Division of Intramural Research

NAEHS Council Update

September 2021

DIR RECRUITMENTS

Tenure-Track Investigator in the Clinical Research Branch
The National Institute of Environmental Health Sciences (NIEHS) is recruiting outstanding candidates for a Tenure-Track Investigator position in the Clinical Research Branch within the Division of Intramural Research at the NIEHS in Research Triangle Park, NC. The individual selected for this position will have a strong record of participation and publications in patient-oriented research, defined as research that requires direct interactions with human subjects and may include the development of new technologies, understanding mechanisms of human disease, therapeutic interventions and/or clinical trials. The Clinical Research Branch is interested in candidates with expertise in areas such as endocrinology, neuroendocrinology, metabolism, exercise, sleep, immune-mediated diseases, pulmonology, and human genetics, among others. Applicants should have an M.D. or equivalent doctoral degree with direct clinical research experience, with three or more years of research training in clinical research and publications and other evidence of the ability to design and carry out original, innovative patient-oriented research. Dr. Alison Motsinger-Reif, Chief of the Biostatistics and Computational Biology Branch serves as chair of the search committee which was launched on July 8, 2019. This recruitment has been temporarily placed on hold.

Medical Director of the Clinical Research Unit
The Division of Intramural Research is seeking an accomplished physician scientist to serve as Senior Clinician in the Clinical Research Branch and Medical Director of the Clinical Research Unit (CRU), a stand-alone facility that sees over 1,000 patients and research participants annually with a budget of over $3M. The CRU not only serves as the research home for experienced clinical investigators, but also as a resource for the outstanding intramural scientists at NIEHS interested in the translational applicability of their work. The Clinical Research Branch is interested in candidates with expertise in areas such as endocrinology, neuroendocrinology, metabolism, exercise, sleep, immune-mediated diseases, pulmonology, and human genetics, among others. Applicants should have an M.D. or equivalent doctoral degree with an outstanding track record in conducting and publishing clinical research. Dr. Michael Fessler, Chief of the Immunity, Inflammation and Disease Laboratory serves as chair of the search committee which was launched on May 25, 2021.

Recruitment of NIH Earl Stadtman Investigators
In addition to targeted recruitment, DIR is actively seeking outstanding scientists through the central NIH Stadtman recruitment mechanism. DIR Principal Investigators have volunteered to serve on 19 of 26 Stadtman subcommittees in 2021-22 representing a range of disciplines central to the NIEHS mission. Applications will be reviewed in October 2021 and outstanding candidates will be identified for interviews at NIEHS starting in November 2021.

NEW HIRES AND CHANGES IN DIR LEADERSHIP

Chief of the Comparative Medicine Branch
Dr. Dondrae Coble has accepted an offer to serve as Chief of the Comparative Medicine Branch (CMB) in DIR and NIEHS Animal Program Director. In his previous role, Dr. Coble was Director of the Animal Resources Core and Attending Veterinarian at the Abigail Wexner Research Institute at Nationwide Children's Hospital (NCH) in Columbus, OH. Dr. Coble is expected to begin his appointment as Senior Scientist and assume the role of CMB Chief in October 2021.

New Tenure-Track Investigators
Dr. Stavros Garantziotis, Medical Director of the NIEHS Clinical Research Unit and head of the Matrix Biology Group, has accepted an offer to join the Immunity, Inflammation and Disease Laboratory as a Tenure Track Investigator. Dr. Garantziotis will continue and expand his independent research program focused on extracellular matrix biology, innate immunity, lung inflammatory diseases, and airway remodeling triggered by the environment. He is expected to start as a Tenure Track Investigator in Winter 2021.

Dr. Carlos Guardia from the Eunice Kennedy Shriver National Institute of Child Health and Human Development has accepted an offer to join the Reproductive and Developmental Biology Laboratory as an Earl Stadtman Tenure Track Investigator. Dr. Guardia will initiate an independent program focused on developing and applying innovative cell biological and model systems to understand placental development and protective functions during pregnancy. He has also been selected as a member of the NIH Distinguished Scholars Program. Dr. Guardia is scheduled to start at NIEHS in November 2021.

New Independent Research Scholar
Dr. Elizabeth Martin is currently an NIGMS-funded Postdoctoral Research Associate Training (PRAT) Fellow working with Dr. Paul Wade in the Epigenetics and Stem Cell Biology Laboratory (ESCBL) at NIEHS. Dr. Martin was selected as an NIH Independent Research Scholar (IRS). Her independent research program will integrate data from humans, mice, and in vitro model systems to address how toxicant exposure impacts the epigenome and will focus on prenatal exposure and developmental origins of health and disease. Dr. Martin is scheduled to start her independent program at NIEHS in September 2021.

SCIENTIFIC UPDATE BY A DIR PRINCIPAL INVESTIGATOR

SARS2 Nsp15 is Mad for U

Robin E. Stanley, Ph.D.
Nucleolar Integrity Group
Signal Transduction Laboratory
DIR, NIEHS

SARS-CoV-2 is the virus responsible for the current Covid-19 global pandemic which has infected millions worldwide. Nsp15 is a viral endoribonuclease found in all coronaviruses that processes viral RNA to prevent detection by the host immune system. Nsp15 is a promising anti-viral target, however how it cuts RNA is poorly understood. Through the combination of cryo-EM, mass spectrometry, biochemistry, and molecular dynamics we are defining how Nsp15 recognizes and processes viral RNA. Atomic resolution structures of Nsp15 bound to RNA in pre and post cleavage states revealed the significance of active site residues in uridine specificity and catalysis. The structures along with a series of biochemical assays have revealed molecular details of how Nsp15 recognizes viral RNA and will hopefully aid in the design of urgently needed anti-viral therapeutics.

TRAINING AND MENTORING

The NIH Fellows Award for Research Excellence "FARE"

The Fellows Award for Research Excellence (FARE) program was started in 1995 to recognize scientific excellence among intramural trainees at all NIH Institutes and Centers. Trainees submit an abstract of their research, which is peer reviewed. The FARE award program is sponsored by the Scientific Directors, the Office of Research on Women's Health, and the Office of Education. Each winner receives a $1500 professional development award. FARE winners will be invited also to present their work at one of the FARE poster sessions that will follow each of the Wednesday Afternoon Lecture Seminars in Bethesda, and to serve as a judge for the FARE competition next year. NIEHS trainees were very successful in the FARE competition this year with the third highest number of awardees among all NIH Institutes and Centers.

The NIEHS Division of Intramural Research has 15 FARE award winners for 2022 :

FARE Awardee	Mentor	Laboratory/Branch
Matias Grodzielski, Ph.D.	John Cidlowski, Ph.D.	Signal Transduction Laboratory
Yosuke Sakamachi, Ph.D.	Stavros Garantziotis, M.D.	Immunity, Inflammation & Disease Laboratory
Alexander C. Foo, Ph.D.	Geoff Mueller, Ph.D.	Genome Integrity & Structural Biology Laboratory
Dana Al-Hasan, Ph.D.	Chandra Jackson, Ph.D., M.S.	Epidemiology Branch
Jennifer Woo, Ph.D., M.P.H.	Dale Sandler, Ph.D.	Epidemiology Branch
Ciro Amato, Ph.D.	Humphrey Yao, Ph.D.	Reproductive & Developmental Biology Laboratory
David Diaz Jimenez, Ph.D.	John Cidlowski, Ph.D.	Signal Transduction Laboratory
Komlan Atitey, Ph.D.	Benedict Anchang, Ph.D.	Biostatistics and Computational Biology Branch
Yun-Gil Roh, Ph.D.	Anton Jetten, Ph.D.	Immunity, Inflammation & Disease Laboratory
Tapas Pradhan, Ph.D.	Anton Jetten, Ph.D.	Immunity, Inflammation & Disease Laboratory
Meredith Frazier Ph.D.	Robin Stanley, Ph.D.	Signal Transduction Laboratory
Stephen Shears, Ph.D.	Stephen Shears, Ph.D.	Signal Transduction Laboratory
Justin Collier, PharmD, Ph.D.	Anton Jetten, Ph.D.	Immunity, Inflammation & Disease Laboratory

Sukanya Saha, Ph.D.	Guohong Cui, Ph.D.	Neurobiology Laboratory
Jicheng Li, Ph.D.	Guohong Cui, Ph.D.	Neurobiology Laboratory

The NIH Pathway to Independence Award (K99/R00)
The Pathway to Independence (PI) Award Program is designed to facilitate receiving an R01 award earlier in an investigator's research career. The primary, long-term goal of the PI Award Program is to increase and maintain a strong cohort of new and talented, NIH-supported independent investigators. The PI Award will provide up to five years of support consisting of two phases. The initial phase will provide 1-2 years of mentored support for highly promising, postdoctoral research scientists. This phase will be followed by up to 3 years of independent R00 support contingent on securing an independent research position. Award recipients will be expected to compete successfully for independent R01 support from the NIH during the career transition award period. The PI Award is limited to postdoctoral trainees who propose research relevant to the mission of one or more of the participating NIH Institutes and Centers.

Casandra Hayne, Ph.D. was awarded a K99 MOSAIC Award (1K99GM143534-01). This central NIH program is funded by NIGMS. Dr. Hayne will be mentored by Dr. Robin Stanley in the Signal Transduction Laboratory.

