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Annals of NIH History

If Only Our Machines Could Talk: An "Oral History" of FACS II

BY E. GORDON MARGOLIN

Gordon Margolin is a retired internist and nephrologist. Before moving to Bethesda, Maryland, in 2010, he was the director of medicine at Cincinnati Jewish Hospital and a professor of medicine, specializing (in later years) in geriatrics, at the University of Cincinnati. In 2011, he began volunteering in the Office of NIH History and Stetten Museum. He conducts oral histories with accomplished scientists. On a recent visit to the Stetten Museum storeroom, he wondered, "Wouldn't these instruments also have great stories to tell? Let's give it a try!" Below is his interview with the machine known as FACS II, a fluorescence-activated cell sorter.

Gordon Margolin: Hello, Mr. FACS II. You have been part of our collections in the NIH Stetten Museum since 1992, when you were donated by **Susan Sharrow**, your operator in the National Cancer Institute's (NCI's) Experimental Immunology Branch (EIB). May I pick your memory stores for our historical collection?

FACS II: Sure! I've been waiting for 26 years for this opportunity, just parked here in storage and mulling over my relevance to the scientific developments of NIH and beyond. Let's do it!

G.M.: What does FACS stand for, and what did you do?

FACS II: FACS stands for fluorescence-activated cell sorter. I was designed using laser technology, which makes the cells

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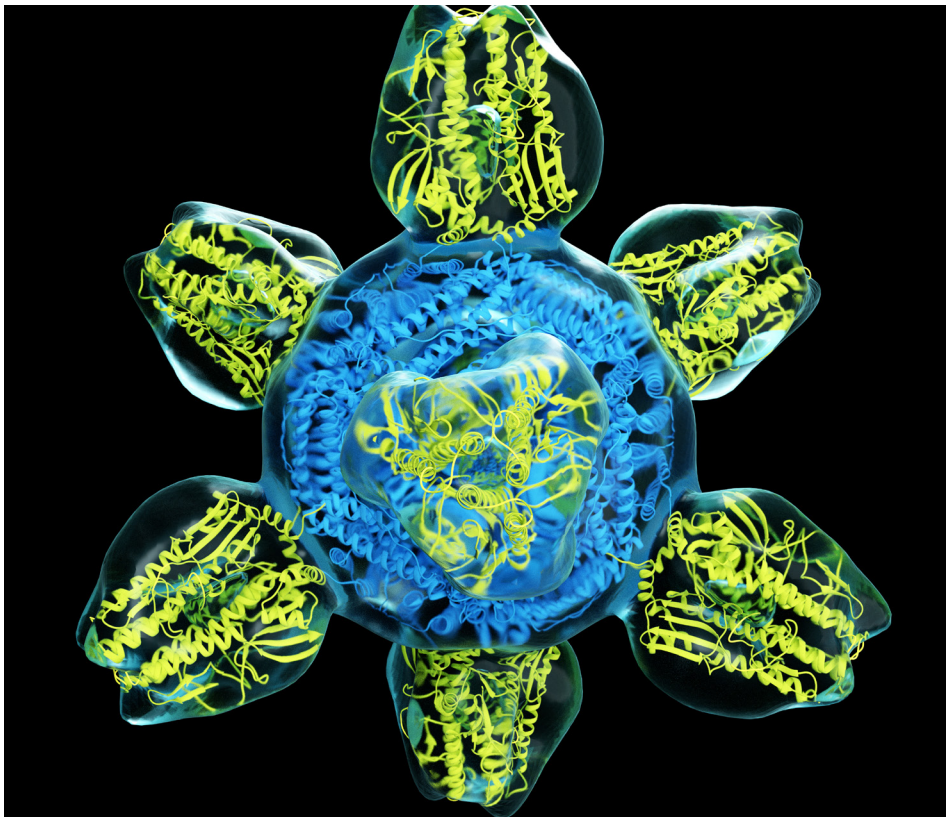
A Potpourri of Science

Report from the 2018 NIH Research Festival



JOHN GALLAGHER AND AUDRAY HARRIS, NIAID

At the NIH Research Festival, NIAID researchers talked about developing a universal flu vaccine. Shown: A prototype that is a hybrid of a scaffold (blue) and influenza hemagglutinin proteins (yellow), engineered to display antibody binding sites common to various human influenza subtypes. **Jeffrey Boyington** (Vaccine Research Center, NIAID) designed the particle.

This year's Research Festival was launched on September 12 by four institute directors who spoke about their institutes' scientific accomplishments and research advances in their own labs. The three-day event, co-chaired by scientific directors **Tom Misteli** (NCI) and **Steven Holland** (NIAID), featured scientific presentations, awards ceremonies, poster sessions, special exhibits, and more.

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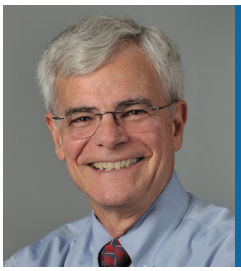


Toward a More Civil Community at the NIH

BY MICHAEL GOTTESMAN, DDIR

"Our hope is that by providing basic training in ethics, preventing misunderstanding, eliminating harassment, encouraging collaboration and sharing, and arriving at a common understanding of the responsible conduct of science and ethical behavior, we will create a positive, civil environment where high morale springs from the inherent intellectual rewards of research, people work effectively together, and science thrives."

I WROTE THESE WORDS 22 YEARS AGO. Little did I imagine that this vision for the NIH would still not be realized today, that all scientists, including women and other underrepresented groups, would still not be equal and integral in our intramural community, and that mutual respect would not be a universal principle guiding all of our human interactions. Although some progress has been made, the time has come to re-energize our efforts and move to complete the task.

On October 22, 2018, NIH Director **Francis Collins** announced a comprehensive plan to develop a culture at NIH that respects all individuals and reduces discriminatory harassment, especially sexual harassment. This plan has several components. See the new "Anti-sexual Harassment" website (https://www.nih.gov/anti-sexual-harassment); the NIH Policy Manual, Chapter 1311 on sexual harassment (https://policymanual.nih.gov/1311); a policy statement on personal relationships in the workplace (https://hr.nih.gov/working-nih/civil/nih-policy-statement-personal-relationships-workplace); a new centralized process to report, evaluate and address allegations of harassment, including sexual harassment, through the NIH Office of Human Resources Civil Program (https://hr.nih.gov/working-nih/civil) which has launched a new web form and hotline number to make reporting an allegation easier.

Disciplinary action, if needed, will be the responsibility of the home institute or center (IC) of the perpetrator found responsible for harassment, but will be monitored centrally.

A main focus of the relationship policy is what to do in matters concerning close personal relationships between people in inherently unequal positions at the NIH in which one may have real or perceived influence over the welfare and/or career of another. Such relationships, should they develop, need to be reported to the designated IC official and managed so as to avoid any appearance of coercion, favoritism, or distress to all individuals involved, including others who share the same workplace.

The Civil Program has a new web form and toll-free hotline (833-224-3829), each of which can accept both anonymous and identifiable complaints or concerns. However, remaining anonymous may limit the NIH's ability to conduct a thorough inquiry and take corrective action, if warranted. In early 2019, NIH will launch a carefully constructed survey on workplace climate and harassment to gain insight into workplace climate, and incidents and prevalence of harassment, including sexual and gender harassment, at NIH. The Office of Equity, Diversity, and Inclusion will provide annual training to assure that current staff are aware of expectations and that new staff are informed shortly after their arrival.

NIHers have also been asked to watch a new video (through the HHS Learning Portal at https://ams.hhs.gov/amsLogin/SimpleLogin.jsp), which outlines the NIH policies, tells how to report allegations of harassment, and provides information on other resources.

There are, of course, many questions that you may be asking about these new policies. It is important to note that many NIHers, including anyone with supervisory responsibilities, are required to report to the Civil Program allegations of harassment that are shared with them. If someone has a concern that they want to discuss confidentially and not report, they can consult the NIH Ombudsman Office (https://ombudsman.nih.gov) or the Employee Assistance Program (https://www.ors.od.nih.gov/sr/dohs/HealthAndWellness/EAP/Pages/index.aspx), both of which are not required to report instances of harassment if the target does not wish to do so.

Trainees should continue to seek help from the Office of Intramural Training and Education (https://www.training.nih.gov).

If a mandatory reporter (a supervisor or manager who receives information of an allegation that sexual harassment may have occurred) is unsure about whether an event requires reporting, the Civil Program stands ready to advise. The evidence is strong that once targets of

harassment feel comfortable reporting their experiences and this information is acted upon appropriately, the unacceptable behavior becomes less common.

Underlying all instances of discriminatory harassment is a basic disrespect for the value and personhood of the target of the harassment. And the basis of such behavior is a lack of civility. Enhancing civil behavior must be the primary goal of any culture change at the NIH. Many other benefits will follow including fairness in hiring and advancing all staff at the NIH, parity for women at all levels and positions at NIH, and an open and inclusive environment in which all scientists who come from underrepresented groups have an equal chance to participate and lead.

Studies have also shown that civil environments tend to be more productive than uncivil environments.

If we can achieve these goals, NIH's mission (to "seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability") will be closer to being realized. ●

Source for opening quote: A talk entitled "Encouraging Integrity and Civility in Science at the National Institutes of Health," delivered by Michael Gottesman on November 13, 1996, at the annual meeting on Public Responsibility in Medicine and Research).

For access to all the websites referenced in this essay, go to the Civil Program at https://hr.nih.gov/working-nih/civil/.

New Name: NIH Artificial Intelligence Interest Group

If you are interested in artificial intelligence research, consider joining the Artificial Intelligence Interest Group (AIIG). The group, which was established in 2003 as the "Artificial Intelligence Robotic Pharmaceutical Screening Interest Group," has a sharper focus than before. The AIIG's purpose is to foster communication among scientists with diverse backgrounds whether they are from NIH, FDA, universities, or industry. The members share a common interest in the development of artificial intelligence for the improvement of medical treatments. The group meets every month to discuss a variety of topics including, but not limited to, artificial intelligence, neural networks, algorithms, simulation, fuzzy logic, molecular and biological pattern recognition, biomarkers, digital biomarkers, biosensors, robotic platform technologies, remote diagnosis, autotherapy, and treatment techniques and patient outcomes. For more information about the SIG and instructions for how to join the LISTSERV email list, go to https://oir.nih.gov/sigs/artificial-intelligence-interest-group.

