical abrasion.

This work has revealed that Th17-cell regulation in the mouth differs from that at other barrier sites such as the skin and intestines, where certain microbes have been shown to stimulate Th17-based immunity. The investigators concluded that factors that control Th17



NIKI M. MOUTSPOULOS, NIDCR

NIDCR: Th17 cells are key mediators of immunity at barrier sites such as the oral cavity. The factors that control these cells differ depending on cues unique to each site's environment.

cells differ depending on unique characteristics and environment of each body site. (NIH authors: N. Dutzan, L. Abusleme, T. Greenwell-Wild, N. Bouladoux, L. Brenchley, G. Calderon, T. Break, M. Lionakis, G. Trinchieri, Y. Belkaid, and N. Moutsopoulos, *Immunity* 46:133–147, 2017) ●
[NIDCR SUBMITTED BY CATHERINE EVANS]

Read longer versions of the above briefs and others online at <https://irp.nih.gov/catalyst/v25i2/research-briefs>. The following are online only:

- NINDS, NHGRI, NIAID: NODDING SYNDROME MAY BE CAUSED BY RESPONSE TO PARASITIC PROTEIN
- NIAID: HOW ANTIBODY TREATMENT LED TO SUSTAINED REMISSION OF HIV-LIKE VIRUS
- NICHD: HAIR ANALYSIS MAY HELP DIAGNOSE CUSHING SYNDROME
- NCI, NIDA: PREMATURE DEATH RATES DIVERGE IN THE UNITED STATES BY RACE AND ETHNICITY
- NCI, NHGRI, NIDCD, NIEHS: GENOMIC FEATURES OF CERVICAL CANCER IDENTIFIED

Laskers

CONTINUED FROM PAGE 1

Albert and Mary Lasker Foundation. Scholars can work as principal investigators at NIH for five to seven years and then can either remain on the intramural tenure track or move—with three years of research funding—to a university or other research institution.

The following is a lightly edited version of interviews with the new Laskers.

CHRISTINE CAMPO ALEWINE, M.D., PH.D.

Lasker Clinical Research Scholar, Laboratory of Molecular Biology, Center for Cancer Research, National Cancer Institute



Education: Dartmouth College, Hanover, N.H. (B.A. in chemistry and Asian studies); University of Maryland School of Medicine, Baltimore (Ph.D. in physiology; M.D.)

Training: Residency in internal medicine at Johns Hopkins Hospital (Baltimore); clinical fellow in medical oncology at NCI's Laboratory of Molecular Biology

Came to NIH: In 1998–1999 as postbac, Cancer Research Training Award Fellow, NCI's Laboratory of Pathology; in 2011–2014 as a clinical fellow; became an assistant clinical investigator in 2014

Outside interests: Tennis; hiking; quilting; Girl Scout troop leader; spending time with her husband and their two daughters

Website: <https://irp.nih.gov/pi/christine-alewine>

Current research: My work focuses on developing treatments for pancreatic cancer, a devastating disease that kills more than 40,000 Americans each year. I am studying recombinant immunotoxins, which are antibody-based anticancer therapeutics that deliver a very potent bacterial toxin specifically to cancer cells. The bacterial toxin halts protein synthesis in the cancer cell. SS1P and LMB-100 are two recombinant immunotoxins that we are testing in the clinic for patients with solid tumors, including pancreatic cancer. Our long-term goal is to develop effective treatment options for these patients.

How did you become interested in science?

I have always wanted to be a scientist. As a kid, I was interested in dinosaurs and stars. Once I got to college, I fell in love with chemistry.

What about medicine?

When I was at Dartmouth, one of my hallmates in the dorm almost died of meningococcal meningitis. I remember the people in the white bunny suits (likely from the Centers for Disease Control and Prevention) roaming the halls and cleaning up the dorm. I was struck by how serious the illness was and I wanted to do something that mattered—to help people who were very sick.

What made you decide to get an M.D.-Ph.D.?

During college, I was lucky enough to get an internship with Karen Wetterhahn, a chemistry professor who specialized in understanding the environmental effects of toxic metals. One of the more senior students in Karen's lab was applying to M.D.-Ph.D. programs. I had never heard of this track before but it sounded like it would allow me to combine my interests in basic science and clinical medicine.

What got you interested in cancer research and pancreatic cancer in particular?

I can't really name a particular reason why I have always been so fascinated by cancer. From the time I decided to go to medical school, I knew that I wanted to be an oncologist. Through all my years of training, I never found any subject more interesting: How do your very own cells go bad and turn cancerous? I wanted to understand why that happens and do something about it. Pancreatic cancer is a terrible disease with its very own nasty personality. Unfortunately, although we are learning more and more about the biology of pancreatic tumors, we still don't have effective drugs to treat our patients with this disease.

What attracted you to NIH?

There are very few places today where one can take what one works on in the lab and bring it to patients and back with the ease that we can at NIH. It's a fantastic opportunity. There is so much protected time to get a lab started and at the same time be able to do clinical trials.

What have you learned so far?

That developing drugs is hard work. It takes so much time before you know what's going on. You have to find something that works, is stable and properly metabolized, and doesn't kill people. It's a really difficult problem.

What's the hardest part of your job?

I hate telling patients who want more treatment that I have nothing else that I can offer them.

Read more online at <https://irp.nih.gov/catalyst/v25i2/lasker-clinical-research-scholars>.


