Division of Intramural Research

NAEHS Council Update

February 2022

DIR RECRUITMENTS

Tenure Track/Eligible Investigator in the Biostatistics and Computational Biology Branch
The National Institute of Environmental Health Sciences (NIEHS), a major research component of the National Institutes of Health (NIH) and the Department of Health and Human Services, is inviting applications for a Tenure-Track or Tenure-Eligible Investigator in the Biostatistics and Computational Biology Branch (BCBB) within the Division of Intramural Research at the NIEHS in Research Triangle Park, NC. Successful applicants will have a Ph.D., M.D. or an equivalent doctoral degree, with training in statistics, biostatistics, or related quantitative discipline, and demonstrated ability to design and carry out original and innovative research. The individual selected for this position will have a strong record of accomplishments in the field of biostatistics. Preference will be given to candidates who specialize in methods for observational and epidemiological data, develop and apply machine learning methods, and/or develop methods for high dimensional and sparse data to enhance our understanding of the effects of the environment on human health. Example application areas include but are not limited to epidemiological and health record data, genetics/genomics, metabolomics, and microbiome studies. This person will be expected to develop an outstanding independent research program that complements other research programs within the BCBB, and the Division of Intramural Research at NIEHS, and is consistent with the mission of the NIEHS and NIH. Dr. Jack Taylor, Senior Investigator in the Epidemiology Branch serves as chair of the search committee which was launched on November 16, 2021.

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.

Deputy Chief of the Comparative Medicine Branch
The National Institute of Environmental Health Sciences (NIEHS) of the National Institutes of Health is searching for a Deputy Chief /Deputy Animal Program Director of the Comparative Medicine Branch (CMB). Minimum qualifications include a DVM/VMD from an AVMA-accredited or approved college or university, a current license to practice veterinary medicine in any state in the United States and board certification by the American College of Laboratory Animal Medicine. CMB provides a broad range of services and collaborative support for NIEHS intramural research programs by providing training for investigators and technicians, post-approval compliance monitoring, quality assurance support for research projects, consultation with investigators planning animal research projects, and administrative and professional staffing for

the Institutional Animal Care and Use Committee (ACUC). CMB also plans and conducts independent research in support of animal care, use and welfare advancement. CMB participates in the training of residents in an ACLAM approved laboratory animal medicine training program. The Deputy Chief will be responsible for assisting the Chief, CMB with the management of an AAALAC accredited animal care and use program and for support of NIEHS animal research programs that have a strong emphasis on rodent animal models. CMB is responsible for management of the NIEHS animal care and use program, which includes facility management, animal procurement and housing, animal health surveillance and disease diagnosis, clinical veterinary services, rodent breeding, technical and surgical assistance, animal imaging, behavioral phenotyping, quality assurance of materials used in animal-based research and animal food, bedding, and water, and professional advice to the institute on animal related issues. The NIEHS Animal Care and Use Program is fully accredited by AAALAC, International. CMB supports approximately 120 active animal research projects for scientists in the Division of Intramural Research. A daily inventory of over 40,000 rodents is maintained. The Deputy Chief will have supervisory responsibility of section heads within CMB and will serve on the NIEHS ACUC as well as other committees as directed by the Chief, CMB. Dr. Paul Wade, Senior Investigator in the Epigenetics and Stem Cell Biology Laboratory and Chair of the NIEHS Animal Care and Use Committee serves as Chair of the search committee which was launched on January 20, 2022.

Recruitment of NIH Earl Stadtman Investigator Finalists

In addition to targeted recruitment, DIR is actively seeking outstanding scientists through the central NIH Stadtman recruitment mechanism. Six outstanding candidates from the 2021-2022 Stadtman search representing a range of disciplines central to the NIEHS mission were interviewed during December 2021 through February 2022. Due to the COVID-19 pandemic these were conducted virtually. Offers will be extended to top candidates in February and March 2022 following discussions among DIR and NIEHS leadership.

NEW APPOINTMENTS IN DIR

Chief of the Comparative Medicine Branch

Dondrae Coble, D.V.M., DACLAM was appointed Chief of the Comparative Medicine Branch (CMB) and NIEHS Animal Program Director. Dr. Coble joins NIEHS from Nationwide Children's Hospital where he served as Animal Program Director and Attending Veterinarian. He obtained his Bachelor of Science in Laboratory Animal Science at North Carolina Agriculture and Technical State University, received his Doctor of Veterinary Medicine from Tuskegee University College of Veterinary Medicine, and completed a rotating medicine and surgery internship at Florida Veterinary Specialists. He completed residency training in laboratory animal medicine at Emory University and the Yerkes National Primate Research Center. He served on the faculty of the Ohio State University College of Veterinary Medicine since 2011 where he was a clinical veterinarian and matriculated to Professor in the Department of Veterinary Preventive Medicine. He is currently a Diplomate in the American College of Laboratory Animal Medicine, a certified aquatic veterinarian and an ad hoc Specialist for AAALAC International.