You can also contact the chair **June Lee**, at LeeJun@mail.nih.gov.

New Name: Protein Trafficking and Organelle Dynamics Interest Group

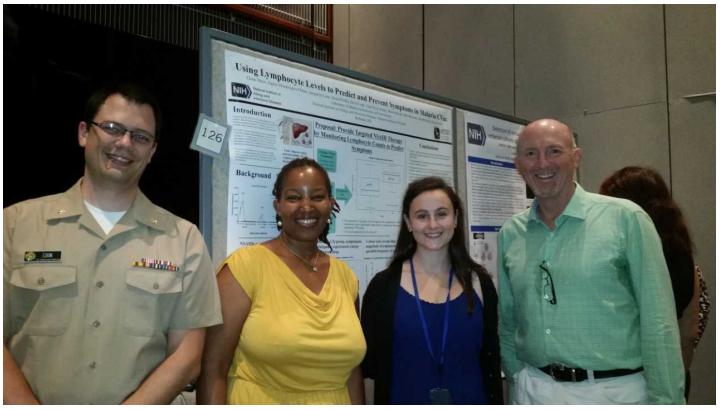
Another SIG has also revised its name to reflect how the interests of its members have changed. The "Protein Trafficking and Organelle Dynamics Interest Group" used to be known as simply the "Protein Trafficking Interest Group." But that was before more PIs on campus began working on organelle-related biology. The goal of the Protein Trafficking and Organelle Dynamics Interest Group is to promote interaction among institutes and laboratories that are studying protein trafficking and organelle dynamics. Current areas of research interest include protein biogenesis and quality control, protein translocation across membranes, protein transport between organelles, membrane and lipid dynamics, endocytosis and exocytosis, organelle biogenesis and turnover, membrane-contact sites, autophagy, pathogen-membrane interaction, cytoskeleton dynamics, and membrane fusion. The interest group organizes monthly meetings (September–May) that feature presentations by senior fellows or PIs on well-developed research projects on campus. Also, the group frequently invites well-established scientists in related fields to discuss their new exciting findings. For more information about the SIG and instructions for how to join the LISTSERV, go to https://oir.nih.gov/sigs/protein-trafficking-organelle-dynamics-interest-group. Or you can contact one of the committee chairs: **Yihong Ye** (yihongy@mail.nih.gov), **Matthias Machner**, (machnerm@mail.nih.gov), or **Nihal Altan-Bonnet** (nihal.altan-bonnet@nih.gov). ●

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

From the Fellows Committee

My Summer of Learning...and...Surprises...at the NIH

BY ELANA SHAW, EMORY UNIVERSITY



Summer intern Elana Shaw (third from left) took part in the 2018 Summer Poster Day, held on August 9. Members of her lab stopped by to show their support. Pictured, from left: David Cook, Agnes Mwakingwe-Omari (PI), Elana, and Patrick Duffy.

"Elana, you are here first and foremost to learn," National Institute of Allergy and Infectious Diseases staff clinician **Agnes Mwakingwe-Omari** told me on the first day of my summer internship with the Laboratory of Malaria Immunology and Vaccinology (LMIV).

And so, during my first few weeks, I read paper after paper after paper until I wasn't just familiar with our malaria vaccine protocol but I was well informed about other malaria vaccine experiments worldwide. I learned how and why some attempts had failed and others showed promise. Then, my PI and the clinicians in the lab explained the immunological basis for our malaria chemoprophylaxis vaccine, CVac.

The CVac regimen calls for three monthly intravenous injections containing live malaria parasites. During those three months, participants are given antimalarial drugs to control which parasitic life-stages they are exposed to. Ideally, the CVac regimen would both provide protective immunity against future malaria infections and give scientists a glimpse into how the immune system reacts to different stages of the parasite's life-cycle.

I quickly learned, however, that promising scientific logic is meaningless without a massive amount of manpower, organization, and teamwork to bring it to fruition. To start, it was extremely difficult to recruit patients for the phase 1 trial. As part of the recruitment team, I called hundreds of numbers provided by the Office of Patient Recruitment, hung posters at the NIH and local colleges, manned tables at farmers' markets, and even plastered fliers in bathroom stalls. All of this to, hopefully, recruit 10 individuals.

Recruiting for the study taught me how to effectively explain the LMIV's complicated CVac protocol to people from a wide variety of backgrounds. The search for patients forced me to become comfortable talking to people about their medical histories.

Recruitment also helped me to fully understand the impact of the LMIV's malaria vaccine research by putting faces to the disease. Through conversations with potential volunteers, I was astonished to find that, in Bethesda, I am surrounded by people who have been personally affected by malaria. These individuals told me their stories and conveyed passions for finding a malaria vaccine equal to or surpassing those being developed by the LMIV scientists.

Unfortunately, one of the exclusion criteria for our study was having had a diagnosis of malaria within the past 10 years. Consequently, many of our most ardent potential volunteers were unable to participate in the trial. However, they all expressed gratitude for and excitement about the LMIV's malaria vaccine research and offered to help in any way they could. One young man, who had suffered from malaria as a child when he was living in Africa, even offered to help advertise for our trials in the future.

During my time as an intern for the LMIV, I learned more than I ever could have imagined about humanity, medicine, and clinical research. I even got to conduct my own research on an oddly foreboding drop in blood lymphocyte concentrations that tends to occur before people experience malaria symptoms.

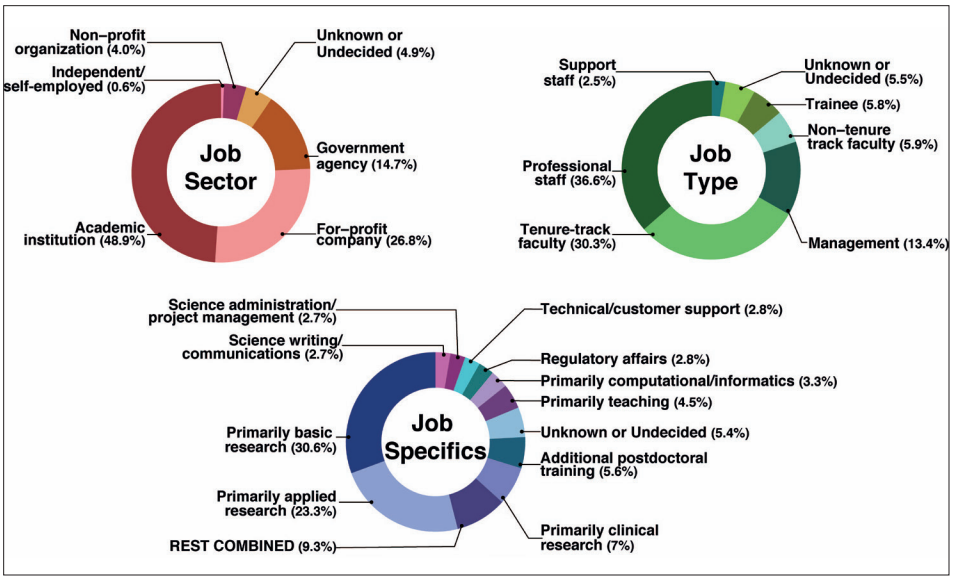
However, the coolest part of having been an intern for the LMIV is yet to occur. I expect that one day, when I am reading the newspaper, I will come across an article celebrating a malaria vaccine that has over 90 percent efficacy. The LMIV will have made it and I will be incredibly proud of all the study recruitment posters I valiantly placed in bathroom stalls and of my small role in the gargantuan battle against malaria. ●

Elana Shaw is a junior, majoring in chemistry, at Emory University (Atlanta, Georgia). During the summer of 2018, she worked as an intern in NIAID and helped to recruit for the clinical trial called "Sanaria PfSPZ Challenge with Pyrimethamine Chemoprophylaxis (PfSPZ-CVac Approach): Phase 1 Dose Escalation Trial to Determine Safety and Development of Protective Efficacy after Exposure to only Pre-erythrocytic Stages of *Plasmodium falciparum*."

Making Informed Career Decisions

New Tool Helps NIH Postdocs Visualize Employment Trends

BY ROBIN ARNETTE, NIEHS



NATURE BIOTECHNOLOGY

The NIEHS study categorized career outcomes for NIEHS postdocs by sector, type, and job specifics. The authors envision that this approach will help young scientists make career decisions based on data and not anecdotal evidence.

Scientists looking for jobs after completing their training may soon have a new tool that helps them evaluate various career paths. Developed by a team led by **Tammy Collins** (National Institute of Environmental Health Sciences), the tool uses a method that differs from others in that it creates a standard career-outcome taxonomy that classifies careers in the biomedical sciences by sector, type, and job specifics. Until now, the lack of standardized measures has made it difficult for postdocs to make informed decisions about their career prospects. The creators hope this novel approach will be useful throughout NIH as well as for academic and research institutions around the world.

Team members collected detailed career outcomes—by searching through PubMed, social media, alumni websites, Google, Board of Scientific Counselors reviews, and more—for some 900 NIEHS postdoctoral fellows over the past 15 years. Lead author and NIEHS computer scientist **Hong Xu** analyzed the data using the R Project for Statistical Computing, a free online program that displays data using graphs and charts. The study appeared earlier this year in the journal *Nature Biotechnology* and is the first standardized method for categorizing career outcomes of NIEHS postdocs (*Nat Biotechnol* **36:**197–202, 2018; DOI:10.1038/nbt.4059).

"As we sought to determine how to make sense of detailed career outcomes in a standardized way, we used a bottom-up approach, rather than forcing the data into any particular naming system already being employed," said Collins, who is the director of the NIEHS Office of Fellows' Career Development. "We looked at what our postdocs were specifically doing, and asked what is the most logical way to categorize and visualize the information."

The careers project began in 2013 as a way to establish a snapshot of career trajectories for NIEHS postdocs and to report the findings to NIH. The researchers found distinct differences between domestic and international NIEHS postdocs in the kinds of jobs they landed. About half of the postdocs were from the United States and half were from other countries. U.S. postdocs were more likely than their international counterparts to enter for-profit companies to do applied research.

In contrast, international postdocs were almost twice as likely as their U.S. peers to enter academic tenure-track positions and do basic research. Notably, 70 percent of those academic positions were outside the United States. Overall, nearly half of all NIEHS postdocs went into the academic sector, which was surprising to some, because many young scientists thought that doing a government postdoctoral fellowship might hinder their chances of getting a tenure-track position in academia.