COURTNEY DAYLE FITZHUGH, M.D.

Lasker Clinical Research Scholar, Sickle Cell Branch, National Heart, Lung, and Blood Institute



Education: University of California, Los Angeles (B.S. in biology); University of California, San Francisco, School of Medicine (M.D.)

Training: Combined residency in internal medicine and pediatrics, Duke University Medical Center (Durham, N.C.); combined fellowship in adult hematology and pediatric hematology/oncology, NIH and Johns Hopkins Hospital (Baltimore)

Came to NIH: In 1999–2000 as a Clinical Research Training Program fellow in NHLBI; in 2005–2007 for clinical fellowship training; returned in 2007 for research fellowship training in NHLBI's Molecular and Clinical Hematology Branch; in 2012 became an assistant clinical investigator in the Laboratory of Early Sickle Mortality Prevention, Sickle Cell Branch, NHLBI

Outside interests: Cooking; traveling; playing board games; watching movies

Website: <https://www.nhlbi.nih.gov/research/intramural/researchers/pi/fitzhugh-courtney>

Current research: Sickle-cell disease (SCD) is associated with debilitating complications including stroke, intense pain, and kidney failure, as well as early mortality. Although matched-sibling

bone-marrow transplantation offers the best treatment for people with SCD, only 15 to 20 percent of these patients have a complete sibling match. But more than 90 percent have at least a half-match such as a parent, child, or half-matched siblings. We are developing an alternative option that involves such haploidentical donors.

Our lab employs a regimen that focuses on creating a tolerant state for donor and recipient cells in order to achieve stable mixed chimerism. We are trying to deplete donor and recipient lymphocytes and allow them to grow under the cover of immunosuppressive drugs that will promote tolerance. We are attempting to identify biomarkers that are associated with early graft rejection and evaluating whether prompt treatment leads to prevention or reversal of graft rejection. In addition, we are exploring whether biomarkers associated with transplant tolerance can indicate whether immunosuppressive drugs can be withdrawn. We hope our work will result in a wide range of treatment options for patients with SCD.

How did you get interested in medicine and sickle-cell disease?

My dad is a family-practice physician, and ever since I was a little girl, I have wanted to be a doctor, too. I was in college when I first became interested in SCD: My mom had organized a holiday party at a children's hospital for children with the disease; I went and enjoyed talking with the patients and painting their faces (in a face-painting activity).

What about sickle-cell disease research appeals to you?

Because SCD is a chronic illness, I can take care of children and adults. SCD

affects every organ system and can cause pain and even a stroke. I see extremely sick people whom no one else will transplant. Many are on dialysis, have elevated pressure in their lungs, or have heart failure. I feel that I can really make a difference. I want to keep people from dying early.

How did you become interested in NIH?

When I was in medical school, I came to NIH as a Clinical Research Training Program fellow and worked with **John Tisdale** (NHLBI). We used the immunosuppressant drug rapamycin to induce tolerance for bone-marrow transplants performed on normal mice and sickle-cell mice. I did the transplants on the mice, saw patients with SCD in clinic, and wrote a protocol for patients with SCD. I just loved it.

What's hot in your field right now?

Gene therapy and gene editing for SCD. Dr. Tisdale's group is working on that—taking the patient's own cells, inserting the normal gene, and attempting to correct the sickle mutation directly.

Is there anything else you'd like to tell us?

It's amazing to see how the lives of patients with SCD are transformed. They had never been able to predict when debilitating painful crises would come. Now, with successful treatment, they can actually make plans and live normal lives.

To learn more about the Lasker Clinical Research Scholars Program, go to <https://www.nih.gov/research-training/lasker-clinical-research-scholars>.

Laskers

CONTINUED FROM PAGE 11

JUNG-MIN LEE, M.D.

Lasker Clinical Research Scholar, Women's Malignancies Branch, Center for Cancer Research, National Cancer Institute



Education: Yonsei University Wonju College of Medicine in Wonju City, South Korea (M.D.)

Training: Residency in internal medicine, Holy Family Hospital, Catholic University Medical College (Seoul, South Korea); research fellowship in pathology and cell biology at Thomas Jefferson University (Philadelphia); residency in internal medicine at the Albert Einstein Medical College (New York); clinical research fellowship on breast-cancer functional imaging at the Memorial Sloan-Kettering Cancer Center (New York); medical oncology/hematology fellow in NCI's Medical Oncology Branch

Came to NIH: In 2008–2012 for training; in 2012 became an assistant clinical investigator in NCI

Outside interests: Going to museums; traveling; swimming; meditating

Website: <https://ccr.cancer.gov/Womens-Malignancies-Branch/jung-min-lee>

Current research: My research is focused on cancers that share similar molecular abnormalities: *BRCA* mutation-associated breast or ovarian cancer, high-grade epithelial ovarian cancer, and triple negative breast cancer (TNBC). I am the principal investigator for ongoing phase 1–3 studies testing a PARP inhibitor (olaparib) in combination

with carboplatin or cediranib and other biologic agents. In the clinical trials, I am examining the hypothesis of whether there is a clinical synergy of the combination of targeting key proteins in the DNA-damage repair pathways, cell cycle, tumor microenvironment, and immune checkpoints. We are studying potential biomarkers of response to targeted agents that are pertinent to TNBC and high-grade epithelial ovarian cancer. We launched our clinical trial (15-C-0145) to test a hypothesis that the increased antigenic microenvironment by olaparib or cediranib will make cancer cells more susceptible to immune-checkpoint inhibitor therapy. Olaparib is a drug that may inhibit cancer cells' ability to repair DNA damage. Cediranib is a drug that may stop the growth of blood vessels that feed cancer cells. In phase 1 of the study, we demonstrated that the combination of these drugs is safe and clinically active in a subgroup of women cancer patients; in phase 2 we will determine how effective the combination treatments are for ovarian cancer and other solid tumors. I am delighted by the enthusiasm of our patient community for this protocol.