NIH Emerging Global Leader Award (K43):
Dr. Temitope (Temi) Adedeji, a Visiting Fellow in the Wade group received an NIH Emerging Global Leader Award (K43) from the NIH Fogarty International Center.

Science Communication Fellowship:
Dr. Emily Werder an IRTA Postdoctoral fellow in Dale Sandler's group was selected to participate in the prestigious Science Communication Fellowship program.

The Science Communication Fellowship is a nine-month program for early career PhD scientists who want to maximize the impact of their work to benefit public health and the environment, and share their passion for science. Fellows are chosen from the fields of green chemistry/engineering and the environmental health sciences, and work in academia and government.

NIGMS PRAT Awards:
Two DIR fellows were honored with prestigious NIGMS Postdoctoral Research Associate Training (PRAT) Awards. These awards are funded by NIGMS for 3 years. Dr. Liz Garcia-Peterson will be mentored by Dr. Xiaoling Li in the Signal Transduction Laboratory and Dr. Saniya Rattan will be mentored by Dr. Humphrey Yao in the Reproductive and Developmental Biology Laboratory.

NIH Matilda White Riley Early-Stage Investigator Award
Kaitlyn Lawrence, Ph.D., an IRTA Postdoctoral Fellow in the Chronic Disease Epidemiology Group within the Epidemiology Branch was recognized with the Matilda White Riley Early-Stage Investigator Award by the NIH. Dr. Lawrence is currently focused on assessing the interplay among climate, environmental contaminants, social factors, and genomics and how these relate to respiratory and other chronic disease endpoints.

Society of Toxicology Best Postdoctoral Publication Award
Suzanne Martos, Ph.D., IRTA Postdoctoral Fellow in the Environmental Epigenomics and Disease Group with the Immunity, Inflammation and Disease Laboratory was honored with the annual SOT award for her publication in *Cell Reports Medicine*:

Martos SN, Campbell MR, Lozoya OA, Wang X, Bennett BD, Thompson IJB, Wan M, Pittman GS, Bell DA. Single-cell analyses identify dysfunctional CD16+ CD8 T cells in smokers. *Cell Rep Med*. 2020 Jul 21;1(4):100054. doi: 10.1016/j.xcrm.2020.100054. PMID: 33163982; PMCID: PMC7644053.

2021 NIH Virtual Postbac Poster Days – Outstanding Posters
189 of the 950 posters presented at NIH Postbac Poster Day were recognized as outstanding (top 20% of all posters). Ten NIEHS posters presenters were recognized as outstanding.

Alexander Merder
Kamiya Bridges
Kathleen Embury
Lauren Gullett
Ruth Parsons
Sanya Mehta
Sarah Chong
Sarah Sleiman
Suzanna Kafer
Sydney Fry

2021 NIH Summer Internship Program
NIEHS hosted 57 summer interns from May through August 2021. The 2021 program was entirely virtual. The NIEHS program included a Welcome Event on June 7, 2021, Career Panel on June 18, 2021, Zoom Poster Session on July 29, 2021. The NIH Office of Intramural Training and Education (OITE) offered scientific bootcamps, journal clubs and workshops throughout the summer and the NIH Summer Presentation Week was held August 3-4, 2021.

Poster Award Winners in DIR:

Undergraduate 2nd Place:
Mlana Lore
Dr. Laura Bisogno and Dr. Trevor Archer
Epigenetic and Stem Cell Biology Laboratory

Undergraduate 3rd Place (tie):
Spencer Maranto
University of North Carolina- Chapel Hill
Dr. Jesse Cushman

Neurobiology Laboratory

Undergraduate 3rd Place (tie):
Kayen Tang
Vassar College
Dr. Ayland Letsinger and Dr. Jerry Yakel
Neurobiology Laboratory

Undergraduate Honorable Mention:
Shawn Mathew
University of North Carolina- Chapel Hill
Dr. Lalith Perera
Genome Integrity and Structural Biology Laboratory

Undergraduate Honorable Mention:
Kim Nguyen
University of North Carolina- Chapel Hill
Dr. Justin Collier and Dr. Anton Jetten
Immunity, Inflammation and Disease Laboratory

Graduate Winners:

Graduate 1st Place:
Opal Patel
University of North Carolina- Chapel Hill
Dr. Kaitlyn Lawrence and Dr. Dale Sandler
Epidemiology Branch

Graduate 2nd Place (tie):
Yilda Macias
New Mexico State University
Dr. Katie O'Brien and Dr. Dale Sandler
Epidemiology Branch

Graduate 2nd Place (tie):
Rachel Thompson
Grand Valley State University
Dr. Ann Von Holle and Dr. Clarice Weinberg
Biostatistics and Computational Biology Branch

Graduate Honorable Mention:
Sharonda Lovett
Boston University
Dr. Katie O'Brien and Dr. Dale Sandler
Epidemiology Branch

2021 Virtual NIEHS Biomedical Career Symposium

The Twenty Fourth Annual NIEHS Biomedical Career Symposium was held virtually on August 26-27, 2021, with more than 500 attendees from twenty-two U.S. states and seven foreign countries: Japan, Iceland, India, Canada, South Korea, Nigeria, and the United Kingdom. The event featured more than 100 invited professionals who provided career advice on how to effectively apply to specific jobs through tailoring CV/Resumes and gave examples on how to successfully network. Participants also had opportunities to communicate one-on-one with biomedical professionals through CV/Resume reviews held virtually August 30-31, 2021.

Keynote & Workshop Speakers

- Tammy Collins, Ph.D., Director, Office of Fellows' Career Development, NIEHS, NIH
- Lori Conlan, Ph.D., Director, Office of Postdoctoral Services, OITE, NIH
- Dara Wilson-Grant , M.S.Ed., L.P.C.A., Associate Director of Postdoctoral Affairs at UNC-Chapel Hill and owner of Careers in Bloom, UNC-Chapel Hill and Careers in Bloom

Career Forum Panelists

- Benjamin Bobay, Ph.D., Senior Research Associate, Duke University NMR Facility
- Franziska Bollmann, Ph.D., KBI Biopharma
- Lisa Federer, Ph.D., National Library of Medicine, NIH
- Cynthia Fuhrmann, Ph.D., Assistant Dean of Career and Professional Development; Associate Professor of Biochemistry and Molecular Pharmacology, University of Massachusetts
- Sara Grimm, Ph.D., Integrative Bioinformatics Support Group, NIEHS
- Virginia Guidry, Ph.D., North Carolina Department of Health and Human Services
- Jenna Guynn, Ph.D., Director of Scientific & Regulatory Affairs, Reynolds American, Inc.
- Amy Hafez, Ph.D., AAAS Science and Technology Policy Fellow at NIH Office of Science PolicyNIH- OSP
- Joshua Hall, Director of BBSP Admissions; Director of UNC PREP, UNC Chapel Hill
- Dana Hancock, Ph.D., Senior Director, GenOmics, Bioinformatics, and Translational Research Center, RTI International
- Julie Horvath, Ph.D., Head of the Genomics & Microbiology Research Lab, North Carolina Museum of Natural Sciences
- Folami Ideraabdullah, Ph.D., Associate Professor; Department of Genetics & Department of Nutrition, UNC Chapel Hill
- Sravya Kattula, Ph.D., Research Scientist, Sanofi
- Melissa Li, Ph.D., Scientific Consultant; Grant Writing Specialist, Eva Garland Consulting, LLC
- Keisha Melodi McSweeney-Gussow, Ph.D., Senior Scientific Reviewer, FDA
- Kathryn Meurs, Ph.D., Associate Dean of Research and Graduate Studies, North Carolina State University College of Veterinary Medicine
- Amanda Parrish, Ph.D., Director of Regulatory Affairs and Quality, Duke University
- Ruth Pobee, Ph.D., University of Illinois at Chicago

- Aparna Purushotham, Ph.D., Senior Clinical Scientist, PRA Health Sciences
- Daniel Riordan, Ph.D., Staff Computational Biologist, 10X Genomics
- Erin Romes, Ph.D., Senior Process Development Scientist, Grifols
- Raquel Ybanez Salinas, Ph.D., Assistant Director of Career Development, The University of Texas MD Anderson Cancer Center
- Fenella Saunders, Ph.D., Editor-in-Chief for American Scientist magazine and Director of Science Communications and Publications for Sigma Xi American Scientist magazine
- Farrah Shapiro, Ph.D., Clinical Research Specialist, Rho
- Natalie Shaw, M.D., Pediatric Neuroendocrinology Group, NIEHS
- Clare Smith, Ph.D., Assistant Professor, Duke University
- Sharon Soucek, Ph.D., Director, Office of Technology Transfer, NIEHS
- Jason Watts, M.D., Ph.D., Stadtman Investigator, NIEHS