"We hope that the taxonomy, definitions, and visualization methods presented will eliminate a key hurdle in career outcome reporting and analysis—inspiring others to use our methodology so that more finely tuned, meaningful, institution-level information will be available for cross-comparisons within the global scientific research community," the authors wrote in their paper. "Having this institution-level information will allow prospective and current doctoral candidates to evaluate their career prospects based on real data, rather than anecdotes. Likewise, this information will allow institutions to critically evaluate the effectiveness of their programs, so that data-driven decisions can be made to provide programming that supports student transitions into the modern career environment." ●

For more information, go to https://www.niehs.nih.gov/careers/research/fellows/alumni-outcomes/index.cfm or contact Tammy Collins (984-287-3651 or tammy.collins@nih.gov).

FACS II Oral History

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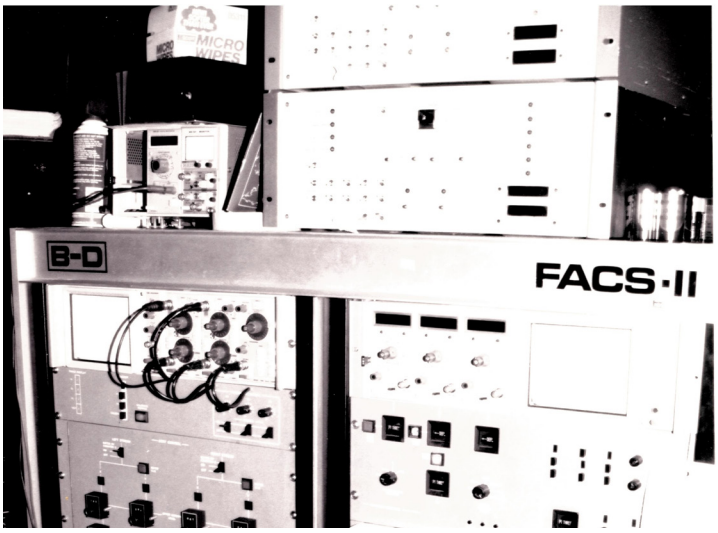


OFFICE OF NIH HISTORY

The laser-based FACS II, which arrived at NIH in 1976 and was retired to the NIH Stetten Museum in 1992, was the first flow cytometer to analyze the cell cycle in yeast, study and sort cells from a mouse brain, and analyze fluorescent liposomes and their interactions with cells. Among the other cells the FACS II sorted and analyzed were T cells, B cells, dendritic cells, stem cells, and cancer cells from bone marrow, spleen, thymus, blood, skin, brain, and other organs.

fluoresce brightly, and inkjet-printer technology, which provides my droplet-sorting ability. I can sort cells according to fluorescent tags attached to their surfaces. In 1969, **Leonard Herzenberg** at Stanford University in Stanford, California, created the first instrument that used fluorescence labeling to rapidly separate, count, and identify single live cells from a mixture of cells. (By the way, Len worked at NIH in the 1950s before he took the position at Stanford.) His machine could sort up to 1,000 cells per second. This technology, also known as flow cytometry, was an extension of single-cell analysis based on physical characteristics that had been applied in hematology and cytopathology in the 1930s. I'm sure you remember the Coulter counter (evaluated at NIH in the 1950s), which was an early instrument used to identify and count the various cells in the blood of your patients.

G.M.: Yes, I do remember that. How did you get to NCI's EIB?

FACS II: Early in the 1970s, some members of NCI's intramural research program decided that my special abilities could be useful in cancer and immunological studies. Ultimately, Becton-Dickinson created me—a two-laser FACS—and delivered me to NCI in 1976 to replace a 1973 FACS I machine that was based on the Herzenberg prototype. Boy, did I ever get busy. At that time, NIH had the only immunology laboratory—outside of Stanford University—that operated a laser-based flow cytometry cell sorter. I was made available to investigators from throughout the NIH and elsewhere on the entire East Coast. Of course, using me required lots of new studies, particularly ones that sought to learn about the surface molecules of different cells. Being able to identify appropriate fluorescent tags allowed me to separate selected cells from the mixtures. The EIB group, especially Susan Sharrow, undertook these developments and guided and controlled my accomplishments.

G.M.: You went through some changes over the years. Tell me about them.

FACS II: Oh gosh! Many of the improvements made to me were technical. I was the first two-laser FACS that Becton-Dickinson made. I could measure three to four colors of fluorescence. Later I was modified to include a third laser that allowed me to measure six colors. Modern FACS machines have six or more lasers and can measure at least 30 colors.

G.M.: How was your data displayed?

FACS II: When I was delivered to NIH in 1976, my data output was displayed on an oscilloscope and captured on Polaroid instant film so it could be analyzed. NIH computer engineers later designed and built a computer interface for me so that my data could be collected and stored in a digital format. Computer programmers wrote software to analyze the data. Stanford scientists were designing interfaces around the same time, but the manufacturers didn't provide computers with flow cytometers until the mid-1980s. Also, NCI scientists invented the Texas Red fluorescent dye to use with my second laser.

G.M.: Can you tell me in what areas you were particularly productive, and cite some examples that proved important?

FACS II: Because my technology was so new, almost every experiment I did revealed something to the scientists who used me. Our group published the first report that immune-cell subpopulations and maturity could be identified by the intensity of the fluorescent-labeled antibodies used to tag cells before FACS sorting. I was the first flow cytometer to analyze the cell cycle in yeast, study and sort cells from a mouse brain, and analyze fluorescent liposomes and their interactions with cells.

My work resulted in over 135 peer-reviewed publications. Studies included cell separation and/or analyses of mouse, rat, monkey, and human cells from individuals that were normal, had cancer, suffered from immune-related diseases, or were undergoing therapy. I sorted and/or analyzed T cells; B cells; dendritic cells; Langerhans cells; many other immune cells subsets and stem cells; and glial cells and cancer cells from bone marrow, spleen, thymus, blood, skin, brain, and other organs. I get tired just thinking about all that work!

G.M.: Goodness! How much could you do in a day?
FACS II: I could sort about 2,000 cells per second, which translates to more than 500 million individual cells in eight hours. (My work day was usually more than eight hours, though.)

G.M.: How big was a sample?
FACS II: One sample could be anywhere from 10,000 cells to hundreds of millions of cells. At the time when my data output had to be captured by Polaroid instant photographs, I could analyze only about a dozen samples. Once I could send the data to a computer, however, I could analyze 100 samples in a day. Modern machines can sort 10,000 cells per second and can analyze more than a thousand samples a day.

G.M.: So why were you retired?
FACS II: Good question. I was very durable, averaging only one day down annually. But it was difficult to modify me and add new features. The EIB scientists wanted the increased speed and capabilities provided by digital technology. I guess "aging issues" and development of new technology catch up with all of us machines, but I am proud that I was able to contribute for 16 years.

G.M.: Other than your opportunity to advance scientific knowledge, what other contribution to NIH have you made?
FACS II: **John Wunderlich**, the NCI principal investigator who supervised the FACS laboratory in EIB, decided that this unexplored technology would best be developed by allowing all NIH investigators and outside scientists free and open access to the FACS. In 1976, this policy was quite a radical idea. The EIB FACS laboratory might have been one of the first core facilities at NIH. Susan Sharrow worked with interested investigators to operate me and guide my accomplishments. Some of the same investigators who used me early on eventually established new FACS laboratories in the NCI and in the National Institute of Allergy and Infectious Diseases as well as in more than 50 institutions around the world. The simple idea of open access not only promoted more rapid development of the technology, but it also allowed many scientists to work more closely together and to cross the artificial boundaries of separate labs, branches, laboratories, and institutes.

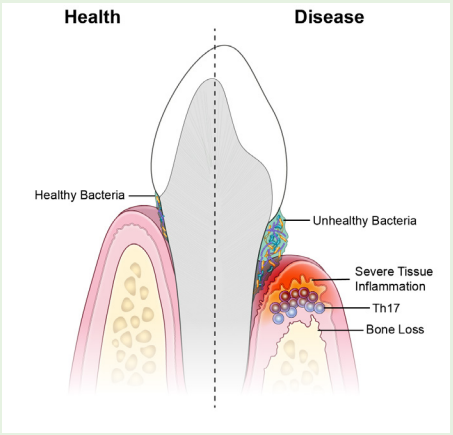
G.M.: Is there anything else you'd like to say?
FACS II: I am confined here in storage with hundreds of other devices that contributed in earlier years to major scientific advances at NIH. Maybe someday I and the others could be displayed. This would remind our scientists not to discard their retiring instruments. They should be donated to the NIH Stetten Museum so they can be kept for future use for similar "histories" or exhibits here on the campus. I feel honored that my value has been properly recognized and recorded. I thank you for this opportunity to respond to your queries and to reminisce about my contributions to NIH and to science at large. ●

Many thanks to Stetten Museum Curator **Michele Lyons** and to NCI Staff Scientist and EIB Flow Cytometry Facility Manager **Susan Sharrow** for their help with this article. Lyons provided provenance information regarding FACS II. Sharrow, whose continuous involvement in flow cytometry spans almost 45 years, was kind enough to confirm and expand the FACS-II story.

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
NCCIH: National Center for Complementary and Integrative Health
NCI: National Cancer Institute
NEI: National Eye Institute
NHGRI: National Human Genome Research Institute
NHLBI: National Heart, Lung, and Blood Institute
NIA: National Institute on Aging
NIAAA: National Institute on Alcohol Abuse and Alcoholism
NIAID: National Institute of Allergy and Infectious Diseases
NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIBIB: National Institute of Biomedical Imaging and Bioengineering
NICHD: Eunice Kennedy Shriver National Institute of Child Health and Human Development
NIDA: National Institute on Drug Abuse
NIDCD: National Institute on Deafness and Other Communication Disorders
NIDCR: National Institute of Dental and Craniofacial Research
NIDDK: National Institute of Diabetes and Digestive and Kidney Diseases
NIEHS: National Institute of Environmental Health Sciences
NIGMS: National Institute of General Medical Sciences
NIMH: National Institute of Mental Health
NIMHD: National Institute on Minority Health and Health Disparities
NINDS: National Institute of Neurological Disorders and Stroke
NINR: National Institute of Nursing Research
NLM: National Library of Medicine
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



NIDCR

NIDCR: A new study suggests that periodontal disease is driven by Th17 immune cells, which are triggered by an unhealthy bacterial community.