How did you become interested in medicine and cancer research?

I grew intrigued with cancer biology when I was in medical school. At first, I was interested in the biology of liver cancer, the most common cause of cancer death in Korea. Later, I had great mentors who were cancer experts at Jefferson, Memorial Sloan Kettering, and NCI. They had a huge impact on the direction and momentum of my research.

What excites you about your work?

It's exciting whenever I see a patient who benefits from a clinical trial. In the 1980s and 1990s, there were limited treatment options for ovarian and other cancers. Now

there are novel treatment strategies—including pathway-specific immune checkpoint kinase inhibitors, angiogenesis inhibitors, and DNA-repair inhibitors. Understanding molecular mechanisms and working on hypothesis-driven clinical trials at NIH has helped me mature as a physician-scientist.

How did you choose to come to NIH?

I heard a lot of good things about NIH from my mentor in South Korea. He was an expert in liver cancer and did a fellowship at NIH in the 1980s. He talked about the opportunities for international collaborations and NIH's strong support for translational research. He told me that NIH was one of the best places in the world to work.

What is important to you about your work with patients?

Patients come to NIH with hope. My close cousin recently died from breast cancer. I feel obligated to set a good example as a researcher and clinician. The patients come first. It's very important to spend extra time with them—holding their hands, explaining what's going on with their treatment, and just caring. As long as I do my best, patients appreciate it—even when the results are disappointing and their tumors don't respond to the treatment.

Is there anything else you'd like to share?

I am an Asian immigrant woman physician. I came to the United States at age 26 and had to overcome language, culture, and societal changes. In 2014, I participated in a one-year leadership program—the NCI Senior Executive Enrichment and Development Program (SEED). The SEED has helped me gain the strength and confidence to share my enthusiasm, positive attitude, and passion for research. My career goal is to be a driver of change and advancements that will help our patients.


FRANK I. LIN, M.D., NCI-CCR

Lasker Clinical Research Scholar, Chief, Targeted Radionuclide Therapy Section, Molecular Imaging Program, Center for Cancer Research, National Cancer Institute



Education: Stanford University, Stanford, Calif. (B.S. in biological science); University of Utah, Salt Lake City (M.S. in medical informatics); Medical College of Wisconsin, Milwaukee (M.D.)

Training: Internal medicine residency, Kaiser Permanente (San Francisco); nuclear-medicine residency, University of California, Davis (Sacramento, Calif.); PET/CT fellow, Stanford University

Came to NIH: In 2010

Outside interests: Going to museums, parks, nature centers, and playgrounds with his wife and their two daughters

Website: <https://ccr.cancer.gov/molecular-imaging-program/frank-i-lin>

Current research: My research involves treating cancer through harnessing the power of unstable elements with thermodynamically unstable nuclei that naturally undergo radioactive decay. During radioactive decay, the unstable nucleus reconfigures toward a more stable one and releases energy in the form of radiation or ejected atomic particles. Radiation and ejected material such as alpha particles (each of which is made up of two neutrons and two protons) and beta particles (ejected electrons) kill

cells by damaging cellular DNA. By linking these radioactive isotopes to other molecules that selectively target tumors, we can focus the resultant radiation damage and give high doses of radiation to cancer cells while minimizing injury to healthy tissue. Unlike external-beam radiation therapy, which tends to be a localized form of treatment, this targeted radionuclide therapy (tRNT) is a systemic therapy that is given intravenously and can treat widespread and even micro-metastases. I use high-LET (linear energy transfer) radioactive agents such as alpha emitters conjugated to small molecule carriers that, unless bound to a target tumor cell, are cleared quickly from the body with minimal adverse effects on healthy tissue. I currently work with pheochromocytoma/paraganglioma, mesothelioma, and prostate cancer, but tRNT has broad applications and can be used to treat a variety of other malignancies.

What got you interested in medicine?

My interest started in the family—my father is a physician and my mother was a nurse. Although I had considered other interests and careers such as engineering and computer science, I felt my calling was in medicine. Perhaps as a compromise, I chose a medical specialty (nuclear medicine) that was technology and computer-oriented.

What excites you about your work?

I think my work is exciting because tRNT attacks cancer cells in a different way compared to other systemic therapies and may be effective in controlling tumors even when other forms of treatment have failed. Having tRNT as a novel class of therapy broadens the existing array of therapeutic agents that oncologists can use to help their patients. Furthermore, the field of tRNT is underdeveloped right now and the prospect of being an advocate for and being able to

further advance this very deserving field is tremendously exciting for me.

Why are you interested in tRNT?