New Tenure-Track Investigators

Dr. Carlos Guardia from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) joined 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 started at NIEHS in November 2021.

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 2022.

DIR STAFF UPDATES

Kathy Laber-Laird, D.V.M., retired from her role as Chief of the NIEHS Comparative Medicine Branch (CMB). Among other accomplishments, Laber-Laird earned consecutive exemplary ratings from AAALAC International, an accreditation body that certifies laboratory animal care at research institutions. She also expertly managed the NIEHS animal care program throughout the COVID-19 pandemic. Before joining NIEHS in 2013, Dr. Laber-Laird was Professor and Vice Chair of the Department of Comparative Medicine at the Medical University of South Carolina and Director of Laboratory Animal Resources at the Veterans Administration Medical Center in Charleston. She earned her Doctorate in Veterinary Medicine at Michigan State University in 1984. Dr. Laber-Laird has served as an active member and officer in numerous professional societies, including the American Association for Laboratory Animal Science (AALAS) and AAALAC International. In 2018, she received the AALAS Joseph J. Garvey Management Award, which recognizes outstanding leadership in the care, quality, and humane treatment of animals used in biomedical research.

BSC REVIEW OF THE EPIDEMIOLOGY BRANCH

The NIEHS DIR Board of Scientific Counselors reviewed the Epidemiology Branch, December 5-7, 2021

Members of the Board of Scientific Counselors that Attended:

- Kathleen M. Caron, Ph.D., BSC Chair, Professor and Chair, Department of Cell Biology and Physiology, University of North Carolina at Chapel Hill, Chapel Hill, NC
- Anita H. Corbett, Ph.D., Samuel C. Dobbs Professor of Genetics, Cell and Developmental Biology, Emory University, Atlanta, GA
- Sylvie Doublié, Ph.D., Professor, Department of Microbiology and Molecular Genetics, University of Vermont, Burlington, VT
- Sarah K. England, Ph. D., Professor, Department of Obstetrics and Gynecology at the Washington University School of Medicine, St. Louis, MO
- Katherine B. Ensor, Ph.D., Noah G. Harding Professor of Statistics and Director, Center for Computational and Economic Systems at the George R. Brown School of Engineering, Rice University, Houston, TX
- Jeffrey J. Hayes, Ph.D., Professor and Chair, Department of Biochemistry and Biophysics, Shohei Koide Professor in Biochemistry and Biophysics, University of Rochester School of Medicine, Rochester, NY
- Deanna Kroetz, Ph.D., Professor, Department of Bioengineering and Therapeutic Sciences, School of Pharmacy, University of California, San Francisco, CA
- Frances M. Leslie, Ph.D., Professor Emerita, Department of Pharmaceutical Sciences, School of Pharmacy, University of California, Irvine, CA
- Jose A. Luchsinger, M.D., Professor of Medicine and Epidemiology and Vice-Chair for Clinical & Epidemiologic Research, Columbia University, New York, NY
- Fernando J. Martinez, M.D., M.S., Chief of Pulmonary and Critical Care Medicine Division, Bruce Webster Professor of Medicine, Weill Cornell Medical Center, New York, NY
- Carl Hashimoto, Ph.D., *Ex Officio* BSC Member, Director of Faculty Development, Office of Intramural Research, NIH, Bethesda, MD

Ad Hoc Reviewers that Attended:

- Elizabeth R. Bertone-Johnson, Sc.D., S.M., Professor of Epidemiology and Chair, Department of Health Promotion & Policy, School of Public Health & Health Sciences, University of Massachusetts, Amherst, MA
- Daniel J. Buysse, M.D., Professor of Sleep Medicine and Psychiatry, Clinical and Translation Science, University of Pittsburgh School of Medicine, Pittsburgh, PA
- Deidra C. Crews, M.D., Associate Director for Research Development Johns Hopkins Center for Health Equity and Professor of Medicine, Division of Nephrology, Johns Hopkins Bayview Medical Center, Baltimore, MD