NIDCR, NIAID, NIDCD, NCI: IMMUNE CULPRITS LINKED TO INFLAMMATION AND BONE LOSS IN GUM DISEASE

An unhealthy population of microbes in the mouth triggers specialized immune cells that inflame and destroy tissues, leading to periodontal disease, according to a study led by researchers from NIDCR and the University of Pennsylvania School of Dental Medicine (Philadelphia). The researchers observed that T helper–17 (Th17) cells were much more prevalent in the gum tissue of people with periodontitis than in the gums of their healthy counterparts, and that the amount of Th17 cells correlated with disease severity.

Th17 cells generally live in barrier sites—such as the mouth, skin, and digestive tract—and are known to protect against certain infections. But they are also linked to inflammatory diseases such as psoriasis and colitis. The scientists found that, in mice with periodontitis, eliminating oral microbes prevented the expansion of Th17 cells in the gums while leaving other immune cells unaffected.

The researchers also studied a group of 35 patients, at the NIH Clinical Center, with a gene defect causing them to lack Th17 cells. The patients were less susceptible to gum disease and had less inflammation and bone loss compared with age- and gender-matched volunteers. The findings could have implications for new treatment approaches for gum disease and periodontitis. (NIH authors: N. Dutzan, L. Abusleme, T. Greenwell-Wild, C.E. Zuazo, T. Ikeuchi, L. Brenchley, C. Hurabielle, D. Martin, R.J. Morell, A.F. Freeman, V. Lazarevic, G. Trinchieri, S.M. Holland, Y. Belkaid, and N.M. Moutsopoulos, *Sci Trans Med* **10**:eaat0797, 2018; DOI:10.1126/scitranslmed.aat0797)

[BY CATHERINE EVANS, NIDCR]

NIEHS: GENETICS AND POLLUTION DRIVE SEVERITY OF ASTHMA SYMPTOMS

Some asthma sufferers have more severe reactions than others to air pollution caused by traffic. NIEHS researchers and others may have figured out why: It has to do with different genetic profiles. The scientists examined four particular single-nucleotide polymorphisms (SNPs) involved in a biochemical pathway that leads to inflammatory responses. They gathered information about the SNPs, severity of asthma symptoms, and residential addresses of 2,704 participants with asthma.

The researchers found that asthma sufferers who were hyper-responders and lived closer to heavily traveled roads had the worst asthma symptoms, such as difficulty breathing, chest pain, cough, and wheezing, compared with the other groups. (NIH authors: S.H. Schurman, M.A. Bravo, C.L. Innes, W.B. Jackson 2nd, J.A. McGrath, M.L. Miranda, and S. Garantziotis, *Sci Rep* **8**:Article number 12713, 2018; DOI:10.1038/s41598-018-30865-0)

NIAID: PROBIOTIC BACILLUS ELIMINATES STAPHYLOCOCCUS BACTERIA

A new method of battling antibiotic-resistant superbugs is on the horizon. Researchers at the NIAID and two universities in Thailand revealed how oral Bacillus, a bacterium found in probiotic digestive supplements, can be used to fight superbugs such as methicillin-resistant *Staphylococcus aureus* (MRSA). When undisturbed, *S. aureus* lives benignly in the gut and nose of 30 percent of the general population. It only causes serious illness when the immune system is compromised or the bacteria break into the bloodstream through a wound.

The typical treatment entails the administration of antibiotics, which are not always effective and may even result in the *S. aureus* becoming resistant to them. NIH researchers and their colleagues found that in 200 volunteers from rural Thailand (who were not expected to be as affected by food sterilization or antibiotics as people in urban areas), no *S. aureus* were found in gut and nose samples when Bacillus were present.

Then using chromatography and mass spectrometry techniques, the researchers discovered a class of lipopeptides called fengycins that inhibit *S. aureus* growth. The next step is to test probiotics containing *Bacillus subtilis* to see whether they can eliminate *S. aureus* in people. (NIH authors: P. Piewngam, Y.Zheng, T.H. Nguyen, S.W. Dickey, H.-S. Joo, A.E. Villaruz, K.A. Glose, E.L. Fisher, R.L. Hunt, B. Li, J. Chiou, G.Y.C. Cheung, and M.L. Otto, *Nature* 2018; DOI:10.1038/s41586-018-0616-y)

[BY AUTUMN HULLINGS, NCI]

NCCIH, NINDS: BROADER UNDERSTANDING OF HIGH-IMPACT CHRONIC PAIN

NIH researchers with colleagues at Kaiser Permanente Washington Health Research Institute (Seattle) have come up with a new classification for a type of chronic pain that leaves its sufferers so disabled that they can't work and/or have trouble with routine self-care activities.

Of the 40 million people in the United States who have chronic pain, almost a quarter have high-impact chronic pain (HICP)—pain lasting three or more months in conjunction with at least one major activity restriction. Using data from the 2011 National Health Interview Survey (15,670 adults), the researchers assessed the prevalence, characteristics, health status, and health-

care usage of the chronic-pain population. By differentiating the different types of chronic pain, the researchers hope to refine clinical treatments and identify interventions that can shape policy and improve the health of those with HICP. (NIH authors: M.H. Pitcher, M. Von Korff, M.C. Bushnell, and L. Porter, *J Pain* 2018; DOI:10.1016/j.jpain.2018.07.006)

[BY AUTUMN HULLINGS, NCI]

NIAID: NOVEL VACCINE FOR LASSA FEVER AND RABIES

Scientists at NIAID and three universities have designed and tested a dual vaccine to protect people from both rabies and Lassa Fever (LF), which is highly fatal and for which no vaccine exists. LF can have varying symptoms in humans, ranging from mild illness to hemorrhage, and is widespread in West African countries such as Nigeria. Africa is also at high risk for rabies in humans. The investigational vaccine, called LASSARAB, showed promise in preclinical testing in mice and guinea pigs. The researchers plan to evaluate the vaccine in nonhuman primates before conducting clinical trials. (NIH authors: K.R. Hagen, K. Cooper, P.B. Jahrling, and R.F. Johnson, *Nature Commun* **9**:4223, 2018; DOI: 10.1038/s41467-018-06741-w)

[BY EIMEAR HOLTON, NIAID]

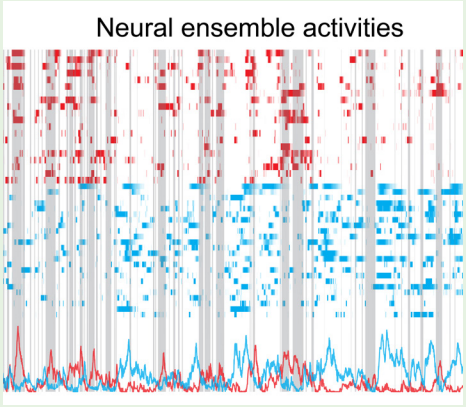
NICHD, NIMH: NEURONS ABSORB AND RELEASE WATER WHEN FIRING

Conventional functional magnetic resonance imaging (fMRI) technologies track neuronal activity indirectly by recording changes in blood flow and blood oxygen concentration as a proxy for metabolic activity. But researchers from NICHD and NIMH, and outside collaborators may have found a better way to measure brain activity: tracking active water cycling (AWC), which, they found, is characteristic of neuronal firing. The scientists made the discovery by simultaneously tracking neuronal activity and transmembrane water cycling in cultures of rat neurons. When neurons communicate, potassium and sodium ions move through the cell membrane. When the rat neurons were stimulated to fire, fMRI imaging revealed that the ion exchanges were accompanied by an increase in the number of water molecules moving into and out of the cell. This novel characteristic could lead to the development of an improved method of monitoring the brain's circuitry by tracking AWC using fMRI. This method could also lead to a better understanding of the brain's electrochemical activity and function, and ultimately of neural disease. (NIH authors: D. Plenz and P.J. Basser, *Magnetic Resonance in Medicine*, 2018; DOI:10.1002/mrm.27473)

[BY EIMEAR HOLTON, NIAID]

NICHD, NCI, NIDDK, CC, NHLBI: REDUCING METABOLIC RISK IN CHILDREN

Sedentary children are at greater risk of developing abnormalities in glucose homeostasis—and at risk for developing diabetes—especially if they are overweight or obese. NICHD researchers found that brief interruptions in sedentary behavior—such as short bouts of walking—improved glucose metabolism in 35 children ages 7–11 years who were overweight or obese. "If this intervention provides sustained improvement in glucose metabolism . . . widespread implementation into school or after-school care centers could provide notable improvement in glucose homeostasis in the community setting and potentially slow the onset of type 2 diabetes in youth," the authors wrote in their paper. (NIH authors: M.M. Broadney, B.R. Belcher, D.A. Berrigan, R.J. Brychta, I.L. Tigner Jr., F. Shareef, A. Papachristopoulou, J.D. Hattenbach, E.K. Davis, S.M. Brady, S.B. Bernstein, A.B. Courville, B.E. Drinkard, K.P. Smith, D.R. Rosing, P.L. Wolters, K.Y. Chen, and J.A. Yanovski, *Diabetes Care* **41**:2220–2228, 2018; DOI:10.2337/dc18-0774)



NIDA: The above plots show the ON (red) and OFF (blue) neural-ensemble activities recorded by a head-mounted miniature microscope when a mouse freely interacted socially with another mouse. Gray bars represent the period when the mouse explored his environment including possible social interactions.

NIDA: BRAIN ENSEMBLES THAT TUNE ON OR OFF TO SOCIAL EXPLORATION

The brain's medial prefrontal cortex (mPFC) is important for social behavior, but the mechanisms by which mPFC neurons code real-time social exploration remain largely unknown. An international team led by NIDA scientists used miniature fluorescence microscopes to record calcium activities from hundreds of excitatory neurons in the mPFC in the brains of mice as they interacted socially with other mice. The animals were given a series of social-behavior tests in the absence or presence of the psychedelic drug phencyclidine (PCP), which alters social behaviors. The scientists found that ensembles, which are distinct and dynamic neural groups, are tuned on or off to social exploration, and dysfunctions in these ensembles are associated with abnormal social exploration elicited by PCP.