For most physicians who specialize in nuclear medicine, the bulk of their work deals with the evaluation of disease through imaging. While this work is important, I have always wanted to be able to offer patients treatment for the diseases that we see on our imaging scans. Fortunately, as a nuclear-medicine physician, I was trained to do just that—treat diseases, most commonly cancer, using radionuclides. I am fortunate that the NIH is giving me this opportunity to pursue my dream through the Lasker Clinical Research Scholars program.

What inspires you?

People who have the compassion to help people and who also have the ability to do so.

What attracted you to NIH?

The NIH is the premier center of medical research in the United States. I wanted to be a part of this research tradition.

Is there anything else you'd like to share?

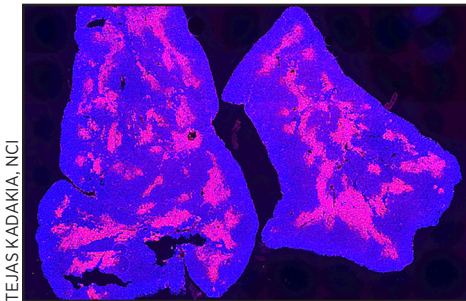
I am in the midst of training to become a board-certified medical oncologist through the fellowship program here at the NIH. In addition to being able to run combinational trials of tRNT with more conventional chemotherapy, immunotherapy, or other targeted agents, I also hope to increase awareness of this promising class of therapeutic agents among my future medical-oncology colleagues. The practice of medicine is still in many ways siloed, with each medical specialty entrenched in its own ways. There is a need for physicians who can understand different perspectives coming from different medical specialties involved in cancer care. ●



The Thymus: A Small Organ with Huge Immunological Impact

Special from the NIH Thymus Symposium

BY OMOZUSI ANDREWS, NIAID



TEJAS KADAKIA, NCI

This image of a mouse thymus shows all cells in the thymus; the lighter portion indicates the thymus medulla.

SCIENTISTS ONCE THOUGHT THAT THE thymus—a little organ in your upper chest—was a vestigial leftover without a major function. It wasn't until the early 1960s that Australian immunologist Jacques Miller made an amazing discovery: The thymus is the place where T cells, the major effector cells of the immune system, are generated.

We now know that the thymus receives precursors of T cells, called thymocytes, from the bone marrow and helps them to mature into full-fledged T cells (such as CD4 or CD8 cells) that are trained to attack foreign cells. NIH researchers have played a key role in moving the field of thymus research forward.

Transforming the field

In 2000, **Alfred Singer's** group at the National Cancer Institute (NCI) transformed the field of thymus biology by demonstrating a novel selection mechanism for thymocyte lineage choice and maturation, called the “kinetic signaling” model. A major revelation of this study was that lineage fate decisions are made by the “kinetics,” and not the “strength,” of the T-cell receptor signaling as previously thought. This seminal finding was highlighted in 2016 in the *Journal of Immunology* as a “Pillar of Immunology” article for its countless citations, for changing the conventional view

on thymocyte selection and maturation, and for advancing thymus research (*J Immunol* **196**:1985–1997, 2016).

In 2012, Singer with **Remy Bosselut** (NCI) instituted the inaugural NIH Thymus Symposium to highlight thymus-focused immunology basic research. Since then, there has been an explosion of new discoveries and information so that the next thymus symposium was certainly overdue. After four years, the second NIH Thymus Symposium was held on December 9, 2016, to gather new insights on thymus research, examine the implications, and spark collaboration among thymus-research enthusiasts. Attendees and presenters included scientists and fellows from within the NIH and as far away as France and Japan.

New Insights and implications

Thymocytes, the precursor of T cells, develop in a region of the thymus called the thymic cortex; selected thymocytes proceed to the thymic medulla and become mature T cells; and eventually the T cells are released into the bloodstream. Yousuke Takahama (Tokushima University in Tokushima, Japan) described how the protein C-C motif chemokine receptor type 7 (CCR7) is essential for the cortex-to-medulla migration and for establishing self-tolerance, thereby preventing tissue-specific autoimmunity. Consequently, he found that in mice, the deletion of CCR7's binding partners—C-C motif ligands 21A and 19—had a negative effect on establishing immune tolerance.

Wanjun Chen (National Institute of Dental and Craniofacial Research) elucidated the essential role that transforming growth factor- β plays in the development of immune-suppressive regulatory T cells (Tregs). Understanding how Tregs develop might lead to the identification of molecular-targeted therapies for autoimmune diseases

(*Proc Natl Acad Sci U S A* **111**:E465–473, 2014).

Although it was once thought that the maturation of T cells took place entirely within the thymus, recent evidence has shown otherwise. The current editor-in-chief of the *Journal of Immunology*, Pamela Fink (University of Washington in Seattle), provided clues about how newly generated T cells, called recent thymic emigrants (RTEs), go through a final maturation step outside the thymus. Immature RTEs are ineffective at mounting adequate immune responses. Understanding RTE biology is important because they are overrepresented in neonates and in adults recovering from lymphopenia, and may play a role in several diseases including ulcerative colitis, chronic myeloid leukemia, and autoimmune thyroid disease.

After listening to several other enlightening talks on thymus-related research, the scientists were eager to interact at the reception at the end of the day. Some of the interactions may stimulate collaborations that will advance the field of thymus research. ●

The symposium was chaired by **Dinah Singer, Paul Roche, Vanja Lazarevic** (all from NCI), and **Richard Hodes** (National Institute on Aging), and sponsored by the NCI Center of Excellence in Immunology and the NIH Cytokine Interest Group.