CV/Resume/LinkedIn Reviewers

- Adriana Bankston, Ph.D., Science Policy-Principal Legislative Analyst University of California Office of Federal Governmental Relations
- Marianne Barrier, Ph.D., Lab Manager, Genomics and Microbiology Research Lab, NC Museum of Natural Sciences
- Amy Blackburn, M.S.Ed., Student Services Director for the Department of Population Health Sciences, Duke University
- Patrick Brandt, Ph.D., Director of Career Development and Outreach, University of North Carolina at Chapel Hill
- Paul Burke, III, Human Resources Director, KBI Biopharma
- Brian Chorley Ph.D., Research Scientist, EPA
- Tammy Collins, Ph.D., Director of the Office of Fellows' Career Development, National Institute of Environmental Health Sciences (NIEHS)
- Angela Davis, Human Resources Specialist, National Institutes of Health (NIH)
- Laura DiMichele, Ph.D., Sr. Scientist II and Project Manager at Cato Research, Vice President, Clinical Strategy, CATO SMS
- Heather Franco, Ph.D., Principal Proposal Manager, PPD
- Cynthia Fuhrmann, Ph.D., Assistant Dean of Career and Professional Development in the Graduate School of Biomedical Sciences; Associate Professor of Biochemistry and Molecular Pharmacology University of Massachusetts
- Doreen Grech, Ph.D., VP Business Development, Asklepios
- Joshua Hall, Ph.D., Director of BBSP Admissions; Director of UNC PREP, UNC Chapel Hill
- Allyn Howlett, Ph.D., Assistant Dean of the Graduate School of Arts and Sciences and Director of the Office of Post-doctoral Education, Wake Forest University
- Jennifer Levy, Ph.D., Assistant Director of Graduate Student Services, Duke University
- Keisha Melodi McSweeney-Gussow, Ph.D., Senior Scientific Reviewer, FDA
- Virginie Papadopoulou, Ph.D., Research Assistant Professor, University of North Carolina at Chapel Hill

- Ruth Pobee, Ph.D., Sr. Research Specialist, Emergency Medicine, University of Illinois at Chicago
- Amy Rawls, Ph.D., HR Leader and Business Partner and President ASR Business Partnering, LLC
- Erin Romes, Ph.D., Senior Process Development Scientist, Grifols
- Raquel Ybanez Salinas, Ph.D., Assistant Director of Career Development, The University of Texas MD Anderson Cancer Center
- Denise Saunders, Ph.D., Career Counselor and Consultant to the Office of Intramural Training and Education, National Institutes of Health (NIH)
- Fenella Saunders, Ph.D., Editor-in-Chief for American Scientist magazine and Director of Science Communications and Publications for Sigma Xi, American Scientist magazine
- Amy Skinner, Ph.D., Toxicologist in the Division of Hematology and Oncology Toxicology, FDA
- Sharon Soucek, Ph.D., Director, Office of Technology Transfer, NIEHS
- Robin Stanley, Ph.D., Principal Investigator of the Nucleolar Integrity Group, National Institute of Environmental Health Sciences (NIEHS)
- Sarah Windsor, Ph.D., Life Science Talent Engagement Coordinator, North Carolina Biotechnology Center
- Tracey du Laney, Ph.D., Senior Director, Science and Technology Development, North Carolina Biotechnology Center

DIR RESEARCH ACCOMPLISHMENTS FOR FY 2021

The Pandemic Vulnerability Index: A Dashboard monitors local magnitude and source of COVID-19 vulnerability

Expert groups have coalesced around a roadmap to address the current COVID-19 pandemic centered on social distancing, monitoring case counts and health care capacity, and, eventually, moving to pharmaceutical interventions. However, responsibility for navigating the pandemic response falls largely on state and local officials. To make equitable decisions on allocating resources, caring for vulnerable subpopulations, and implementing local- and state-level interventions, access to current pandemic data and key vulnerabilities at the community level are essential (National Academies of Sciences, Engineering, and Medicine 2020). Although numerous predictive models and interactive monitoring applications have been developed using pandemic-related data sets (Wynants et al. 2020), their capacity to aid in dynamic, community-level decision-making is limited. We developed the interactive COVID-19 Pandemic Vulnerability Index (PVI) Dashboard (https://covid19pvi.niehs.nih.gov/) to address this need by presenting a visual synthesis of dynamic information at the county level to monitor disease trajectories, communicate local vulnerabilities, forecast key outcomes, and guide informed responses.

Marvel SW, House JS, Wheeler M, Song K, Zhou YH, Wright FA, Chiu WA, Rusyn I, Motsinger-Reif A, Reif DM. The COVID-19 Pandemic Vulnerability Index (PVI) Dashboard: Monitoring County-Level Vulnerability Using Visualization, Statistical Modeling, and Machine Learning. *Environ Health Perspect*. 2021 Jan;129(1):17701. doi: 10.1289/EHP8690. Epub 2021 Jan 5. PMID: 33400596; PMCID: PMC7785295.

Exposures Early in Life May Set the Stage for Breast Cancer

Research based on the NIEHS Sister Study suggests that women who were gestated in a pregnancy complicated by pre-eclampsia may be at increased risk for breast cancer. In related work also based on the Sister Study, we found evidence that the risk of breast cancer increases at ages near the age at which an older sister had earlier been diagnosed with breast cancer, even if that onset was late in life. This correlation in the timing of onset suggests that early life shared exposures, perhaps acting jointly with genetic factors, may set a specific risk trajectory for breast cancer.

Von Holle A, O'Brien KM, Sandler DP, Weinberg CR. Evidence for familial clustering in breast cancer age of onset. *Int J Epidemiol*. 2021 Mar 3;50(1):97-104. doi: 10.1093/ije/dyaa201. PMID: 33247915; PMCID: PMC7938508.

Natural sugar can be inhaled as a new treatment for COPD exacerbations

We found that inhaling unfragmented hyaluronan improves lung function in patients suffering from severe exacerbation of chronic obstructive pulmonary disease (COPD). Hyaluronan, a sugar secreted by living tissue that acts as a scaffold for cells, is also used in cosmetics as a skin moisturizer and as a nasal spray to moisturize lung airways. In our patients, hyaluronan shortened the amount of time they stayed in intensive care unit and decreased their number of days in the hospital. The study is also a good example of how examining the impacts of environmental pollution on the lungs can lead to viable treatments. Several years ago, we had

showed that exposure to pollution causes hyaluronan in the lungs to break down into smaller fragments. These fragments irritate lung tissue and activate the immune system, leading to constriction and inflammation of the airways. Inhalation of healthy, unfragmented hyaluronan reduces inflammation by outcompeting the smaller hyaluronan fragments. We applied the same concept in COPD exacerbation and showed that it works.

Galdi F, Pedone C, McGee CA, George M, Rice AB, Hussain SS, Vijaykumar K, Boitet ER, Tearney GJ, McGrath JA, Brown AR, Rowe SM, Incalzi RA, Garantziotis S. Inhaled high molecular weight hyaluronan ameliorates respiratory failure in acute COPD exacerbation: a pilot study. *Respir Res*. 2021 Feb 1;22(1):30. doi: 10.1186/s12931-020-01610-x. PMID: 33517896; PMCID: PMC7847749.

Increased body fat linked to delayed breast development and increased testosterone levels in girls

In the Body Weight and Puberty Study, NIEHS researchers followed 90 pubertal girls over 4 years with serial blood draws for reproductive hormones and breast ultrasounds to determine breast maturation. Total body fat was determined at baseline using dual-energy x-ray absorptiometry, or DXA. Girls with higher body fat had higher blood levels of follicle stimulating hormone, inhibin B, estrone, and androgens, such as testosterone. Girls with higher body fat also underwent menarche (the first menstrual period) earlier but demonstrated delayed breast development compared with girls with less total body fat.

Ortega MT, McGrath JA, Carlson L, Flores Poccia V, Larson G, Douglas C, Sun BZ, Zhao S, Beery B, Vesper HW, Duke L, Botelho JC, Filie AC, Shaw ND. Longitudinal Investigation of Pubertal Milestones and Hormones as a Function of Body Fat in Girls. *J Clin Endocrinol Metab*. 2021 May 13;106(6):1668-1683. doi: 10.1210/clinem/dgab092. PMID: 33630047; PMCID: PMC8118584.

Anti-MDA5 Autoantibodies in Juvenile Dermatomyositis Constitute a Distinct Phenotype

The myositis syndromes are systemic autoimmune diseases with characteristic muscle inflammation and weakness, and organ damage. Patients with idiopathic inflammatory myopathies often have autoantibodies which are specific to their disease, called myositis specific autoantibodies. This study defined the presence of anti-MDA5 autoantibodies in 7.7% of a large cohort of juvenile myositis in North America. Patients with anti-MDA5 autoantibodies had more frequent weight loss, adenopathy, arthritis, interstitial lung disease, and less frequent falling and less severe myositis than other common myositis autoantibody subgroups. Their season of onset differed from patients with anti-synthetase autoantibodies, who had a spring season of diagnosis. In this study, patients with anti-MDA5 autoantibodies has comparable outcomes, but with the ability to discontinue steroids more rapidly, and less frequent flares and more frequent remission.

Mamyrova G, Kishi T, Shi M, Targoff IN, Huber AM, Curiel RV, Miller FW, Rider LG; Childhood Myositis Heterogeneity Collaborative Study Group. Anti-MDA5 autoantibodies associated with juvenile dermatomyositis constitute a distinct phenotype in North America. *Rheumatology (Oxford)*. 2021 Apr 6;60(4):1839-1849. doi: 10.1093/rheumatology/keaa429. PMID: 33140079; PMCID: PMC8023991.