These findings underscore the importance of mPFC "on" and "off" neural ensembles for proper social-exploratory behavior and pave the way for future studies related to neural-circuit dysfunctions in psychiatric disorders. (NIH authors: B. Liang, L. Zhang, G. Barbera, W. Fang, J. Zhang, Y. Li, and T. Lin, *Neuron* 2018; DOI:10.1016/j.neuron.2018.08.043)

[FROM NIDA SCIENCE HIGHLIGHTS, 10/9/18, HTTPS://WWW.DRUGABUSE.GOV/NEWS-EVENTS LATEST-SCIENCE]

2018 Research Festival: Plenary Sessions

Plenary I: The Institute Directors

BY VALERIE VIRTA, NLM

Diana Bianchi (NICHD): "The Most Important Nine Months of Your Life"

"What happens during the time you are in the womb influences your lifelong health," said Bianchi. The NICHD Human Placenta Project aims to understand the role of the placenta—in the mother and baby—in health and disease both before and after birth. "Pregnancy is a stress test for risk of later diseases such as myocardial infarctions, stroke, diabetes, [and, later,] vascular dementia in the mother," said Bianchi.

There are fetal origins for cardiovascular disease, hypertension, cancer, obesity, allergies, and even mental illness, that stem from problems with the placenta. Birth weight outside normal ranges is a huge risk factor for all these conditions. NICHD-supported research includes extramural work using microvascular imaging to visualize fetal and maternal circulation to noninvasively assess placental health; an intramural-extramural collaboration to develop a wireless device that continuously monitors oxygenation of the placenta; intramural research on genomics, placenta-omics, and ways to reduce invasive fetal tests. Bianchi also described her prenatal genomics research in her lab at the National Human Genome Research Institute.

Joshua Gordon (NIMH) : "Mental Health Research: Priorities and Progress"

"Death by suicide…has been increasing continually for the past almost 20 years…particularly in children and adolescents," said Gordon, who highlighted suicide prevention, mapping neural circuits, and computational psychiatry as three priority research areas for NIMH. Extramural investigators showed that if all people who come to the emergency room were asked if they were thinking about suicide, "you identify about twice as many people who are at risk for suicide [than] if you only asked the people that you have some clinical suspicion about." NIMH intramural researchers have developed a suicide-screening tool called the Ask Suicide-screening Questions (ASQ) that works in children.

NIMH researchers are also using optogenetics and other neurocircuitry technologies to map neural circuits in anxiety disorders in mice; and computational methods to build accurate models of how neurocircuits work to understand and predict psychiatric problems. His own research (his lab is in the National Institute of Neurological Disorders and Stroke) focuses on neural activity and genetics in mouse models of psychiatric diseases.

MARLEEN VAN DEN NEST

Four institute directors were featured in the Research Festival's opening plenary session. Clockwise from top left: Diana Bianchi (NICHD), Joshua Gordon (NIMH), Anthony Fauci (NIAID), and Patricia Flatley Brennan (NLM).

Patricia Flatley Brennan (NLM): "Advancing Health through Accelerating Information Access"

"The National Library of Medicine is almost 180 years old and we've been able to touch almost every single discovery of health information in the past 20 years," said Brennan. She went on to describe four research programs that focus on bioinformatics resources: computational approaches to basic biology; computational approaches to improve public health; tools for better research; and discovery from health data. Among the many projects she mentioned was using computational approaches to identify new proteins resulting from CRISPER-Cas editing, predict causes of mutations in cancer-driving genes, and quickly identify emerging foodborne pathogens; using data assimilation to help individuals forecast glucose levels after meals; developing better tools to interpret and synthesize research findings in the mass collections of journal articles; and using machine learning to detect social-media posts indicating prescription-medication abuse. Brennan, who is a registered nurse with a Ph.D. in industrial engineering, has a lab in the National Institute of Nursing Research where she uses virtual reality to predict how well patients will manage after being discharged from the hospital.

Anthony Fauci (NIAID): "Ending the HIV Epidemic"

Fauci, who has been studying HIV and AIDS since the disease emerged in the early 1980s, discussed advances in treatment and prevention of the AIDS pandemic. In 1996, with the advent of protease inhibitors, anti-retroviral therapy (ART) could be used to treat people with AIDS and keep the virus below detectable levels in the blood indefinitely. "Individuals who were clearly

on their way to dying were getting out of bed, going back to work, going back to their normal life," said Fauci. Today, there are even better drugs. There are now 21 million people on ART and 10 million deaths were averted from 2000 to 2016.

Prevention strategies have been "highly effective alone or in combination," said Fauci. For example, research has shown that the one-pill-a-day pre-exposure prophylaxis (PrEP) regime is more than 95 percent effective in preventing the acquistion of HIV infection. Even better would be a long-term injectable dose of PrEP or, better still, an HIV vaccine. NIAID's Vaccine Research Center is working hard on developing such a vaccine. "I am really quite confident that within our lifetime…we will actually see the end of the HIV/AIDS pandemic."

To watch a videocast of the "Plenary I: The IC Directors" session, which took place on Wednesday, September 12, 2018, go to https://videocast.nih.gov/launch.asp?25039.

Plenary II: Unity Is Strength: A Journey into Disease Discovery and Treatment

BY JOANNA CROSS, NIMH

"Primary defects of immune function" and a "new lysosomal-storage disease" may sound like a strange combination of topics for a plenary session. But they do have something in common: Research advances in both areas have depended on successful collaborations that cross institute boundaries and are between basic scientists and clinicians. **Jennifer Kanakry** (NCI-CCR) and **Luigi Notarangelo** (NIAID) teamed up to talk about their collaboration on primary immunodeficiency diseases (PIDs); **William Gahl** (NHGRI) and **Joseph Mindell** (NINDS) told their story of how they identified and treated a new lysosomal-storage disease.

Although PID can be treated with allogeneic bone-marrow transplants (in which a person receives hematopoietic stem cells from a donor), there are many complications. To reduce the likelihood of transplantation rejection, a process known as conditioning (consisting of chemotherapy and/or radiation) can be implemented ahead of time. But it can have severe short- and long-term side effects including organ damage.

In collaboration with NIAID investigators, Kanakry led a clinical trial at NIH to test a conditioning strategy that contained no radiation and lower amounts of chemotherapy. There were low rates of transplant rejection and acute graft-versus-host disease, and no chronic graft-versus-host disease.

But the disease mechanisms need to be better understood. Notarangelo focuses on PIDs caused by mutations of recombination activating gene 1 (*RAG1*) and *RAG2*. His group discovered that normal function of the RAG proteins is critical to enable cross-talk between developing T cells and thymic epithelial cells. Through this cross-talk, self-reactive T cells are either eliminated in the thymus or are converted to T regulator (Treg) cells, whose function is to prevent autoimmunity. In patients with partial defects of RAG protein function, the generation and diversity of Treg cells are compromised, leading to autoimmune manifestations. By correcting the *RAG* gene defect in patient-derived induced pluripotent stem cells, Notarangelo's team has been able to restore the capacity to generate T cells in a test tube. This corrective ability may have possible implications for the development of gene therapy for PID.

The second collaboration highlighted was between the Undiagnosed Diseases Program (UDP) and researchers in NINDS. The result was the diagnosis of a new lysosomal storage disease. Gahl, who

CONTINUED ON PAGE 12

MARLEEN VAN DEN NEST

Scientific directors Tom Misteli (NCI's Center for Cancer Research) and Steven Holland (NIAID) co-chaired the festival this year. They along with other scientific directors, took part in one of the poster sessions. Shown: Misteli discussing his poster with festival attendees.

2018 Research Festival

CONTINUED FROM PAGE 11

is the director of the UDP, described two recent cases, beginning with an 18-month-old girl who suffered from failure to thrive, intestinal problems, and an unusual form of albinism (her skin and hair were affected, but not her eyes). She also displayed a phenotype indicative of a lysosomal storage disorder. The UDP subsequently learned of a second patient—a 14-month-old boy from Ghana—who had similar symptoms in addition to enlarged liver, spleen, and kidneys. Genetic sequencing determined, that the both children had a de novo mutation in *CLCN7*, a gene that encodes a chloride transporter that helps determine pH concentrations within the lysosome.

Mindell took over the story and told how loss-of-function mutations in *CLCN7* cause osteopetrosis. Yet neither patient had that. Gahl and Mindell discovered that the mutation in the UDP cases caused the lysosomes to become too acidic. They knew that chloroquine, an FDA-approved drug to treat malaria, could decrease acidity in lysosomes as a side effect. So they recommended giving it to the two children.

With treatment, the boy has improved: His kidneys have decreased in size, and he can roll over (he couldn't before). The girl is being treated at the University of Colorado School of Medicine (Aurora, Colorado); the results haven't been reported yet.

The presenters emphasized how collaborations can speed up the journey to great discoveries and, in the process, find new treatments that may improve the lives of many patients.

To watch a videocast of the "Plenary II: Immunodeficiency, Rare Diseases, Genetic Disorders, and Membrane Proteins" session, which took place on Thursday, September 13, 2018, go to https://videocast.nih.gov/launch.asp?25041.

MARLEEN VAN DEN NEST

Jeffery K. Taubenberger (left) and Audray K. Harris (right) are studying influenza in their efforts to develop a universal flu vaccine. Pamela A. Guerrerio and Ian Myles (second and third from left) are investigating food and skin allergies, which are are co-occuring more frequently now than in the past.

Plenary III: Devising Strategies to Combat Allergies and Flu

BY MANJU BHASKAR, NINDS

Whether they research annoying allergies or killer flus, NIH scientists are intent on finding therapeutic strategies that may rid the world of these scourges. Four NIAID researchers shared their stories: **Ian Myles** and **Pamela A. Guerrerio** on food and skin allergies; and **Jeffery K. Taubenberger** and **Audray K. Harris** on influenza and flu vaccines.

Myles spoke about a rosier future for atopic dermatitis (AD), also known as eczema. The underlying pathology of AD includes impaired skin-barrier function, susceptibility to *Staphylococcus aureus* skin infections, immune dysregulation, and cutaneous dysbiosis. Myles and his team found that topical treatment with *Roseomonas mucosa*, a bacterium naturally present on the skin, relieves disease severity in mouse and cell-culture models as well as in humans. The group is continuing its studies and expanding clinical trials to determine whether bacteria transplants can effectively treat AD.

AD plays a role in the development of food allergies (FA), too. Over the past few decades, both AD and FA haved increased in the prevalence. "Up to 66 percent of children with food allergies also have atopic dermatitis and up to 40 percent of children with atopic dermatitis have food allergies," Guerrerio said. Regulatory T cells (Tregs) play a central role in the development of food tolerance—in mice—but it's not clear what happens in humans. Tregs are linked to the development of peanut allergy (PA) in people. She and colleagues analyzed blood samples from children with and without PA or peanut sensitivity and determined that exposure to peanuts through the skin can prime the development of peanut-specific effector T cells (Teff), which promotes sensitization to peanuts.