- Dana M. Dabelea, M.D., Ph.D., Conrad M. Riley Professor of Epidemiology and Pediatrics and Director of the LEAD Center, Colorado School of Public Health, Anschutz Medical Campus, University of Colorado Denver, Aurora, CO
- A. Heather Eliassen, Sc.D. Professor, Departments of Nutrition and Epidemiology, Harvard T.H. Chan, School of Public Health, Boston, MA
- Christine D. Cole Johnson, Ph.D., M.P.H., Chair, Department of Public Health Sciences, Director, HFHS Center for Allergy, Asthma & Immunology Research, Henry Ford Cancer Institute, Detroit, MI
- Timothy L. Lash, D.Sc., M.P.H., O. Wayne Rollins Distinguished Professor of Epidemiology and Chair, Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA
- Thomas A. LaVeist, Ph.D., Dean and Weatherhead Presidential Chair in Health Equity, School of Public Health & Tropical Medicine, Tulane University, New Orleans, LA
- Stacey Missmer, Sc.D., Professor, Department of Obstetrics, Gynecology & Reproductive Biology, Michigan State University, Grand Rapids, MI
- Polly Newcomb, Ph.D., M.P.H., Professor, Cancer Prevention Program, Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA
- Kari E. North, Ph.D., Professor of Epidemiology, Director, CVD Genetic Epidemiology Computational Laboratory, Gilling's School of Global Public Health, University of North Carolina, Chapel Hill, NC
- Alpa V. Patel, Ph.D., Senior Vice President, Population Science, Principal Investigator, Cancer Prevention Studies, American Cancer Society, Kennesaw, GA
- Susan M. Pinney, Ph.D., Professor of Epidemiology, Department of Environmental & Public, Health Sciences, Director, Center for Environmental Genetics, University of Cincinnati College of Medicine, Cincinnati, OH
- Whitney R. Robinson, Ph.D., M.S.P.H., Associate Professor, Division of Women's Community and Population Health, Department of Obstetrics & Gynecology, Duke University School of Medicine, Durham, NC
- Jennifer A. Rusiecki, Ph.D., Professor of Epidemiology, Preventive Medicine and Biostatistics, Uniformed Services University of the Health and Sciences, Bethesda, MD
- Lauren R. Teras, Ph.D., Scientific Director, Epidemiology Research, Leader Breast & Hematologic Cancer Research, Department of Population Science, American Cancer Society, Atlanta, GA
- Mary Turyk, M.P.H., Ph.D., Professor, Epidemiology and Biostatistics, School of Public Health, Institute for Environment Science and Policy, University of Illinois, Chicago, IL
- Marsha Wills-Karp, Ph.D., Professor and Chair, Department of Environmental Health and Engineering, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Agenda

Sunday, December 5 – Zoom meeting
Closed Evening Session

4:00 - 5:00 p.m.	Welcome and Discussion of Past Board Reviews, Drs. Rick Woychik, Darryl Zeldin, Dale Sandler and Kathleen Caron
5:00 – 6:00 p.m.	BSC Discussion of Review, Dr. Kathleen Caron and panel

Monday, December 6 - Zoom meeting
Morning Session

9:30 - 9:45 a.m.	Welcome, Drs. Kathleen Caron and Richard Woychik
9:45 - 10:15	Overview, Epidemiology Branch, Dale Sandler, Ph.D.
10:15 - 10:45	Women's Health Group, Donna Baird Ph.D.
10:45 - 11:00	Break
11:00 – 11:50	Open Q&A Session: Chronic Disease Epidemiology, Dale Sandler, Ph.D. Genomics and Environment in Respiratory and Allergic Health Group, Stephanie London, M.D.
11:50 – 12:25	Closed 1:1 Sessions with Investigators, Drs. Sandler and London

Afternoon Session

12:30 – 1:45	Closed Working Lunch
1:50 – 3:20	Poster Session
3:20 – 3:35	Break
3:35 – 5:00	Closed Sessions with Trainees and Staff Scientists

Tuesday December 7 - Zoom Meeting
Morning Session

10:00 – 10:50	Open Q&A Session: Fertility and Reproductive Health Group, Anne Marie Jukic, Ph.D. Perinatal and Early Life Epidemiology Group, Kelly Ferguson, Ph.D.
10:50 – 11:00	Break
11:00 – 11:50	Open Q&A Session: Environment & Cancer Epidemiology Group, Alexandra White, Ph.D. Social & Environmental Determinants of Health Equity Group, Chandra Jackson, Ph.D.
11:55 - 12:55	Closed 1:1 Sessions with Investigators, Drs. Jukic, Ferguson, White and Jackson
12:55 - 2:15	Lunch Break
2:15 - 3:45	Closed BSC Discussion and completion of individual review assignments
3:50 – 5:00	Closed Session and Debriefing to NIEHS/DIR Leadership
5:00 pm	Adjourn