Air pollution and breast cancer linked by new tissue marker
In a population of women without breast cancer who donated normal tissue to the Komen Tissue Bank, we found that residential levels of fine particulate matter was associated with a breast tissue marker that is related to a higher risk of breast cancer. This marker, terminal duct lobular units or TDLUs, is the site where most breast cancers arise. Women who lived in areas of higher air pollution had on average a higher count of TDLUs in their breast tissue. These results suggest that air pollution levels may modify the normal breast tissue characteristics in a way that is associated with a higher risk of developing breast cancer.

Niehoff NM, Keil AP, Jones RR, Fan S, Gierach GL, White AJ. Outdoor air pollution and terminal duct lobular involution of the normal breast. *Breast Cancer Res*. 2020 Sep 24;22(1):100. doi: 10.1186/s13058-020-01339-x. PMID: 32972455; PMCID: PMC7513536.

Improved prediction of breast cancer using DNA methylation
Scientists at NIH have developed a new method to predict breast cancer risk based on DNA methylation. Existing breast cancer prediction methods use inherited genetic variation or questionnaire-based information to estimate risk. The new risk score uses information on blood DNA methylation, a naturally occurring chemical modification to DNA, that changes with age and exposure. In their study, the investigators find that the DNA methylation-based score provides new information about a woman's breast cancer risk not captured by existing measures. They also report that the new DNA methylation-based score can be combined with existing genotype and questionnaire-based models, resulting in substantially improved breast cancer prediction.

Kresovich JK, Xu Z, O'Brien KM, Shi M, Weinberg CR, Sandler DP, Taylor JA. Blood DNA methylation profiles improve breast cancer prediction. *Mol Oncol*. 2021 Aug 19. doi: 10.1002/1878-0261.13087. Epub ahead of print. PMID: 34411412.

Discrimination is Associated with higher Type II Diabetes Risk
Using data from the Sister Study, we investigated the relationship between racial/ethnic discrimination and type 2 diabetes mellitus risk. Among 33,000 White, Black and Hispanic/Latina women, we found that three in four Black women and one in three Hispanic/Latina women reported everyday discrimination. We also found that experiencing major discrimination was marginally associated with higher type II diabetes mellitus risk. Anti-discrimination efforts may help mitigate racial/ethnic disparities in T2DM risk.

Gaston SA, Atere-Roberts J, Ward J, Slopen NB, Forde AT, Sandler DP, Williams DR, Jackson CL. Experiences with Everyday and Major Forms of Racial/Ethnic Discrimination and Type 2 Diabetes Risk among White, Black, and Hispanic/Latina Women: Findings from the Sister Study. *Am J Epidemiol*. 2021 Jul 2:kwab189. doi: 10.1093/aje/kwab189. Epub ahead of print. PMID: 34215871.

Air Emissions from Swine Industrial Livestock Operations and Sleep Health among Residents in Nearby Residential Communities

Air emissions containing, for instance, hydrogen sulfide, ammonia, and particulate matter can contribute to a cascade of biological effects including compromised lung function but also poor mood and distress, which can all influence sleep. To better understand the relationship, we investigated air emissions from swine industrial livestock operations and sleep health among 80 residents in 16 nearby residential, largely African-American communities in North Carolina. We found that nightly swine odor was associated with lower nightly sleep duration and that hydrogen sulfide detection was associated with more sleep awakenings. These findings essentially underscore the importance of emissions reduction and odor abatement as public health goals when designing technology solutions to waste management.

MacNell NS, Jackson CL, Heaney CD. Relation of repeated exposures to air emissions from swine industrial livestock operations to sleep duration and awakenings in nearby residential communities. *Sleep Health*. 2021 Jun 27:S2352-7218(21)00085-1. doi: 10.1016/j.sleh.2021.05.001. Epub ahead of print. PMID: 34193392.

Poor Sleep and Sleep Apnea are Associated with Chronic Kidney Disease

Poor sleep may contribute to chronic kidney disease (CKD), but few studies have investigated the association between multiple objectively measured sleep dimensions and CKD. Using data from the Multi-Ethnic Study of Atherosclerosis Sleep Ancillary Study, we investigated the between sleep dimensions and CKD using in-home polysomnography, wrist actigraphy and a sleep questionnaire. Among the 1895 White, Black, Hispanic/Latino, and Asian participants, we found that very short sleep and sleep apnea associated hypoxia were both associated with a higher prevalence of CKD, which highlights the potential role for novel interventions.

Jackson CL, Umesi C, Gaston SA, Azarbarzin A, Lunyera J, McGrath JA, Jackson Ii WB, Diamantidis CJ, Boulware E, Lutsey PL, Redline S. Multiple, objectively measured sleep dimensions including hypoxic burden and chronic kidney disease: findings from the Multi-Ethnic Study of Atherosclerosis. *Thorax*. 2021 Jul;76(7):704-713. doi: 10.1136/thoraxjnl-2020-214713. Epub 2020 Dec 4. PMID: 33277428; PMCID: PMC8175452.

Translational, Epidemiological, and Patient-Centered Outcomes Research is Necessary to Advance Care for Patients with Central Sleep Apnea

Central sleep apnea (CSA) is common among patients with heart failure and has been strongly linked to adverse outcomes, so it is important to identify and prioritize areas for future research regarding CSA in heart failure. We identified 11 specific research priorities in several key areas: control of breathing and pathophysiology leading to CSA, variability across individuals and over time, techniques to examine CSA pathogenesis and outcomes, impact of device and pharmacological treatment, and, implementing CSA treatment for all individuals. Given the increasing prevalence of heart failure and its burden on individuals, society, and the healthcare system, targeted research to improve knowledge of CSA pathogenesis and treatment is a priority.

Orr JE, Ayappa I, Eckert DJ, Feldman JL, Jackson CL, Javaheri S, Khayat RN, Martin JL, Mehra R, Naughton MT, Randerath WJ, Sands SA, Somers VK, Badr MS. Research Priorities for Patients with Heart Failure and Central Sleep Apnea. An Official American Thoracic Society Research Statement. *Am J Respir Crit Care Med*. 2021 Mar 15;203(6):e11-e24. doi: 10.1164/rccm.202101-0190ST. PMID: 33719931; PMCID: PMC7958519.

Exposome approach to Advance Health Equity

This commentary was developed as a result of a virtual workshop hosted by the National Academies of Sciences, Engineering, and Medicine in June 2020 focused on integrating the science of aging and environmental health research. After attending a workshop hosted by the National Academies of Science, Engineering, and Medicine, we deduced that the utility of environmental aging biomarkers would be greatly reduced if they are developed without considering broader societal factors— like structural racism— that impinge on racial health equity. So, to advance health equity, a "compound" exposome approach should be widely adopted in this field of research. This should include: broadening the exposure-disease pathway across more domains, including the social exposome and neighborhood factors; increasing recruitment and retention of racially diverse study populations and researchers; and improving the use and interpretation of race through the publication and dissemination process.

Nwanaji-Enwerem JC, Jackson CL, Ottinger MA, Cardenas A, James KA, Malecki KMC, Chen JC, Geller AM, Mitchell UA. Adopting a "Compound" Exposome Approach in Environmental Aging Biomarker Research: A Call to Action for Advancing Racial Health Equity. *Environ Health Perspect*. 2021 Apr;129(4):45001. doi: 10.1289/EHP8392. Epub 2021 Apr 6. PMID: 33822649; PMCID: PMC8043128.

Chromatin remodeler shapes the fate of stem cells

NIEHS researchers have revealed how a chromatin remodeler called INO80 controls the fate of stem cells. INO80 can regulate gene activity by altering the structure of chromatin, which is a substance consisting of DNA and proteins such as histones. The researchers showed that INO80 enhances the binding of a histone protein called H2A.Z to key DNA sequences during stem cell fate transitions. This event triggers the modification of other histones and decreases the activity of nearby genes. Because INO80 and H2A.Z have been heavily implicated in development and disease, this molecular pathway may play a similar role in controlling cell fate across diverse biological contexts.

Yu H, Wang J, Lackford B, Bennett B, Li JL, Hu G. INO80 promotes H2A.Z occupancy to regulate cell fate transition in pluripotent stem cells. *Nucleic Acids Res*. 2021 Jul 9;49(12):6739-6755. doi: 10.1093/nar/gkab476. PMID: 34139016; PMCID: PMC8266661.

Human ancestry affects your cell's reprogramming to pluripotency

Human induced pluripotent stem cells (iPSCs) are pluripotent cells that are derived from adult somatic cells. iPSCs can both self-renew and be differentiated into other cell-types, enabling the generation of unique and personalized disease models. IRP researchers, led by Trevor K. Archer, Ph.D., demonstrate that genetic heterogeneity is associated with iPSC reprogramming efficiency

as well as other dynamic biological processes, including breast cancer. The findings provide insights intro ancestry-dependent regulation of cell fate and reprogramming. Importantly, the diversity of their cohort allowed for the identification of a greater number of associated genes than would be achieved using single ancestries, highlighting the value of incorporating ancestrally diverse research models to understand and promote human health.