In another study (involving 77 participants, ages 2 to 20 years), Guerrerio found that children with AD and FAs (especially to milk) exhibit impaired growth, whereas those with AD alone are often overweight or obese.

On the influenza front, Taubenberger noted that 2018 is the 100th anniversary of the deadly 1918 influenza pandemic that killed an estimated 50 to 100 million people in a few months. "That virus mutated and was genetically updated by reassortment to

become the annual recurrent seasonal flu strains we have today," he said.

In the mid-1990s, Taubenberger's high-containment laboratory at the Armed Forces Institute of Pathology (Washington, D.C.) genetically sequenced and reconstructed the virus, based on preserved lung tissue from several 1918 victims. When he came to NIAID in 2006, he and his team began using what they had learned about the pathogenicity of the 1918 flu to guide the development of universal influenza vaccines. His lab is beginning a clinical evaluation of these vaccine candidates in phase 1 studies.

The structural biology of influenza and other viruses is being examined in Audray Harris's lab. Using biochemical analyses, cryoelectron microscopy methods, and image analysis, his team determined the composition and 3-D structural organization of influenza virus–like particles of the 1918 flu. Current flu vaccines target the head region of hemagglutinin (HA), which is responsible for binding the virus to cells in the upper respiratory tract and elsewhere. But the HA subtype is changing constantly, so vaccines need to be updated annually to keep up. Even then there's no guarantee that they will be effective against all flu strains. Scientists are beginning to target the HA-stem region, which doesn't change as much as the head region.

Harris's group is designing nanoparticles that will have the correct structure to target the HA-stem region. The lessons learned could aid in the development of new vaccines for flu and other pathogens. ●

To watch a videocast of the "Plenary III: Food and Skin Allergies, and Virus Pathogenesis and Vaccine Development" session, go to https://videocast.nih.gov/launch.asp?26045.

More photos and longer articles online at https://irp.nih.gov/catalyst/v26i6/2018-research-festival-plenary-sessions

Showcasing VR's Potential for Biomedicine

BY KATHRYN DEMOTT, NEI

Virtual reality (VR) systems have hit a sweet spot. Enhancements in resolution and interactive capacity have come together at a reasonable price point. Judging from the range of VR demos at the NIH Research Festival, the NIH community has plenty of ideas for tapping into the technology's biomedical potential. The NIH Library and the Virtual and Augmented Reality Interest Group (VARIG) teamed up to provide a variety of VR demos ranging from viewing molecules to biomedical-training simulations.

"VR provides an immersive experience that keeps people from getting distracted by real life, and that's been a game changer for training applications," said **Victor Cid**, senior computer scientist for the NLM's Disaster Information Management Research Center. He developed a prototype VR-based training system to conduct hospital disaster-management exercises, which are critical for helping health-care facilities prepare for disasters.

Other systems are exploring VR's empathy-building potential. The National Eye Institute showcased a VR simulation of what vision is like for people with cataracts or age-related macular degeneration, two of the most common conditions leading to vision loss. Users experience how difficult each disorder makes shopping in a supermarket and seeing at night in an urban setting. A Google cardboard version that turns your smartphone into an inexpensive VR viewer is in development. The simulator can educate caregivers and may even motivate people to take steps to keep their eyes healthy.

The Zebrafish Brain Browser, designed in **Harold Burgess**'s lab in the Eunice Kennedy Shriver National Institute of Child Health and Human Development, uses the open-source platform Extensible 3-D, enabling users to interact with imaging data from the fish's brain. Those data include volumetric rendering of gene expression patterns in transgenic fish. Images can be uploaded for comparison with the transgenic lines. For information, visit http://www.zbbrowser.com/. A Google cardboard VR version is available by clicking "VR" at the website. ●

To find out more about VARIG and to join its LISTSERV, go to https://oir.nih.gov/sigs/virtual-augmented-reality-scientific-interest-group-varig. New members are always welcome.

NEI

Shopping in a grocery store is complicated by the loss of central vision from age-related macular degeneration, as this view from the NEI eye-disease simulator shows.

2018 Research Festival: Selected Concurrent Symposia

THE CHEMISTS

BY LAURA STEPHENSON CARTER

NIH CHEMISTS WIELD POWERFUL TOOLS that probe biological processes, decipher the makeup of molecules, and create a foundation upon which treatments for diseases ranging from cancer to HIV/AIDS are derived. Some of the chemists were on hand at the Research Festival to share their success stories.

"There's such a diversity of chemists [at NIH] even though there aren't very many of us," said **Amy Newman** (NIDA), a mild-mannered chemist who does addiction research using target-directed fluorescent molecules and a fierce-sounding technique called STORM (short for direct stochastic optical reconstruction microscopy). In her search for potential therapies for substance-use disorders, she combines state-of-the-art synthetic organic chemistry techniques with molecular modeling to develop atypical dopamine-transporter blockers to treat cocaine- and methamphetamine-use disorders.

Chemists also rely on several techniques to probe the structure and function of the nucleic acids, RNA and DNA. For the past few years, **John "Jay" Schneekloth Jr.** (NCI) has been using small-molecule microarrays to screen a chemical library of some 20,000 compounds in hopes of finding therapeutically relevant nucleic-acid targets. He recently identified a druglike compound that binds to the HIV transactivation response hairpin.

But it's hard for chemists to keep up with HIV, which has managed to outwit the drugs used to treat it by developing resistance to them. Those drugs, used alone or in combination, target several parts of the viral replication cycle. **Dan Appella** (NIDDK), however, has synthesized two mercaptobenzamide molecules that are "hitting some other aspect of the HIV replication cycle" and may have found an HIV weak spot. He is examining whether these molecules can be further developed into new drugs to combat HIV infection.

Chemists are at work in the arena of neurodegenerative diseases, too. **Jennifer Lee** (NHLBI) is harnessing the power of biochemical and biophysical techniques to decipher the molecular mechanisms of amyloid formation such as what's found in the brains of those with Alzheimer, Parkinson, and Huntington diseases. She's observed conformational heterogeneity in the COOH-terminal region of alpha synuclein, a protein involved in amyloid formation.

Another area that chemists are tackling is metastatic cancer and the perinuceolar compartments (PNCs), subnuclear bodies that are increased in metastatic cell lines such as breast, colorectal, and ovarian cancers. **Juan Jose Marugan** (NCATS) led a team that formulated about 150 derivatives of a compound that could reduce PNC prevalence in metastatic cells and named the best one metarrestin. It could kill metastatic cancer cells—including lung, liver, pancreatic, prostate, and breast cancer—in mice. Plans for human trials are underway.

FARE awardee **Michael Luciano** (NCI-CCR), in **Martin Schnermann's** lab, is also applying his chemical expertise to finding ways to defeat cancer. He is helping to develop new small-molecule imaging agents that can be used in fluorescence-guided surgery for cancer. The new agents, which are brighter and more chemically stable than conventional fluorophores, illuminate tumor margins and highlight nerves and other sensitive areas that should be avoided.

The "Chemical Biology" concurrent symposium took place on Thursday, September 13, 2018, and was chaired by Clifton Barry (NIAID) and Joel P. Schneider (NCI-CCR).

GENOME EDITING

BY ALLISON CROSS, NCI

SEVERAL RESEARCHERS PRESENTED their work using CRISPR-Cas genome-editing technologies and newer forms of genome editing that may one day lead to advanced therapies for diseases.

Visiting fellow **Sergey Shmakov** (NCBI), in **Eugene Koonin's** group, described how computational approaches to explore the diversity of CRISPR-Cas systems allowed him to identify six new type II CRISPR-Cas subtypes that have the potential for becoming novel genome-editing and regulatory tools.

And immunologist **Franziska Petermann** (NIAMS), a fellow in **John O'Shea's** lab, explained that thanks to CRISPR-Cas9, she determined that the long, noncoding RNA NeST regulates interferon gamma expression as a cis-acting enhancer by inducing chromatin-loop formation.

NHLBI's Transgenic Core Facility, led by **Chengyu Liu**, is using CRISPR-Cas9 techniques to generate mutant mice used by researchers like **Lothar Hennighausen** (NIDDK). Liu described how Hennighausen's lab examined mutations at CRISPR target sites and throughout the entire genome using whole-genome sequencing, which provided evidence that CRISPR-Cas9 does not do any damage such as introducing mutations outside the target site. But "CRISPR editing frequently wreaks genomic havoc at sites it is supposed to cleanly mutate, thus limiting its usefulness," said Henninghausen.

To offset some of the problems with CRISPR-Cas9 editing, researchers are searching for new genome editors. FARE awardee **Hye Kyung Lee** (in Hennighausen's lab) shared her work in which she used deaminase base editing, a newer form of CRISPR-Cas9-mediated editing. Lee

analyzed the genome of mutant mice generated using cytosine base editors (CBE) and an adenine base editor (ABE) and found that the editors have different fidelities, with ABE being more specific than CBE.

Although CRISPR-Cas9 has its limitations, it is being widely used in many areas of both basic and translational research. **Jens Kalchschmidt** (NIAMS), a fellow in **Rafael Casellas'** lab, described how he used CRISPR-Cas9 to study the mammalian Mediator complex, which regulates transcription by RNA polymerase II.

Kyung-Rok Yu (NHLBI), a postdoctoral fellow in **Cynthia Dunbar's** lab, uses CRISPR-Cas9-mediated editing to engineer the nonhuman primate stem and progenitor cells (HSPC) and study aging and advanced therapies for hematologic diseases. He also described his work aimed at making chimeric antigen receptor T-cell (CAR-T) immunotherapy possible for people with acute myeloid leukemia.

The"Cell-based Gene Editing and CRISPR" session was held on September 12, 2018, and chaired by Lothar Hennighausen (NIDDK).

A SINGLE CELL CAN TELL US A LOT

BY BRANDI CAROFINO, NCI

High-throughput sequencing has transformed research and patient care and paved the way for the personalized-medicine revolution. Now that we can isolate and sequence single cells, we can see what is happening within discrete cell populations in normal or diseased tissue and how this process changes over time.

An example of this approach was presented by **Belinda Hauser** (NIDCR), a postdoc working with **Matthew Hoffman**. Hauser is using single-cell RNA sequencing to define cell types during salivary gland development. She hopes this information can be used to help regenerate gland function in patients with head and neck cancer, who have been treated with radiation that often destroys their salivary glands.