Read more online, including two more talks highlighted in “More Glimpses into the Thymus,” by **Mugdha Samant** (NEI), at <https://irp.nih.gov/catalyst/v25i2/the-thymus-a-small-organ-with-huge-immunological-impact>.

Behavioral and Social Sciences Research Festival

Celebrating the Past, Looking to the Future

BY TRACEY GOLDNER, NCI

“THERE IS A BROKEN PIPELINE BETWEEN basic and applied behavioral and social sciences research,” NIH Associate Director for Behavioral and Social Sciences Research **William Riley** told the crowd that had gathered for the inaugural NIH Behavioral and Social Sciences Research Festival on December 2, 2016. He challenged his colleagues to think about how they could accelerate the application of basic behavioral and social sciences findings to areas such as interventions, clinical trials, and even real-life settings.

“We initiated this annual festival to highlight some of the recently funded behavioral and social sciences research that the NIH supports,” said Riley, who is also the director of the NIH Office of Behavioral and Social Sciences Research (OBSSR). The festival also “bring[s] together behavioral and social scientists within the NIH extramural and intramural communities to network with each other, share scientific ideas, and explore ways to advance this research.” In fiscal year 2016, NIH funded 2,600 extramural grants associated with behavioral and social sciences research including studies on migraines and mindfulness, crowd-sourced longitudinal sensor data, and the effects of bipolar disorder on caregivers.

In addition to Riley’s keynote speech, the festival featured three panel discussions, a town hall meeting, and a poster session.

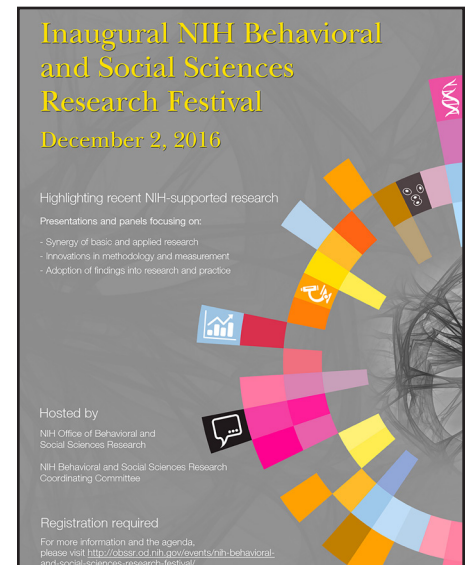
Lisbeth Nielsen, the chief of the Individual Behavioral Processes Branch at the National Institute on Aging moderated the first panel—“Synergy of Basic and Applied Behavioral and Social Sciences.” Gene Brody (University of Georgia in Atlanta), one of the three panelists, described his project that tracked African-American youth living in rural counties with high poverty and unemployment rates.

Economic adversity during childhood can lead to negative health consequences through adulthood. But Brody found that positive parenting behaviors may have beneficial effects on young adults’ health.

Panelist Barbara Fredrickson (University of North Carolina at Chapel Hill) described her research that focuses on how positive emotions underlie healthy changes in thinking patterns, social behavior, health, and physiological reactions. One of her former graduate students, NCI postdoc **Elise Rice**, is exploring the health applications of the basic processes she had begun to study in Fredrickson’s lab.

The second panel—on “Innovative Research Infrastructure, Methods, and Measures in Behavioral and Social Sciences Research”—also featured three presenters and was moderated by **Richard Moser**, a research psychologist in NCI’s Behavioral Research Program. **Argyris Stringaris** (National Institute of Mental Health), who uses imaging and other methods to measure irritability in children, explained why measurements matter. Irritability is associated with the development of depression and other negative outcomes. Another presenter, Eun-Young Mun (Rutgers University in New Brunswick, New Jersey) reviewed the dangers of overusing meta-analysis and systematic reviews and encouraged researchers to consult methodologists in assessing the strength of meta-analyses.

NCI epidemiologist **Gila Neta** hosted the third panel—on the “Adoption of Behavioral and Social Sciences Research Findings into Research and Practice.” The panel had four speakers including Sarah Gehlert (Washington University in St. Louis), who works with the Transdisciplinary Research in Energetics and Cancer Center (TREC),



THE SCIENTIFIC CONSULTING GROUP, INC.

and Alan Mendelsohn (New York University School of Medicine in New York). Gehlert discussed how the TREC initiative brought together researchers from different disciplines to strengthen research on obesity, physical activity, and diet. Mendelsohn studies how mother-child interactions such as reading and playing can lower maternal stress and improve school readiness and child development.

The town hall meeting gave researchers a chance to connect and talk about ways they could work together. The poster session showcased many behavioral and social services research projects.

Sounds as if that broken pipeline is already on the mend as scientists continue to learn how to translate their research findings into practice and improve public health. ●

Read more online at <https://irp.nih.gov/catalyst/v25i2/behavioral-and-social-sciences-research-festival>. To watch a videocast, go to <https://videocast.nih.gov/launch.asp?20043>.