Bisogno LS, Yang J, Bennett BD, Ward JM, Mackey LC, Annab LA, Bushel PR, Singhal S, Schurman SH, Byun JS, Nápoles AM, Pérez-Stable EJ, Fargo DC, Gardner K, Archer TK. Ancestry-dependent gene expression correlates with reprogramming to pluripotency and multiple dynamic biological processes. *Sci Adv*. 2020 Nov 20;6(47):eabc3851. doi: 10.1126/sciadv.abc3851. PMID: 33219026; PMCID: PMC7679169.

Making an egg: bridges are important

A collaboration between Dr. Diana Laird's lab from USCF and NIEHS researchers found that the bridges connecting the cells in the ovary are important in early oocyte development. They used genetic, genomic, and 3-dimensional imaging tools to show that the bridges coordinate and buffer the transition from primordial germ cells to meiotic germ cells through dilution of regulatory factors.

Soygur B, Jaszczak RG, Fries A, Nguyen DH, Malki S, Hu G, Demir N, Arora R, Laird DJ. Intercellular bridges coordinate the transition from pluripotency to meiosis in mouse fetal oocytes. *Sci Adv*. 2021 Apr 7;7(15):eabc6747. doi: 10.1126/sciadv.abc6747. PMID: 33827806; PMCID: PMC8026130.

Suicide of the defective clones

A collaboration between Dr. Diana Laird's lab from USCF and NIEHS researchers found that in fetal testis, errors in germ cells lead to programmed cell death, leaving only survival of only the high-quality gametes. Their findings explained why many germ cells are eliminated and how germline integrity is maintained during development.

Nguyen DH, Soygur B, Peng SP, Malki S, Hu G, Laird DJ. Apoptosis in the fetal testis eliminates developmentally defective germ cell clones. *Nat Cell Biol*. 2020 Dec;22(12):1423-1435. doi: 10.1038/s41556-020-00603-8. Epub 2020 Nov 16. PMID: 33199844; PMCID: PMC8389187.

A protein from mosquitos that inhibits viral infections

The mosquito protein AEG12 strongly inhibits the family of viruses that cause yellow fever, dengue, West Nile, and Zika and weakly inhibits coronaviruses. AEG12 works by destabilizing the viral envelope, breaking its protective covering. Although the protein does not affect viruses that do not have an envelope, the findings could lead to therapeutics against viruses that affect millions of people around the world.

Foo ACY, Thompson PM, Chen SH, Jadi R, Lupo B, DeRose EF, Arora S, Placentra VC, Premkumar L, Perera L, Pedersen LC, Martin N, Mueller GA. The mosquito protein AEG12 displays both cytolytic and antiviral properties via a common lipid transfer

mechanism. *Proc Natl Acad Sci U S A*. 2021 Mar 16;118(11):e2019251118. doi: 10.1073/pnas.2019251118. PMID: 33688047; PMCID: PMC7980415.

Deciphering the mechanism of heparan sulfate recognition by sulfotransferases to improve synthesis of pharmacological tools and potential therapeutics.
Current techniques to synthesize heparan sulfates for pharmacological tools take advantage of natural proteins to generate precise sulfation modifications on heparan sulfate chains. There are 7 isoforms of 3-O sulfotransferases (3OST), some of which have different specificities. For example, 3OST-1 produces anticoagulant heparan sulfate while 3OST-3 can be used to produce HS that blocks herpes simplex one viral entry. In this study, we solved crystal structures of 3OST-3 with heparan sulfate and identified specificity differences between 3OST-1 and also discovered a mode of substrate/product inhibition, the knowledge of which should improve production of heparan sulfate biological tools and therapeutic design.

Wander R, Kaminski AM, Xu Y, Pagadala V, Krahn JM, Pham TQ, Liu J, Pedersen LC. Deciphering the substrate recognition mechanisms of the heparan sulfate 3-O-sulfotransferase-3. *RSC Chem Biol*. 2021 May 28;2(4):1239-1248. doi: 10.1039/d1cb00079a. PMID: 34458837; PMCID: PMC8341778.

Polymerase γ efficiently replicates through many natural template barriers but stalls at a specific G-rich sequence
NIEHS intramural investigators have determined that most DNA secondary structures are not an impediment to mitochondrial DNA replication. However, they did discover that a G-rich quadruplex structure at the Heavy Strand Promoter for transcription causes the mitochondrial replisome to stall. This site is also an initiation site for a large mitochondrial DNA deletion of 3985 base pairs that is identified in several mitochondrial patients with progressive external ophthalmoplegia. The presence of this deletion in humans correlates with UV exposure, and the NIEHS researchers found that efficiency of polymerase γ DNA synthesis is reduced after this G-quadruplex is exposed to Ultraviolet light.

Sullivan ED, Longley MJ, Copeland WC. Polymerase γ efficiently replicates through many natural template barriers but stalls at the HSP1 quadruplex. *J Biol Chem*. 2020 Dec 18;295(51):17802-17815. doi: 10.1074/jbc.RA120.015390. PMID: 33454015; PMCID: PMC7762954.

Even skin shielded from sun shows genome-wide DNA changes from UV light in white and in Black individuals
Paper describes accurate measurements of the various types of somatic genome changes that we found in skin fibroblasts and melanocytes from 21 donors ranging in ages from 25 to 79 years, which allowed to distinguish age related from age independent changes. The cohort contains both white and African American donors, allowing an estimation of the impacts of skin color on mutagenesis. The study revealed the complete spectrum and determined the range of somatic genome changes and their etiologies in healthy human skin fibroblasts and melanocytes and highlighted molecular mechanisms underlying these changes. This introduces a base line for defining disease levels of genome instability in skin.

Saini N, Giacobone CK, Klimczak LJ, Papas BN, Burkholder AB, Li JL, Fargo DC, Bai R, Gerrish K, Innes CL, Schurman SH, Gordenin DA. UV-exposure, endogenous DNA damage, and DNA replication errors shape the spectra of genome changes in human skin. *PLoS Genet*. 2021 Jan 14;17(1):e1009302. doi: 10.1371/journal.pgen.1009302. PMID: 33444353; PMCID: PMC7808690.

LIG1 syndrome mutations remodel a cooperative network of ligand binding interactions to compromise ligation efficiency

Human DNA ligase I (LIG1) is the main replicative ligase and it also seals DNA breaks to complete DNA repair and recombination pathways. Immune compromised patients harbor hypomorphic LIG1 alleles that compromise LIG1 activity through poorly defined mechanisms. To understand the molecular basis of LIG1 syndrome mutations, we determined high resolution X-ray structures and performed systematic biochemical characterization of LIG1 mutations. Our results unveil a network of plastic DNA-LIG1 interactions that connect DNA substrate engagement with productive binding of Mg2+ cofactors for catalysis, and suggest that disease pathology of LIG1 syndrome could be modulated by Mg2+ levels.

Jurkiw TJ, Tumbale PP, Schellenberg MJ, Cunningham-Rundles C, Williams RS, O'Brien PJ. LIG1 syndrome mutations remodel a cooperative network of ligand binding interactions to compromise ligation efficiency. *Nucleic Acids Res*. 2021 Feb 22;49(3):1619-1630. doi: 10.1093/nar/gkaa1297. PMID: 33444456; PMCID: PMC7897520.

Extrinsic Proofreading ensures DNA is replicated with incredibly high accuracy

The most accurate process occurring in biology is the replication of its genetic material, DNA. This high accuracy prevents mutations in DNA that can cause diseases in humans. We have demonstrated that one of the major processes responsible for the high fidelity of replication is the ability of one of the three major replicases to remove mismatches base pairs made by it or its partners. This occurs by binding the mismatched base directly to DNA polymerase delta's exonuclease active site and removing the mismatch to prevent mutations. Failure of such "extrinsic" proofreading of replication errors may lead to the mutations that cause diseases such as cancer.

Zhou Z, Lujan SA and Kunkel TA. Extrinsic proofreading by DNA polymerase d contributes to replication fidelity in yeast. *Nature Structural Molecular Biology*, 2021 in press.

How cells achieve high accuracy of DNA replication

The accuracy of DNA replication is a crucial factor for the mechanisms by which cells and organisms produce mutations. To gain understanding in this area we are studying the accuracy (fidelity) of DNA replication in the bacterium Escherichia coli, which is a useful model system for these questions. The bacterial chromosome is replicated by the DNA polymerase III holoenzyme (HE), whose accuracy we have studies in detail. In particular, we have discovered that the two DNA strands are not replicated with the same accuracy. Specifically, the lagging strand is replicated more accurately than the leading strand. We have also deciphered the entire genome sequence of an E. coli strain important for biotechnical applications. We have also

investigated the structures of several dGTPase enzymes important for DNA replication accuracy by means of their effect on the DNA precursor concentrations.

Bouvette J, Liu HF, Du X, Zhou Y, Sikkema AP, da Fonseca Rezende E Mello J, Klemm BP, Huang R, Schaaper RM, Borgnia MJ, Bartesaghi A. Beam image-shift accelerated data acquisition for near-atomic resolution single-particle cryo-electron tomography. *Nat Commun*. 2021 Mar 30;12(1):1957. doi: 10.1038/s41467-021-22251-8. PMID: 33785757; PMCID: PMC8009872.