FARE awardee **Lingling Miao** (NIAMS), a postdoc in **Isaac Brownell's** lab, is also using single-cell sequencing to define a developmental process in skin. Miao studies Merkel cells, touch sensors that are especially abundant in areas such as the fingertips, lips, and face. By carefully isolating this tiny subpopulation of epidermal cells from mouse skin, she identified discrete subsets of cells at different stages of differentiation, including those that cluster with keratinocytes and likely represent early Merkel-cell precursors.

Representing an even smaller biological fraction, single-nucleus RNA sequencing is being performed by **Ariel Levine** (NINDS) and colleagues to map neuronal activity in spinal tissue in mice. Nuclei can be isolated from frozen tissue, which ensures that cellular activity at the time of the experiment is preserved. She hopes what she learns will one day help people who've had a stroke or spinal cord injury.

Single-cell RNA sequencing can also be leveraged to develop treatment strategies for individuals with rare syndromes. **Keisuke "Chris" Nagao** (NIAMS) described a patient with drug-induced hypersensitivity that failed to respond to all conventional treatments. After comparing gene expression between the affected patient and healthy control subjects, Nagao detected in the patient an expansion of certain memory T cells that had a high expression of the *JAK3* and *STAT1* genes and reactivation of human herpesvirus 6. He found that the patient improved dramatically when tofacitinib, an inhibitor of the protein Janus kinase, and valganciclovir, an antiviral agent, were administered.

Robert Hufnagel (NEI) also discussed how high-throughput exome sequencing can help drive disease-gene discovery in rare neurodevelopmental disorders. He equated his technique to "a magnet trying to pull out the needles from a very large haystack" to narrow the list of potentially causative genetic variants. By using this approach in a cohort of 128 patients with neuro-ocular syndromes, he was able to implicate variants in the *UBA2*, *CSDE1*, and *SUN1* genes, independently confirmed the association in additional families, and used zebrafish (*Danio rerio*) CRISPR genetically engineered models to validate his findings.

Another example of how the power of high-throughput technologies can be harnessed to improve patient care was presented by **Jun Wei** (NCI-CCR). His group is trying to tailor treatments for children and adults with cancer. He described how NCI's ClinOmics program, which uses genomic approaches to help guide the treatment of NIH Clinical Center patients with cancer, enables precision therapy, provides exome- and deep-targeted cancer-gene-panel sequencing of normal and tumor tissue. These data have been used to provide molecular profiles of 81 diagnoses for 255 NCI-CCR patients.

The "High-Throughput Sequencing–From Single Cell Sequencing to Changing Patient Care" concurrent symposium was chaired by Amy Hsu (NIAID) and Matthew Kelley (NIDCD).

MACHINE LEARNING, DATA SCIENCE AND HACKATHONS: THE FUTURE IS NOW

BY VALERIE VIRTA, NLM

Machine learning, deep learning, and other artificial intelligence technologies are no longer only in the movies. Science fiction is coming to life in projects all over the NIH. (Read more online at website listed below.)

Read more online at https://irp.nih.gov/catalyst/v26i6/2018-research-festival-selected-concurrent-symposia.

Recently Tenured

KEVIN M. BROWN, NCI-DCEG

AHMED M. GHARIB, NIDDK

EYTAN RUPPIN, NCI-CCR

MARTIN J. SCHNERMANN, NCI-CCR

NAOMI TAYLOR, NCI-CCR

KEVIN M. BROWN, PH.D., NCI-DCEG

Senior Investigator, Laboratory of Translational Genomics, Division of Cancer Epidemiology and Genetics, National Cancer Institute

Education: University of Virginia, Charlottesville, Virginia (B.A. in biology); George Washington University, Washington, D.C. (Ph.D. in genetics)

Training: Postdoctoral fellow, Genetic Basis for Human Disease Division, Translational Genomics Research Institute (TGen, Phoenix)

Before coming to NIH: Investigator, Integrative Cancer Genomics Division, TGen; adjunct professor of Genetic Epidemiology, Mayo Clinic Cancer Center (Scottsdale, Arizona); adjunct research assistant professor, Basic Medical Sciences, University of Arizona College of Medicine (Phoenix); adjunct professor, Molecular and Cellular Biology, Arizona State University (Tempe, Arizona)

Came to NIH: In 2010

Selected professional activities: Faculty, American Association for Cancer Research's Integrative Molecular Epidemiology Workshop; member, American Cancer Society's Tumor Biology and Genomics Study Section

Outside interests: Mountain biking; barbequing

Website: https://irp.nih.gov/pi/kevin-brown

Research interests: My research focuses on the genetic underpinnings of melanoma susceptibility. My lab is identifying the genetic contributions and functional pathways associated with melanoma risk. Although early-stage melanoma is largely curable via surgical resection, outcomes for a significant proportion of late-stage melanoma patients remain poor despite considerable recent progress.

We are trying to gain a better understanding of the genetic factors contributing to melanoma risk so we can facilitate prevention and/or early-detection efforts in at-risk individuals. Also, we are actively involved in ongoing melanoma genome-wide association studies (GWAS) as members of the International Melanoma Genetics Consortium (GenoMEL) and the Melanoma Meta-analysis Consortium. We also work with GenoMEL member groups to use whole-genome and whole-exome sequencing approaches to better understand the genetics of melanoma susceptibility in melanoma-prone families. Lastly, we are also actively involved in ongoing renal-cell cancer GWAS at NCI, as well as meta-analyses with international teams working in the same area.

Beyond identification of novel risk genes and loci, a significant proportion of my research program focuses on functional characterization of cancer-susceptibility loci identified via GWAS. Although significant strides have been made in recent years toward cataloging loci involved in cancer risk, research into how these variants influence risk lags far behind. We are trying to better understand the molecular consequences of risk variants on gene regulation and function as well as the phenotypic effects of allele-specific gene functions. We perform fine-mapping of risk-associated regions, targeted and genome-wide expression analysis, gene-regulation and epigenetic work, and bioinformatic analysis of large genomic datasets.

Our current projects include a large-scale study of the influences of germline genetic variation on both gene regulation and cellular phenotypes in melanocytes and melanoma cells; functional genomic screens to identify genes that mediate phenotypes associated with early-stage tumor progression; large-scale reporter screens to identify risk-associated genetic variants conferring allele-specific gene regulatory potential; and directed analyses applied to specific susceptibility regions and genes.

AHMED M. GHARIB, M.D., NIDDK

Senior Investigator; Head, Biomedical and Metabolic Imaging Branch, National Institute of Diabetes and Digestive and Kidney Diseases

Education: University of Alexandria, Faculty of Medicine, Alexandria, Egypt (M.D.)

Training: Internship at Alexandria University Hospital, Egypt, and in internal medicine at

NIRAJ H. TOLIA, NIAID

University of Washington (Seattle); residency in nuclear medicine and nuclear cardiology at University of Washington; residency in diagnostic radiology at University of Louisville (Louisville, Ky.); fellow/instructor in cross-sectional imaging at Johns Hopkins Hospital (Baltimore); and fellow in NIH's Imaging Science Training Program

Came to NIH: In 2003 for training; 2004–2005 served as staff clinician in the NIH Clinical Center's Diagnostic Radiology Department, then in NHLBI's Integrated Cardiovascular Imaging Laboratory, and later in NIDDK's Biomedical and Metabolic Imaging Branch; in 2011 became tenure-track investigator

Selected professional activities: Member, research committee, North American Society of Cardiovascular Imaging; member, Cardiovascular Radiology and Intervention Communications Committee, American Heart Association

Outside interests: Enjoys motor sports including cars, motorcycles, and mechanics; spending time with his family

Website: http://bit.ly/2PRELPR

Research interests: My research involves developing new imaging techniques to detect organ damage associated with metabolic and immunological disorders. In 2013, I received the NIH Director's Award for the "development of cutting edge, non-invasive imaging technologies permitting drastically improved resolution and disease detection while reducing the risk to patients."

NIDDK's Biomedical and Metabolic Imaging Branch (BMIB)—which is made up of a multidisciplinary team of biomedical engineers, spectroscopy experts, and biologists—is using new chemical spectroscopic techniques to view organs and improved imaging methodologies (faster and at a higher resolution), and high-contrast techniques without the use of contrast agents.

We applied both computed tomography (CT) and magnetic-resonance imaging (MRI) for coronary imaging in the same patients. This approach allowed for identifying coronary abnormalities in people with HIV, Job syndrome, and Cushing syndrome. We also developed a new technique to image the coronary vessel wall—to characterize atherosclerotic coronary-artery disease—using high-magnetic-field MR scanners without the need for ionizing radiation. A patent application is pending for this new method, which could potentially be used to characterize and study coronary artery disease and its response to lipid-lowering and anti-inflammatory therapies. These imaging techniques have also provided data for mathematical models that predict points of potential atherosclerotic plaque accumulation and possible plaque vulnerability.

As part of the NIH obesity initiative, we have integrated the use of a large-bore high-magnetic-field MR scanner with a metabolic unit to characterize metabolic activity in people with a wide range of body-mass indices. An improvement and technical advancement in MR spectroscopy, developed by the BMIB team, has also been applied to measure fat and certain metabolites in the heart, liver, pancreas, and muscles and to correlate measurements with metabolic activity. We are also using imaging techniques that will allow for early detection and simultaneous quantification of liver fibrosis and inflammation in patients.

EYTAN RUPPIN, M.D., PH.D, NCI-CCR

Senior Investigator, Chief, Cancer Data Science Laboratory, Center for Cancer Research, National Cancer Institute

Education: Tel Aviv University, Tel Aviv, Israel (M.D.; M.Sc. and Ph.D. in computer science)

Training: Internship in medicine at Rabin Medical Center (Petah Tikva, Israel); residency in medicine and psychiatry at Ramat-Chen Psychiatric Center (Tel Aviv); postdoctoral training in computer science at the University of Maryland at College Park (College Park, Md.)

Before coming to NIH: Professor of computer science and medicine, Tel Aviv University; professor and director of Center for Bioinformatics and Computational Biology, University of Maryland at College Park

Came to NIH: In 2018

Outside interests: Playing bridge; hiking

Website: https://ccr.cancer.gov/cancer-data-science-laboratory/eytan-ruppin

Research interests: I am helping to develop computational systems–biology approaches for the multi-omics analysis (genome, proteome, transcriptome, epigenome, and microbiome analysis) of cancer. Members of my lab and I collaborate with other cancer labs to jointly gain a network-level integrative view of the systems we study and predict and test novel drug targets and biomarkers to treat cancer more selectively and effectively.