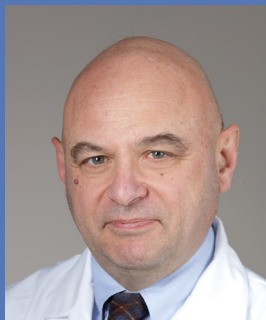
Recently Tenured



ROBERT B. BEST, NIDDK



CHOONSIK LEE, NCI-DCEG



LUIGI D. NOTARANGELO, NIAID

KUMARAN RAMAMURTHI,
NCI-CCR

JIANXIN SHI, NCI-DCEG

ROBERT B. BEST, PH.D., NIDDK

Senior Investigator, Theoretical Biophysical Chemistry Section, Laboratory of Chemical Physics, National Institute of Diabetes and Digestive and Kidney Diseases

Education: University of Cape Town, Cape Town, South Africa (B.Sc. and M.Sc. in chemistry); University of Cambridge, Cambridge, England (Ph.D. in chemistry)

Training: Postdoctoral training at University of Cambridge; postdoctoral training at NIDDK

Before coming to NIH: Royal Society University Research Fellow, Chemistry Department, University of Cambridge; college lecturer at Emmanuel College, University of Cambridge

Came to NIH: In 2004 for training; in 2012 as an investigator in NIDDK

Selected professional activities: Editorial board member of *Scientific Reports*

Outside interests: Running; rowing

Website: <https://irp.nih.gov/pi/robert-best>

Research interests: The Theoretical Biophysical Chemistry Section's main goal is to develop the theoretical framework needed to understand the dynamics of molecules at the single-molecule level. We use theory and molecular simulations to help to explain and understand experimental observations in terms of the complex microscopic processes involved.

Through the impressive achievements of structural biology, much has been learned about the function of proteins and the structures of their stable states, but it is still challenging to study the dynamics and mechanisms of transitions between these states. Experimental information on dynamics is generally limited in resolution. To aid in its interpretation, my lab is developing simulation and theoretical methods for studying macromolecular dynamics and applying them to biologically interesting systems. In doing so, we have resolved several controversies related to ambiguities of experimental interpretation. In complementary work, we have been using empirical data for peptides and macromolecules in solution to further improve the energy functions used in our simulations.

My lab's other recent projects include performing experiments using atomic-force microscopy and optical tweezers to study protein folding in the presence of an external "pulling" force. We also resolved a long-standing discrepancy between small-angle X-ray scattering and Förster resonance energy transfer experiments on intrinsically disordered proteins. In addition, we developed coarse-grained master equations as a tool for interpreting peptide dynamics in simulations and used diffusion models of protein folding. My lab also determined the binding mechanism of intrinsically

disordered proteins. We studied the influence of molecular chaperonins on folding and misfolding as well as the self-association of transmembrane helices. We also identified the mechanisms of substrate transport in hydrogenase enzymes and developed methods for identifying cryptic binding pockets in proteins.

We hope that a deeper understanding of biological processes and how molecules function may one day lead to discoveries that will contribute to improved treatments for diseases and disorders.

These are some of the recently tenured investigators who will be featured in an upcoming issue of the *NIH Catalyst*:

- Theo Heller, NIDDK
- Jose Feraldo-Gomez, NHLBI
- Zhiyong Lu, NLM and NCI
- Anil Chaturvedi, NCI-DCEG
- Peter Crompton, NIAID
- Zhengping Zhuang, NCI-CCR
- Joshua Sampson, NCI-DCEG
- And more



CHOONSIK LEE, PH.D., NCI-DCEG

Senior Investigator and Head of the Dosimetry Unit, Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute

Education: Hanyang University, Seoul, South Korea (B.S.E. in nuclear engineering; M.S. in health physics; Ph.D. in health physics)

Training: Postdoctoral fellow, Innovative Technology Center for Radiation Safety (Seoul); postdoctoral fellow in computational medical physics at the University of Florida (Gainesville, Fla.)

Came to NIH: In 2009

Selected professional activities: Member of the International Commission on Radiological Protection; editorial boards of *Radiation Protection Dosimetry Journal* and *Journal of Radiation Protection*

Outside interests: Reading books; listening to classical music; playing the piano and guitar

Websites: <https://irp.nih.gov/pi/choonsik-lee>; <https://ncidose.nci.nih.gov>

Research interests: The medical use of radiation has increased dramatically over the past few decades for diagnostic purposes as well as for radiation therapy. For example, computed-tomography (CT) scans performed in the United States increased from 3.6 million in 1980 to 70 million in 2007; approximately 10 percent of them were for pediatric patients, who are at higher risk of radiation-related cancer than adults are. To ensure patient safety, we need a better understanding of how the nature and magnitude of radiation doses used in medical procedures affect human health.

One of the ways we can estimate the doses of ionizing radiation delivered to patients is by using computational human phantoms (computer simulations of the human body) and radiation-exposure scenarios coupled with the Monte Carlo model of radiation-transport techniques. (The Monte Carlo model, named for

the international capital of gambling, is a mathematical procedure for generating random numbers and so named because of the element of chance.) Several studies have validated that the simulation approach adequately represents the physical interaction of radiation in the real human body.

I have developed computational human phantoms that are crucial for realistic individualized dose calculations. The International Commission on Radiological Protection has adopted the phantom series as an international reference to ensure the accuracy of individualized organ dosimetry and to estimate and monitor the dose given to patients undergoing diagnostic radiation procedures. I am also developing dosimetry methods to calculate and assess the radiation dose received during diagnostic radiation procedures such as CT scans, radiography, interventional fluoroscopically-guided procedures, and nuclear medicine examinations.