Bhawsinghka N, Glenn KF, Schaaper RM. Complete Genome Sequence of Escherichia coli BL21-AI. *Microbiol Resour Announc*. 2020 Mar 5;9(10):e00009-20. doi: 10.1128/MRA.00009-20. PMID: 32139577; PMCID: PMC7171200.

Reversal of drug-resistance during the treatment of human cancers induced by a unique nitric oxide donor, NCX-4040

Development of resistance to chemotherapeutics during the treatment of human cancers is a serious problem in the clinic, resulting in a poor treatment outcome and survival. Overexpression of ABC efflux proteins (e.g., P-gp/ABCB1, BCRP/ABCG2 and MRP/ABCC1) on the tumor cell membrane is implicated to be one of the main mechanisms for this clinical resistance. Our recent studies indicate that nitric oxide (NO), inhibits ATPase functions of ABC transporters, resulting in reversal of resistance to various anticancer drugs. In this study we have found that nitric oxide and/or active metabolite(s) generated from NCX4040, a nitric oxide donor, inhibited ABC transporter activities by inhibiting their ATPase functions causing reversal of both adriamycin and topotecan resistance in human MDR tumor cells and significantly enhanced drug accumulations in MDR tumor cells. Our studies strongly suggest that tumor specific nitric oxide donors that deliver high amounts of nitric oxide and reactive species to clinical resistant tumors may be extremely useful in treating human tumors overexpressing ABC transporters, including cancer stem cells.

Sinha BK, Perera L, Cannon RE. NCX-4040, a Unique Nitric Oxide Donor, Induces Reversal of Drug-Resistance in Both ABCB1- and ABCG2-Expressing Multidrug Human Cancer Cells. *Cancers (Basel)*. 2021 Apr 2;13(7):1680. doi: 10.3390/cancers13071680. PMID: 33918289; PMCID: PMC8038154.

Identification of a new regulator associated of intraocular pressure and human glaucoma

Chronically elevated intraocular pressure (IOP) is the major risk factor of glaucoma, a leading cause of blindness. Dysfunction of the ocular structure, referred to as trabecular meshwork (TM), which controls the outflow of fluid from the anterior chamber, is the major cause of elevated IOP. We showed that deficiency in the transcription factor GLIS1 causes progressive degeneration of the TM, leading to inefficient drainage from the anterior chamber and elevated IOP. We further established an association between changes in the GLIS1 gene and glaucoma in humans. Our study identifies GLIS1 as a critical regulator of TM maintenance, fluid drainage, and IOP, and a role in human glaucoma. GLIS1 regulates trabecular meshwork function and intraocular pressure and is associated with glaucoma in humans

Nair KS, Srivastava C, Brown RV, Koli S, Choquet H, Kang HS, Kuo YM, Grimm SA, Sutherland C, Badea A, Johnson GA, Zhao Y, Yin J, Okamoto K, Clark G, Borrás T, Zode G, Kizhatil K, Chakrabarti S, John SWM, Jorgenson E, Jetten AM. GLIS1 regulates trabecular meshwork function and intraocular pressure and is associated with glaucoma in humans. *Nat Commun*. 2021 Aug 12;12(1):4877. doi: 10.1038/s41467-021-25181-7. PMID: 34385434; PMCID: PMC8361148.

Deficient quality control of mitochondria causes autoimmune disease

Mitochondrial abnormalities have been noted in lupus, but the causes and consequences are obscure. Polymorphisms in IRGM and other genes that regulate autophagy, a process whereby cells clear damaged mitochondria and other organelles, have been implicated in autoimmune disease. In a paper published in Nature Immunology, NIEHS Investigators report that mice deleted for Irgm1, the homologous gene for human IRGM, have autoimmune disease caused by uncontrolled type I interferon. The Investigators show that this occurs due to defective autophagic clearance of mitochondria, which leads to activation of the innate immune system by uncleared mitochondrial DNA. Taken together, this report identifies failure of mitochondrial quality control as a fundamental cause of autoimmune disease, and outlines the mechanisms by which this occurs.

Rai P, Janardhan KS, Meacham J, Madenspacher JH, Lin WC, Karmaus PWF, Martinez J, Li QZ, Yan M, Zeng J, Grinstaff MW, Shirihai OS, Taylor GA, Fessler MB. IRGM1 links mitochondrial quality control to autoimmunity. *Nat Immunol*. 2021 Mar;22(3):312-321. doi: 10.1038/s41590-020-00859-0. Epub 2021 Jan 28. PMID: 33510463; PMCID: PMC7906953.

Breaking the feedback loop of allergic asthma

NIEHS researchers and their collaborators at NIDDK have identified target molecules that increase the severity of inflammation in an animal model of asthma. The scientists found that a nucleotide sugar, uridine diphosphate-glucose (UDP-G), is released into the airway upon allergen inhalation. By binding to its receptor, P2Y14R, on eosinophils, UDP-G promotes the recruitment of those cells to the airway, which in turn promotes the release of more UDP-G. Antagonists of P2Y14R broke this positive feedback loop, thereby diminishing inflammation and airway hyperresponsiveness, two salient features of asthma. These findings suggest that antagonists of P2Y14R might also be an effective strategy to control allergy-induced asthma in humans.

Karcz TP, Whitehead GS, Nakano K, Nakano H, Grimm SA, Williams JG, Deterding LJ, Jacobson KA, Cook DN. UDP-glucose and P2Y14 receptor amplify allergen-induced airway eosinophilia. *J Clin Invest*. 2021 Apr 1;131(7):e140709. doi: 10.1172/JCI140709. PMID: 33792561; PMCID: PMC8011887.

Albuminuria is a Predictor of Respiratory Disease Mortality

Chronic lower respiratory disease (CLRD) as well as influenza virus infection and pneumonia are major public health concerns. CLRD affects 1 in 12 people worldwide and has progressed from the fourth to the third leading cause of death over the past two decades. Albuminuria is a well-known marker of renal impairment but can also indicate endothelial dysfunction reflecting

systemic vascular damage and has been shown to co-occur with increased capillary permeability. Recent evidence suggests that endothelial dysfunction plays an important role in the pathogenesis of COPD and severe influenza infection. This nationally representative study suggests for the first time that elevated albuminuria is associated with subsequent mortality from CLRD and from influenza and pneumonia, independent of diabetes or chronic kidney disease. After adjusting for covariates, including all comorbidities, a 10-fold increase in albuminuria was associated with an 88% higher mortality risk from CLRD. Likewise, a 10-fold increase in albuminuria was associated with a 103% increase in mortality risk from influenza and pneumonia.

Mendy A, Salo PM, Wilkerson J, Feinstein L, Fessler MB, Thorne PS, Zeldin DC. Albuminuria as a Predictor of Mortality from Chronic Lower Respiratory Disease and from Influenza and Pneumonia. *Ann Am Thorac Soc*. 2021 May 12. doi: 10.1513/AnnalsATS.202009-1226RL. Epub ahead of print. PMID: 33979561.

Role of EPHX3 in Skin Barrier Function

The mammalian epoxide hydrolase 3 (EPHX3) is known to efficiently hydrolyze the linoleate epoxides 9,10-epoxyoctadecamonoenoic acid (EpOME) and epoxyalcohol 9R,10R-trans-epoxy-11E-13R-hydroxy-octadecenoate to corresponding diols and triols in vitro, respectively. We examined the physiological relevance of EPHX3 to hydrolysis of both substrates in vivo. Ephx3−/− mice show no deficiency in EpOME-derived plasma diols, discounting a role for EPHX3 in their formation, whereas epoxyalcohol-derived triols esterified in acylceramides of the epidermal 12R-lipoxygenase pathway are reduced. Although the Ephx3−/− pups appear normal, measurements of transepidermal water loss detected a modest increase compared with the wildtype or heterozygote mice, reflecting a skin barrier impairment that was not evident in the knockouts of EPHX1/microsomal epoxide hydrolase EPHX2/soluble epoxide hydrolase. This barrier phenotype in the Ephx3−/− pups was associated with a significant decrease in the covalently bound ceramides in the epidermis, indicating a corresponding structural impairment in the integrity of the water barrier. Our findings also identify a functional role for EPHX3 in transformation of a naturally esterified epoxide substrate, pointing to its potential contribution in other tissues.

Edin ML, Yamanashi H, Boeglin WE, Graves JP, DeGraff LM, Lih FB, Zeldin DC, Brash AR. Epoxide hydrolase 3 (Ephx3) gene disruption reduces ceramide linoleate epoxide hydrolysis and impairs skin barrier function. *J Biol Chem*. 2021 Jan-Jun;296:100198. doi: 10.1074/jbc.RA120.016570. Epub 2021 Jan 21. PMID: 33334892; PMCID: PMC7948417.

Rescue of synaptic plasticity in Rett syndrome model mice

Perineuronal nets (PNNs), a specialized form of extracellular matrix, are abnormal in the human brain of Rett syndrome (RTT). We previously reported that PNNs function to restrict synaptic plasticity in hippocampal area CA2, which is unusually resistant to long-term potentiation (LTP) and has been linked to social learning in mice. Here we identified a novel window of plasticity in CA2 that is disrupted in a mouse model of RTT (Mecp2-null), where we found PNNs to develop precociously and remain elevated. Further, we provided evidence that LTP could be induced at

CA2 synapses after degrading PNNs in Mecp2-null hippocampus and that CA2 PNNs are negatively regulated by neuronal activity.