In a joint experimental and computational effort, my lab identified the first genome-scale metabolic-modeling-based synthetic lethal drug target to treat renal cancer. Together with our collaborators, we recently developed a new approach for stratifying patients for immunotherapy treatment. We discovered a fundamental link between the dysregulation of the urea cycle and the response to immunotherapy.

We have been studying the value of genetic interactions (GIs) across the whole genome. We and others have shown that

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Recently Tenured

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GIs are critical in tumor development and drug response and that such interactions can be computationally identified by analyzing large-scale genomics and patient data. We have shown that the identified cancer GIs predict the response of cancer patients to many widely used drug treatments, offering a complementary approach to existing mutation-based methods for precision-based cancer therapy. In an effort to fight resistance to cancer therapy, we have identified genome-wide networks that can predict patients' responses and resistance to a majority of the current cancer drugs. Our studies lay the basis for a novel precision-based cancer therapy that, unlike most current approaches, is based on the status of all genes in the tumor.

We are also doing collaborative research in cancer immunotherapy ranging from studying how the dysregulation of the urea cycle modulates the response to checkpoint inhibitors in different cancers; investigating the role of intratumor heterogeneity in shaping the immune response and its effectiveness; and building machine-learning-based predictors of patients' responses to checkpoint therapies for melanoma. Our ongoing collaborative studies focus on genome-wide identification of effective combinations involving checkpoint inhibitors (possibly with targeted therapies) and on further improving the prediction of responses to different immunotherapies.

MARTIN J. SCHNERMANN, PH.D., NCI-CCR

Senior Investigator and Head, Organic Synthesis Section, Chemical Biology Laboratory, Center for Cancer Research, National Cancer Institute

Education: Colby College, Waterville, Maine (B.A. in chemistry and physics); the Scripps Research Institute, La Jolla, Calif. (Ph.D. in organic chemistry)

Training: NIH Kirschstein Postdoctoral Fellowship, University of California, Irvine

Came to NIH: In 2012

Selected professional activities: Councilor for American Society of Photobiology; guest editor for *Molecular Pharmaceutics*

Outside interests: Hiking; playing tennis; playing with his young daughter

Website: https://irp.nih.gov/pi/martin-schnermann

Research interests: My research focuses on the design, synthesis, and application of new small-molecule optical approaches for cancer diagnosis and treatment. A major emphasis has been to develop molecules that harness the unique properties of light in the near-infrared range. These wavelengths (between about 700 and 900 nanometers) are less absorbed by biological macromolecules, enabling applications in various in vivo settings. Our research is unique within the intramural program because we focus on the organic chemistry of fluorescent-probe molecules. In this work, we combine modern organic synthetic methods with physical and organic chemistry principles. This approach allows us to develop compounds with applications for both imaging and drug delivery in a range of challenging biomedical settings.

To enable modern imaging applications, scientists still need improved fluorescent probes. We have identified chemical reactions that facilitate the efficient preparation of molecules that have excellent stability and optical properties. We are particularly focused on developing compounds designed for fluorescence-guided surgical resection of solid tumors, as well molecules that delineate sensitive organs such as the bile duct and ureter. Our novel dyes are also proving useful in super-resolution microscopy applications, where photon output and photostability are particularly critical.

Going forward, we are developing molecules that use even longer wavelengths (greater than 1,000 nm), which can enable in vivo imaging with exceptional resolution at significant tissue depths.

In the area of drug delivery, we have developed some of the first single-photon photocaging reactions (activating molecules with light) that use near-infrared light. In our most significant effort, we are studying and using the photo-oxidative reactivity (oxidation reactions induced by light) of heptamethine cyanines (fluorescent dyes), reactions previously only associated with fluorophore photobleaching and photodegradation. We are combining this approach with antibody targeting methods to develop a general strategy for in vivo drug delivery. Going forward, we are identifying new chemistries that will enable the rapid and targeted release of chemically diverse biological stimuli.

NAOMI TAYLOR, M.D., PH.D., NCI-CCR

Senior Investigator, Pediatric Oncology Branch; Head, Basic to Translational Oncology Section, Center for Cancer Research, NCI

Education: Princeton University (B.Sc. in biology); Weizmann Institute, Rehovot, Israel (M.Sc. in immunology); Yale University (M.D. and Ph.D. in molecular biophysics and biochemistry)

Training: Pediatric residency at Yale–New Haven Hospital; postdoctoral researcher in immunology at the Salk Institute (San Diego); postdoctoral fellow in immunology and stem-cell transplantation at Children's Hospital of Los Angeles (Los Angeles)

Before coming to NIH: Deputy director, Institut de Génétique Moléculaire de Montpellier (Montpellier, France); research director, Institut National de la Santé et de la Recherche Médicale (Inserm) (Paris); Adjunct, Université de Montpellier (Montpellier, France)

Came to NIH: In 2018

Selected professional activities: Vice president, Scientific Council, Foundation for Cancer Research, France; president, Gene Therapy Commission, French Muscular Dystrophy Foundation-AFMTelethon; scientific board, Italian Telethon; scientific council, French

Medical Research Foundation; international advisory board, Institut National du Cancer; scientific advisory board, Regensburg Center for Interventional Immunology, Germany
Outside interests: Traveling with her family to remote locations; keeping up with her partner and her three sons on the ski slopes; cooking for large numbers of friends and family
Website: https://ccr.cancer.gov/Pediatric-Oncology-Branch/naomi-taylor

Research interests: Our new group in the Pediatric Oncology Branch will be combining fundamental and translational approaches to answer key questions about the metabolic regulation of T-cell-effector function and hematopoietic stem-cell (HSC) differentiation in pediatric cancer patients. We will also be developing strategies that enhance thymocyte differentiation and T-cell function.

We will elucidate the metabolic characteristics that promote an optimal antitumor T-cell response in tumor tissue, which consumes high amounts of nutrients and is often anaerobic. Furthermore, we want to understand how a patient's chemotherapy regimen influences the metabolic fitness of effector T cells in the tumor environment.

During the past few years, we have begun to recognize the importance of nutrient resources as critical for the survival and proliferation of HSCs, progenitors, and more mature lineage-committed cells. Indeed, it is now accepted that metabolism regulates HSC "stemness." Our future work will focus on the functions of nutrient transporters and downstream metabolite fluxes in directing HSC maintenance and differentiation.

We are also interested in using thymus-targeting and reconstitution strategies to improve T-cell differentiation after HSC transplantation, which is almost always performed by the intravenous administration of autologous or allogeneic HSCs. In the context of T-cell differentiation, it is presumed that the injected progenitors first home in on the bone marrow, and then some migrate into the thymus. Research from our group and others has shown that the direct intrathymic injection—rather than intravenous administration—of hematopoietic progenitors promotes a more rapid and robust thymopoiesis.

We aim to develop thymic-based strategies that target both hematopoietic progenitors and the diverse thymic stromal environment. We hope to enhance T-cell regeneration and function after HSC transplantation.

NIRAJ H. TOLIA, PH.D., NIAID

Senior Investigator and Chief, Host-Pathogen Interactions and Structural Vaccinology Section, Laboratory of Malaria Immunology and Vaccinology, National Institute of Allergy and Infectious Diseases

Education: Imperial College of Science, Technology and Medicine, London (B.Sc. in biochemistry); Watson School of Biological Sciences, Cold Spring Harbor Laboratory (CSHL), Cold Spring Harbor, New York (Ph. D. in biological sciences)
Training: Postdoctoral research at CSHL
Before coming to NIH: Associate professor, Department of Molecular Microbiology, and director, Structural Biology Core, Washington University School of Medicine (St. Louis)
Came to NIH: In 2018
Selected professional activities: Scientific program committee, American Society of Tropical Medicine and Hygiene
Outside interests: Hiking
Website: https://www.niaid.nih.gov/research/niraj-harish-tolia-phd

Research interests: I study the pathogenesis of infectious diseases. Before I came to NIH, my laboratory at Washington University pioneered the structural and biophysical studies of host-pathogen interactions, antibody neutralization, and immunogen design for malaria. Malaria affects a third of the world's population, especially in sub-Saharan Africa. There are about 200 to 300 million cases per year and approximately half a million deaths annually from malaria. Most fatalities are in children under the age of five.

I contracted malaria myself as a child growing up in Nairobi; that experience spurred my interest in studying malaria and other infectious diseases of global importance.

At NIH, my lab and I are defining how the survival processes of the malaria parasites (*Plasmodium falciparum* and *P. vivax*) are mediated and how they can be exploited for preventative, therapeutic, and diagnostic purposes. This work has direct implications for drug and vaccine development. We use the tools of microbiology, cell biology, biochemistry, biophysics, and structural biology to study proteins and complexes.

In particular, we are studying host-pathogen interactions in malaria in hopes of exploiting them to prevent disease; defining the mechanisms of how antibodies neutralize malaria parasites; and designing and engineering vaccines to protect against the disease. Recently, we described how the *P. vivax* Duffy binding proteins bind to red cells, and how antibodies prevent this interaction and neutralize malaria parasites. We have leveraged this information to design novel immunogens for *P. vivax* vaccines.

In addition, we have established the function and mechanism of action of cell traversal protein for ookinetes and sporozoites (CelTOS), a parasite protein conserved in both *P. falciparum* and *P. vivax*. CelTOS is required for several stages of the malaria-parasite life cycle. These studies form the foundation for the engineering of potent and effective malaria vaccines. ●

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

READ MORE ARTICLES, AND EXPANDED VERSIONS OF THE ONES IN THIS ISSUE, ONLINE AT
https://irp.nih.gov/catalyst/v26i6

NIH IN HISTORY

Out, Out, TB!

The National Library of Medicine's History of Medicine Division has a number of online exhibitions including a collection of public-health posters. This 1919 poster from the American Red Cross promises that tuberculosis (TB) would be "the next to go." During the 19th and early 20th centuries, TB was the leading cause of death in the United States and one of the most dreaded diseases known to mankind. In the 1880s, many TB patients were sent to sanatoriums where rest, fresh air, and a healthy diet helped them recover. Posters such as the one shown became effective educational and fundraising tools in the campaign against TB. To view the "Visual Culture and Public Health Posters" Exhibition, go to https://www.nlm.nih.gov/exhibition/visualculture/index.html. ●

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