Although radiation therapy has been successfully used to treat many types of cancers since the 1920s, there has been an increasing concern about the long-term risk of radiation-induced second cancers among cancer survivors. With external-beam radiation therapy, it is practically impossible to irradiate tumors without some radiation penetrating through the surrounding normal tissues. Many epidemiologic studies have demonstrated late effects including the increased risk of developing second cancers.

However, there are substantial difficulties in reconstructing organ doses for large patient cohorts treated years ago. I am collaborating with extramural clinical medical physicists and oncologists to develop new dose-reconstruction methods in a system called the NCI dosimetry system for radiation treatment (NCIRT). I am working with NCI epidemiologists to apply the tool to multiple epidemiological studies of second cancer in radiotherapy patients. I am also extending NCIRT to proton-therapy patients.

LUIGI DANIELE NOTARANGELO, M.D., NIAID

Senior Scientist, Chief, Immune Deficiency Genetics Section, and Deputy Chief, Laboratory of Host Defenses, National Institute of Allergy and Infectious Diseases

Education: University of Pavia, Pavia, Italy (M.D.)

Training: Residency in pediatrics and subspecialty training in allergy/immunology and human cytogenetics at the University of Pavia; postdoctoral training at NCI's Metabolism Branch

Before coming to NIAID: Professor and chair of Pediatrics at the University of Brescia (Brescia, Italy; 2000–2006); professor of pediatrics, Boston Children's Hospital, Harvard Medical School (Boston; 2006–2016)

Came to NIH: In 1986–1988 for training in NCI; joined NIAID in 2016

Selected professional activities: Past president of the European Society for Immune Deficiencies and of the Clinical Immunology Society; chief editor, *Frontiers in Immunology*

Outside interests: Listening to classical music; playing chess; reading novels; traveling

Website: <https://www.niaid.nih.gov/research/luigi-daniele-notarangelo-md>

Research interests: My lab studies the molecular and cellular mechanisms of human primary immune deficiencies, especially combined immunodeficiencies (CID), with the ultimate objective of improving the diagnosis and treatment of these conditions. We are collaborating with other NIAID investigators as well as several groups worldwide.

People with CID have an increased susceptibility to infections and often manifest immune dysregulation. We study patients who have genetically undefined forms of CID as well as those with known genetic defects. In the former group, we use whole-exome sequencing and many



Recently Tenured

CONTINUED FROM PAGE 17

cellular and molecular techniques to identify novel gene defects including mutations in *DOCK2*, *TTC7A*, *HOIP*, and *EXTL3* that result in decreased concentrations of their proteins. We also have a strong interest in defining the molecular and cellular defects in newborns identified with T-cell lymphopenia.

In patients with CID of known genetic etiology, we are defining the mechanisms underlying immune dysregulation. We are especially interested in human recombination-activating gene (*RAG*) deficiency. We have determined that the severity of clinical manifestations associated with mutations in the *RAG* genes correlates with the residual activity of their resulting proteins and with different degrees of perturbation of the T- and B-cell repertoire's diversity and composition. We are testing the hypothesis that mutations in the coding flank sensitive region of *RAG1* may alter the selection of *V*, *D*, and *J* genes targeted for rearrangement, and that skewing of the repertoire may contribute to autoimmunity. These human studies are complemented by similar efforts in novel animal models that we have generated by editing genes with the CRISPR/Cas system.

My laboratory has also developed a large repository of induced pluripotent stem cells (iPSCs) from patients with CID and other immune deficiencies. We aim to define the pathophysiology of immune and extra-immune manifestations of disease. We want to apply CRISPR/Cas technology to correct the gene defect in patient hematopoietic stem cells and iPSCs as a first step toward a future therapeutic use of this strategy.

KUMARAN RAMAMURTHI, PH.D., NCI-CCR

Senior Investigator, Laboratory of Molecular Biology, Center for Cancer Research, National Cancer Institute

Education: University of California, Los Angeles (B.S. in microbiology and molecular genetics; Ph.D. in molecular biology)

Training: Postdoctoral fellow, Department of Molecular and Cellular Biology (Harvard University, Cambridge, Mass.)

Came to NIH: In 2009

Selected professional activities: Editorial board of the *Journal of Biological Chemistry*; co-director of the NIH-Johns Hopkins University Graduate Partnership Program

Outside interests: Studying to be a master sommelier

Website: <https://irp.nih.gov/pi/kumaran-ramamurthi>

Research interests: I am investigating the fundamental mechanisms of cell differentiation and division to determine how they can go awry during disease. My lab focuses on how proteins localize to particular subcellular locations and assemble to form large structures during development and cell division. We discovered, for example, that the shape of cellular membranes, either convex or concave, may recruit certain membrane shape-sensing proteins to their correct destination, a novel mechanism for subcellular protein localization.

A longstanding challenge in developmental biology is understanding how an organism constructs large structures that help define the way it looks. We are approaching this problem by examining the morphogenesis of a simple organism—a bacterial spore. Spores are dormant cells that are encased in a thick protein shell, or

“coat,” which helps protect the spore from environmental insults. We are using genetic, biochemical, cytological, and biophysical approaches to investigate how the spore coat is assembled.