Carstens KE, Lustberg DJ, Shaughnessy EK, McCann KE, Alexander GM, Dudek SM. Perineuronal net degradation rescues CA2 plasticity in a mouse model of Rett syndrome. *J Clin Invest*. 2021 Aug 16;131(16):e137221. doi: 10.1172/JCI137221. PMID: 34228646; PMCID: PMC8363283.

Scientists create new genetically encoded fluorescent sensors for measuring dopamine levels in the brain

Researchers at the NIEHS and their collaborators at NYU and Peking University created a series of genetically encoded fluorescent sensors for measuring dopamine levels in the brain of live animals. Aberrant signaling of dopamine, a neurotransmitter involved in motor control, learning and memory, and emotion control, has been linked to a host of psychiatric and neurological disorders, such as schizophrenia and Parkinson's disease. The newly developed sensors will help scientists better understand these conditions in animal models.

Sun F, Zhou J, Dai B, Qian T, Zeng J, Li X, Zhuo Y, Zhang Y, Wang Y, Qian C, Tan K, Feng J, Dong H, Lin D, Cui G, Li Y. Next-generation GRAB sensors for monitoring dopaminergic activity in vivo. *Nat Methods*. 2020 Nov;17(11):1156-1166. doi: 10.1038/s41592-020-00981-9. Epub 2020 Oct 21. PMID: 33087905; PMCID: PMC7648260.

NIEHS researchers identify cells involved in development of the external genitalia

The Reproductive Developmental Biology Group at NIEHS found that the external genitalia of male and female mice begin exhibiting different cell populations early in fetal development. We made the discovery by examining the cells that give rise to the male penis and female clitoris. We also found that the genes that respond to androgen hormones, such as testosterone, in males and estrogens in females undergo changes that are sex specific. Identifying different cell populations within the developing penis may help scientists find ways to understand the causes of some external genitalia birth defects that occur in human males. This research was published in Proceedings for the National Academy of Sciences in 2021.

Amato CM, Yao HH. Developmental and sexual dimorphic atlas of the prenatal mouse external genitalia at the single-cell level. *Proc Natl Acad Sci U S A*. 2021 Jun 22;118(25):e2103856118. doi: 10.1073/pnas.2103856118. Epub 2021 Jun 21. PMID: 34155146; PMCID: PMC8237666.

Appropriate Timing of Birth is Dependent on the Isoforms of the Progesterone Receptor

Preterm birth occurs in 10% of pregnancies and imparts a significant health risk to the Moher and child. The progesterone receptor regulates all aspects of pregnancy including the ability of the uterine muscles, the myometrium to relax while the fetus grows and contract during birth. The receptor consists of two isoforms, the shorter A isoform and the longer B isoform. Mice where generated which express either the A of B isoform in the myometrium. This results show that these isoforms had opposite actions. With the B isoform preventing muscle contraction while the A isoform promoted contraction. This is in vivo proof the ratio of thee two isoforms

are critical in ensuring fetal birth occurs at the appropriate time and may add insight to the development of tools to prevent preterm birth

Peavey MC, Wu SP, Li R, Liu J, Emery OM, Wang T, Zhou L, Wetendorf M, Yallampalli C, Gibbons WE, Lydon JP, DeMayo FJ. Progesterone receptor isoform B regulates the Oxtr-Plcl2-Trpc3 pathway to suppress uterine contractility. *Proc Natl Acad Sci U S A*. 2021 Mar 16;118(11):e2011643118. doi: 10.1073/pnas.2011643118. PMID: 33707208; PMCID: PMC7980420.

Identification of a Kinase that Regulates Endometrial Health

With no lysine kinase, WNK1, was shown to be expressed in the endometrium of women and mice. Ablation of WNK1 resulted in mice with uterine disease, endometrial hypoplasia and adenomyosis as a well as reduced fertility. The reduced fertility was due to alteration in the timing of the uterus achieving the ability to allow appropriate embryo implantation. This Kinase is a potential diagnostic and therapeutic target to treat uterine diseases and recurrent pregnancy loss.

Chi RA, Wang T, Huang CL, Wu SP, Young SL, Lydon JP, DeMayo FJ. WNK1 regulates uterine homeostasis and its ability to support pregnancy. *JCI Insight*. 2020 Nov 19;5(22):e141832. doi: 10.1172/jci.insight.141832. PMID: 33048843; PMCID: PMC7710275.

Altered Progesterone Receptor Expression Promotes Hormone Dependent Ovarian Cancer.

Progesterone acting through it's receptor, the progesterone receptor regulate s many female reproductive functions including ovulation . Mice where generated with deregulate expression of the progesterone receptor . These mice developed ovarian tumors. Analysis of the gene expression signatures of these tumors revealed pathways in common with human ovarian cancers. This mouse model will serve a means of identifying the role of hormone signaling in ovarian cancer.

Wetendorf M, Li R, Wu SP, Liu J, Creighton CJ, Wang T, Janardhan KS, Willson CJ, Lanz RB, Murphy BD, Lydon JP, DeMayo FJ. Constitutive expression of progesterone receptor isoforms promotes the development of hormone-dependent ovarian neoplasms. *Sci Signal*. 2020 Oct 6;13(652):eaaz9646. doi: 10.1126/scisignal.aaz9646. PMID: 33023986.

Specificity and Dynamics of a SARS-CoV-2 Nuclease

SARS-CoV-2 is the virus responsible for the current Covid-19 global pandemic which has infected millions worldwide. Nsp15 is a viral endoribonuclease found in all coronaviruses that processes viral RNA to prevent detection by the host immune system. Nsp15 is a promising anti-viral target, however how it cuts RNA is poorly understood. Through the combination of cryo-EM, mass-spectrometry, biochemistry, and molecular dynamics the Stanley Lab determined how Nsp15 recognizes and cleavages viral RNA. The Nsp15 active contains several conserved residues important for uridine specificity and catalysis.

Pillon MC, Frazier MN, Dillard LB, Williams JG, Kocaman S, Krahn JM, Perera L, Hayne CK, Gordon J, Stewart ZD, Sobhany M, Deterding LJ, Hsu AL, Dandey VP, Borgnia MJ, Stanley RE. Cryo-EM structures of the SARS-CoV-2 endoribonuclease Nsp15 reveal insight into nuclease specificity and dynamics. *Nat Commun*. 2021 Jan 27;12(1):636. doi: 10.1038/s41467-020-20608-z. PMID: 33504779; PMCID: PMC7840905.

SARS-CoV-2 Nsp15 is Mad for U

Nsp15 is a viral endoribonuclease from SARS-CoV2 that specifically cuts viral RNA 3' of uridines. Cleavage of the viral RNA by Nsp15 prevents the accumulation of dsRNA and blocks activation of host immune sensors. Aside from its specificity for cleaving uridines, it was unknown if Nsp15 has any additional substrate preferences. The Stanley Lab determined atomic resolution structures of Nsp15 bound to RNA in pre and post cleavage states. The structures along with a series of biochemical assays revealed the molecular details of how Nsp15 recognizes viral RNA and will hopefully aid in the design of urgently needed anti-viral therapeutics.

Frazier MN, Dillard LB, Krahn JM, Perera L, Williams JG, Wilson IM, Stewart ZD, Pillon MC, Deterding LJ, Borgnia MJ, Stanley RE. Characterization of SARS2 Nsp15 nuclease activity reveals it's mad about U. *Nucleic Acids Res*. 2021 Aug 17:gkab719. doi: 10.1093/nar/gkab719. Epub ahead of print. PMID: 34403466.

A single metabolic enzyme supervises cancer cell proliferation

We have uncovered the detailed mechanism by which a single metabolic enzyme, PPIP5K, can directly regulate multiplication of tumor cells. The study helps to understand the metabolic reprogramming required for multiplication of tumor cells and identifies new potential targets for cancer treatment.

Gu C, Liu J, Liu X, Zhang H, Luo J, Wang H, Locasale JW, Shears SB. Metabolic supervision by PPIP5K, an inositol pyrophosphate kinase/phosphatase, controls proliferation of the HCT116 tumor cell line. *Proc Natl Acad Sci U S A*. 2021 Mar 9;118(10):e2020187118. doi: 10.1073/pnas.2020187118. PMID: 33649228; PMCID: PMC7958180.

Targeting a calcium channel opens up new approach for development of immunosuppressants

Ca2+ entry through Orai1 channels activates the NFAT transcription factors, which increase expression of pro-inflammatory cytokines. Here, we show that NFAT1 is tethered directly to the scaffolding protein AKAP79 (A-kinase anchoring protein 79) which, in turn, associates with a stretch of amino acids on the N-terminus of the channel. Interfering with Orai1-AKAP79 interaction suppresses cytokine production, leaving other Ca2+ channel functions intact. Our results reveal the mechanistic basis for how a widely expressed Ca2+ channel is able to activate a vital transcription pathway and identify an approach for generation of immunosuppressant drugs.