NIEHS SCIENCE DAY

The Nineteenth Annual NIEHS Science Day was held on November 19, 2021, as a virtual event due to the COVID-19 pandemic. This "One NIEHS" event is held annually to celebrate the achievements of NIEHS scientists. The virtual event was attended by at least 300 individuals from NIEHS and academic centers across North Carolina. The NIEHS Science Day program consisted of 10 oral presentations and 55 poster presentations by fellows, students, and technicians from DIR and DNTP. Judging for the awards was performed by a panel of 20 extramural faculty from universities located across North Carolina and NIEHS Intramural Scientists.

Mentor of the Year: Janet Hall, M.D., NIEHS Clinical Director
Chief, Clinical Research Branch

Fellow of the Year: Cassandra Hayne, Ph.D., IRTA Postdoctoral Fellow
Nucleolar Integrity Group
Signal Transduction Laboratory, DIR

Best Oral Presentation: Cassandra Hayne, Ph.D., IRTA Postdoctoral Fellow
Nucleolar Integrity Group
Signal Transduction Laboratory, DIR

Best Poster Presentations:

Jacob Gordon, IRTA Predoctoral Fellow (NIH OxCam Program)
Nucleolar Integrity Group
Signal Transduction Laboratory

Kamiya Bridges, IRTA Postbaccalaureate Fellow
Reproductive Developmental Biology Group
Reproductive and Developmental Biology Laboratory

Alicia Chi, Ph.D., IRTA Postdoctoral Fellow
Pregnancy & Female Reproduction Group
Reproductive and Developmental Biology Laboratory

Katie Hudson, Ph.D., IRTA Postdoctoral Fellow
Mechanisms of Genome Dynamics Group
Genome Integrity and Structural Biology Laboratory

Ciro Amato, III, Ph.D., IRTA Postdoctoral Fellow
Reproductive Developmental Biology Group,
Reproductive and Developmental Biology Laboratory

Justin Collier, Pharm.D., Ph.D., IRTA Postdoctoral Fellow
Cell Biology Group
Immunity, Inflammation and Disease Laboratory

DIR PAPERS OF THE YEAR FOR 2021

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.

BACKGROUND & AIMS: The immune compartment is critical for maintaining tissue homeostasis. A weak immune response increases susceptibility to infection, but immune hyperactivation causes tissue damage, and chronic inflammation may lead to cancer development. In the stomach, inflammation damages the gastric glands and drives the development of potentially preneoplastic metaplasia. Glucocorticoids are potent anti-inflammatory steroid hormones that are required to suppress gastric inflammation and metaplasia. However, these hormones function differently in males and females. Here, we investigate the impact of sex on the regulation of gastric inflammation.
METHODS: Endogenous glucocorticoids and male sex hormones were removed from mice using adrenalectomy and castration, respectively. Mice were treated with 5α-dihydrotestosterone (DHT) to test the effects of androgens on regulating gastric inflammation. Single-cell RNA sequencing of gastric leukocytes was used to identify the leukocyte populations that were the direct targets of androgen signaling. Type 2 innate lymphoid cells (ILC2s) were depleted by treatment with CD90.2 antibodies.
RESULTS: We show that adrenalectomized female mice develop spontaneous gastric inflammation and spasmolytic polypeptide-expressing metaplasia (SPEM) but that the stomachs of adrenalectomized male mice remain quantitatively normal. Simultaneous depletion of glucocorticoids and sex hormones abolished the male-protective effects and triggered spontaneous pathogenic gastric inflammation and SPEM. Treatment of female mice with DHT prevented gastric inflammation and SPEM development when administered concurrent with adrenalectomy and also reversed the pathology when administered after disease onset. Single-cell RNAseq of gastric leukocytes revealed that ILC2s expressed abundant levels of both the glucocorticoid receptor (GR) and androgen receptor (AR). We demonstrated that DHT treatment potently suppressed the expression of the proinflammatory cytokines Il13 and Csf2 by ILC2s. Moreover, ILC2 depletion protected the stomach from SPEM development.
CONCLUSIONS: Here, we report a novel mechanism by which glucocorticoids and androgens exert overlapping effects to regulate gastric inflammation. Androgen signaling within ILC2s prevents their pathogenic activation by suppressing the transcription of proinflammatory cytokines. This work revealed a critical role for sex hormones in regulating gastric inflammation and metaplasia.