We discovered that the assembly of the basement layer of the coat depends on a tiny protein, which anchors the coat onto the surface of the developing spore, and that this protein localizes properly by preferentially embedding in convex membranes such as those found on a spore's surface. This shape-sensing protein then recruits an unusual cytoskeletal protein that polymerizes by hydrolyzing adenosine triphosphate to form a stable platform upon which other coat proteins eventually assemble. Recently, using defined components, we reconstituted the spore-coat basement-layer assembly in a test tube to construct synthetic spore-like particles that can be modified to display molecules of interest. We are currently testing whether these synthetic bacterial cells may be used as versatile platforms for the display of vaccines and for tissue-specific delivery of drugs.

If you have been recently tenured, the *NIH Catalyst* will be contacting you soon about including you on these pages. It's a great way for your colleagues to get to know about you and your work.

JIANXIN SHI, PH.D., NCI-DCEG

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

Education: Beijing University, Beijing, China (B.S. in mathematics; B.S. in economics; M.S. in information science); Stanford University, Stanford, Calif. (Ph.D. in statistics)

Training: Postdoctoral fellow, Stanford University School of Medicine

Before coming to NIH: Research scientist in the Health Research and Policy Department and in the Department of Psychiatry and Behavioral Sciences, at Stanford University School of Medicine

Came to NIH: In 2009 as tenure-track investigator in NCI-DCEG

Selected professional activities: Statistics editor for *Journal of National Cancer Institute*; associate editor for *Biostatistics*; associate editor for *Statistics in Biosciences*

Outside interests: Fishing; listening to classical music

Website: <https://irp.nih.gov/pi/jianxin-shi>

Research interests: My research focuses on developing and applying quantitative methods—including statistical genetics, tumor sequencing, and human microbiomics—to analyze high-dimensional genomic data in order to understand cancer etiology and improve cancer prevention.

During my postdoctoral fellowship, I worked on genome-wide association studies to identify common genetic variants associated with the risk of developing complex diseases such as breast cancer, schizophrenia, and major depression. Since joining NCI, I have been developing methods for detecting copy-number variations associated with complex disease

risk and for identifying genetic variants associated with gene expression and DNA methylation traits.

In addition, I collaborated with two other NCI-DCEG senior investigators on a family-based whole-exome sequencing study to identify a founder mutation in the gene *POT1* (which results in the protein Protection of Telomeres 1). I also worked with a scientist at Johns Hopkins University (Baltimore) to develop statistical methods for improving genetic-risk prediction for complex diseases.

Another interesting problem is evaluating the role of genetics in cancer survival. Many studies show that the genomes of tumors influence survival, but researchers do not know whether a patient's own genome affects survival. I have been developing a method for estimating genetic heritability of survival in lung-cancer patients. Preliminary results showed that that common germline genetic variants do not contribute to the variation of survival in these patients. I plan to expand this work to other cancers.

In another collaboration with one of the NCI-DCEG scientists, we are using samples from the Environment and Genetics in Lung Cancer Etiology study to do an integrative genomic analysis of lung cancer. We are characterizing the intratumor heterogeneity to determine what events drive lung cancer and are identifying genomic features that are predictive of clinical outcomes. We also developed statistical methods to analyze the evolution of tumors.

In addition, I am using large-scale prospective studies to estimate the overall contribution of the oral and gut microbiomes to the risk of developing cancers. ●

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

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

NCCHH: 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

NIAMD: 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

NIHES: 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

NIHR: National Institute of Nursing Research

NLM: National Library of Medicine

OD: Office of the Director

OITE: Office of Intramural Training and Education

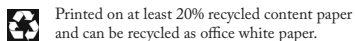
OIR: Office of Intramural Research

ORS: Office of Research Services

ORWH: Office of Research on Women's Health

OTT: Office of Technology Transfer

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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.

Also, we welcome “letters to the editor” for publication and your reactions to anything on the *Catalyst* pages.

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Address correspondence to:
Building 1, Room 333, NIH
Bethesda, MD 20892
Ph: 301-402-1449
Fax: 301-402-4303
e-mail: catalyst@nih.gov

The NIH Catalyst online:
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FROM THE ANNALS OF NIH HISTORY

Hidden Figures in Paper Chromatography

ALMA LEVANT HAYDEN (DIED 1967), a scientist in the then-National Institute of Arthritis and Metabolic Diseases, is demonstrating a technique, called paper chromatography, to screen for steroid substances. With paper chromatography, a drop of liquid containing a mixture of chemicals is placed on porous paper. The chemicals move at different speeds through the paper and give rise to different-colored marks. In this 1952 photo, Hayden is spraying the paper with a reagent to reveal



OFFICE OF NIH HISTORY

the pattern indicating the identity of the substance. Hayden, who had a master's degree in chemistry from Howard University (Washington, D.C.), was among the first minority women scientists working in Washington, D.C., first at NIH and later at the FDA. She was married to NIH chemist **Alonzo Hayden**. Paper chromatography was invented in 1943 by Archer John Porter Martin and Richard Laurence Millington Synge, who shared the Nobel Prize in Chemistry in 1952 for their work. ●

PUBLISHER

MICHAEL GOTTESMAN
Deputy Director for Intramural Research, OD

EDITORS

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CONTRIBUTING WRITERS

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LESLEY EARL
CATHERINE EVANS
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MUGDHA SAMANT
HANNAH VALANTINE

PHOTOGRAPHERS/ILLUSTRATORS

P. BURNS, E. COLE, T. KADAKIA,
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