Kar P, Lin YP, Bhardwaj R, Tucker CJ, Bird GS, Hediger MA, Monico C, Amin N, Parekh AB. The N terminus of Orai1 couples to the AKAP79 signaling complex to drive NFAT1 activation by local Ca2+ entry. *Proc Natl Acad Sci U S A*. 2021 May

11;118(19):e2012908118. doi: 10.1073/pnas.2012908118. PMID: 33941685; PMCID: PMC8126794.

Skin cancer in mice is prevented by increased expression of an anti-inflammatory protein.
Tristetraprolin or TTP is a naturally occurring anti-inflammatory protein that is abnormally regulated in many human cancers. Using a mouse model of chemically-induced skin cancer, we found that the absence of TTP greatly increased the cancer development, whereas overexpression of TTP largely prevented its development. These effects of TTP appeared to be mediated by both pro-inflammatory cytokine and oncogenic pathways, and appeared to reflect TTP's activity in one type of skin cells, the keratinocyte. We concluded that TTP expression in these and other epidermal cells played a major role in the control of skin tumorigenesis.

Assabban A, Dubois-Vedrenne I, Van Maele L, Salcedo R, Snyder BL, Zhou L, Azouz A, de Toeuf B, Lapouge G, La C, Melchior M, Nguyen M, Thomas S, Wu SF, Hu W, Kruys V, Blanpain C, Trinchieri G, Gueydan C, Blackshear PJ, Goriely S. Tristetraprolin expression by keratinocytes protects against skin carcinogenesis. *JCI Insight*. 2021 Mar 8;6(5):e140669. doi: 10.1172/jci.insight.140669. PMID: 33497366; PMCID: PMC8021119.

A mouse model of human autoimmune eye disease is prevented by increased expression of an anti-inflammatory protein.
Non-infectious uveitis is a common cause of blindness in man, and is thought to be mediated by autoimmune and inflammatory reactions within the eye. Pro-inflammatory cytokines play major roles in these processes. We tested whether mice that overexpress tristetraprolin (TTP), an endogenous anti-inflammatory protein that regulates cyokine levels, were protected against a model of autoimmune uveitis. Mice expressing both mutant alleles, resulting in the highest levels of TTP, were completely protected against disease development, whereas mice expressing a single allele were partially protected. These observations show that elevated levels of TTP throughout the body can inhibit the pathogenic processes involved in this model of autoimmune uveitis, and suggest the possible use of TTP-based treatments in humans with related conditions.

Xu B, Tang J, Lyu C, Wandu WS, Stumpo DJ, Mattapallil MJ, Horai R, Gery I, Blackshear PJ, Caspi RR. Regulated Tristetraprolin Overexpression Dampens the Development and Pathogenesis of Experimental Autoimmune Uveitis. *Front Immunol*. 2021 Jan 25;11:583510. doi: 10.3389/fimmu.2020.583510. PMID: 33569048; PMCID: PMC7868398.

Increased expression of an anti-inflammatory protein prevents precancerous stomach changes in a mouse model.
In the stomach, inflammation can lead to gastritis and, eventually, stomach cancer, but the mechanisms that mediate this transition are not known. Using a genetically modified mouse that overexpresses an endogenous anti-inflammatory protein, tristetraprolin or TTP, we examined whether TTP could protect the stomach from the gastritis and metaplasia that results from removal of the adrenal glands. TTP overexpressing mice were completely protected from this form of gastric inflammation and metaplasia, presumably through TTP's effects to dampen pro-inflammatory cytokine production from immune cells. Our results demonstrate that TTP exerts

broad anti-inflammatory effects in the stomach, and suggest that increasing TTP expression might be a therapeutic possibility in the treatment of chronic stomach inflammation leading to cancer.

Busada JT, Khadka S, Peterson KN, Druffner SR, Stumpo DJ, Zhou L, Oakley RH, Cidlowski JA, Blackshear PJ. Tristetraprolin prevents gastric metaplasia in mice by suppressing pathogenic inflammation. *Cell Mol Gastroenterol Hepatol*. 2021 Aug 3:S2352-345X(21)00161-2. doi: 10.1016/j.jcmgh.2021.07.015. Epub ahead of print. PMID: 34358715.

Glucocorticoids and androgens protect the stomach from inflammatory disease
Our Laboratory has discovered a novel role for both glucocorticoid and androgens in the prevention of gastric metaplasia, a precursor to stomach cancer, the anti-inflammatory actions of both of these natural steroids is mediated by suppression of group 2 innate lymphoid cell activation.

Busada JT, Peterson KN, Khadka S, Xu X, Oakley RH, Cook DN, Cidlowski JA. Glucocorticoids and Androgens Protect From Gastric Metaplasia by Suppressing Group 2 Innate Lymphoid Cell Activation. *Gastroenterology*. 2021 Aug;161(2):637-652.e4. doi: 10.1053/j.gastro.2021.04.075. Epub 2021 May 7. PMID: 33971182; PMCID: PMC8328958.

Stress hormone receptors prevent neurodegeneration of the mouse hippocampus
Stress is often associated with numerous human pathologies including cognition impairments and psychiatric disorders. Glucocorticoids and mineralocorticoids are primary stress hormones that regulate brain function by activating the glucocorticoid (GR) and mineralocorticoid receptors (MR). Unexpectedly, we have discovered that mice lacking both these receptors in the brain, but not their single knockout counterparts, show profound neurodegeneration of the hippocampus. These findings demonstrate that combinatorial actions of GR and MR are essential for preserving hippocampal neurons and maintaining hippocampal health.

Oakley RH, Whirledge SD, Petrillo MG, Riddick NV, Xu X, Moy SS, Cidlowski JA. Combinatorial actions of glucocorticoid and mineralocorticoid stress hormone receptors are required for preventing neurodegeneration of the mouse hippocampus. *Neurobiol Stress*. 2021 Jul 21;15:100369. doi: 10.1016/j.ynstr.2021.100369. PMID: 34368410; PMCID: PMC8326231.

An unusual modification of histone is crucial for early embryonic development
Histone crotonylation is a newly identified histone modification that is derived from crotonyl-CoA, an intermediate metabolite during oxidation of fatty acids and amino acids. Despite the fact histone crotonylation is as widespread as histone acetylation, physiological functions associated with this unique histone modification remain almost completely unknown. In a recent study, we showed that histone crotonylation is crucial for early differentiation of endoderm, one of the three primary germ layers that gives rise to endodermal organs such as lung, liver, stomach, intestine, colon, pancreas, bladder and thyroid. We demonstrate that key metabolic enzymes that produce crotonyl-CoA are specifically induced in endodermal cells during differentiation of human

embryonic stem cells (hESCs) in vitro and in mouse embryos, where they function to increase histone crotonylation and enhance endodermal gene expression. Consistently, chemical enhancement of histone crotonylation promotes endoderm differentiation of hESCs, whereas deletion of crotonyl-CoA producing enzymes reduces histone crotonylation and impairs meso/endoderm differentiation in vitro and in vivo. Our study uncovers a histone crotonylation-mediated mechanism that promotes endodermal commitment of pluripotent stem cells, which may have important implications in therapeutic strategies against a number of human diseases.

Fang Y, Xu X, Ding J, Yang L, Doan MT, Karmaus PWF, Snyder NW, Zhao Y, Li JL, Li X. Histone crotonylation promotes mesoendodermal commitment of human embryonic stem cells. *Cell Stem Cell*. 2021 Apr 1;28(4):748-763.e7. doi: 10.1016/j.stem.2020.12.009. Epub 2021 Jan 14. PMID: 33450185; PMCID: PMC8026719.

Early neural differentiation is under metabolic control of SIRT1

Sphingolipids, a group of abundant natural lipids enriched in the brain, are important structural components of cell membranes and prominent signaling molecules controlling cell growth, differentiation, and death. Defects in degradation of these lipids are associated with several human neurodegenerative diseases, however, molecular mechanisms governing their metabolism remain unclear. In a recent study, we report that sphingolipid degradation is under transcriptional control of SIRT1, a highly conserved protein deacetylase that is sensitive to the metabolic status of cells, in mouse embryonic stem cells (mESCs). We found that deletion of SIRT1 results in accumulation of sphingomyelin in mESCs, primarily due to reduction of a sphingomyelin degradation enzyme called SMPDL3B. Mechanistically, SIRT1 regulates transcription of Smpdl3b through c-Myc. Functionally, accumulation of sphingomyelin in SIRT1 deficient mESCs makes their membranes more fluid and reduces their ability to develop into neuronal cells. Furthermore, when female mice are fed a high-fat diet, their embryos lacking the gene for SIRT1 accumulate sphingolipids, which in turn impairs the neural development of their offspring. Our findings discover a key regulatory mechanism for sphingolipid metabolism and neural differentiation, further imply that pharmacological manipulation of SIRT1-mediated sphingomyelin degradation might be beneficial for treatment of human neurological diseases.

Fan W, Tang S, Fan X, Fang Y, Xu X, Li L, Xu J, Li JL, Wang Z, Li X. SIRT1 regulates sphingolipid metabolism and neural differentiation of mouse embryonic stem cells through c-Myc-SMPDL3B. *Elife*. 2021 May 27;10:e67452. doi: 10.7554/eLife.67452. PMID: 34042046; PMCID: PMC8216717.