Izumi G, Nakano H, Nakano K, Whitehead GS, Grimm SA, Fessler MB, Karmaus PW, Cook DN. CD11b+ lung dendritic cells at different stages of maturation induce Th17 or Th2 differentiation. *Nat Commun*. 2021 Aug 19;12(1):5029. doi: 10.1038/s41467-021-25307-x. PMID: 34413303; PMCID: PMC8377117.

Dendritic cells (DC) in the lung that induce Th17 differentiation remain incompletely understood, in part because conventional CD11b+ DCs (cDC2) are heterogeneous. Here, we

report a population of cDCs that rapidly accumulates in lungs of mice following house dust extract inhalation. These cells are Ly-6C+, are developmentally and phenotypically similar to cDC2, and strongly promote Th17 differentiation ex vivo. Single cell RNA-sequencing (scRNA-Seq) of lung cDC2 indicates 5 distinct clusters. Pseudotime analysis of scRNA-Seq data and adoptive transfer experiments with purified cDC2 subpopulations suggest stepwise developmental progression of immature Ly-6C+Ly-6A/E+ cDC2 to mature Ly-6C-CD301b+ lung resident cDC2 lacking Ccr7 expression, which then further mature into CD200+ migratory cDC2 expressing Ccr7. Partially mature Ly-6C+Ly-6A/E-CD301b- cDC2, which express Il1b, promote Th17 differentiation. By contrast, CD200+ mature cDC2 strongly induce Th2, but not Th17, differentiation. Thus, Th17 and Th2 differentiation are promoted by lung cDC2 at distinct stages of maturation.

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.

Perineuronal nets (PNNs), a specialized form of extracellular matrix, are abnormal in the brains of people with 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 report that PNNs appear elevated in area CA2 of the hippocampus of an individual with RTT and that PNNs develop precociously and remain elevated in area CA2 of a mouse model of RTT (Mecp2-null). Further, we provide evidence that LTP could be induced at CA2 synapses prior to PNN maturation (postnatal day 8-11) in wild-type mice and that this window of plasticity was prematurely restricted at CA2 synapses in Mecp2-null mice. Degrading PNNs in Mecp2-null hippocampus was sufficient to rescue the premature disruption of CA2 plasticity. We identified several molecular targets that were altered in the developing Mecp2-null hippocampus that may explain aberrant PNNs and CA2 plasticity, and we discovered that CA2 PNNs are negatively regulated by neuronal activity. Collectively, our findings demonstrate that CA2 PNN development is regulated by Mecp2 and identify a window of hippocampal plasticity that is disrupted in a mouse model of RTT.

Welch BM, Keil AP, Bommarito PA, van T' Erve TJ, Deterding LJ, Williams JG, Lih FB, Cantonwine DE, McElrath TF, Ferguson KK. Longitudinal exposure to consumer product chemicals and changes in plasma oxylipins in pregnant women. *Environ Int*. 2021 Dec;157:106787. doi: 10.1016/j.envint.2021.106787. Epub 2021 Jul 24. PMID: 34314981; PMCID: PMC8490329.

BACKGROUND: Exposure to consumer product chemicals during pregnancy may increase susceptibility to pregnancy disorders by influencing maternal inflammation. However, effects on specific inflammatory pathways have not been well characterized. Oxylipins are a diverse class of lipids that act as important mediators and biomarkers of several biological pathways that regulate inflammation. Adverse pregnancy outcomes have been associated with circulating oxylipin levels in pregnancy. In this study, we aimed to determine the longitudinal associations

between plasma oxylipins and urinary biomarkers of three classes of consumer product chemicals among pregnant women.
METHODS: Data come from a study of 90 pregnant women nested within the LIFECODES cohort. Maternal plasma and urine were collected at three prenatal visits. Plasma was analyzed for 61 oxylipins, which were grouped according to biosynthetic pathways that we defined by upstream: 1) fatty acid precursor, including linoleic, arachidonic, docosahexaenoic, or eicosapentaenoic acid; and 2) enzyme pathway, including cyclooxygenase (COX), lipoxygenase (LOX), or cytochrome P450 (CYP). Urine was analyzed for 12 phenol, 12 phthalate, and 9 organophosphate ester (OPE) biomarkers. Linear mixed effect models were used for single-pollutant analyses. We implemented a novel extension of quantile g-computation for longitudinal data to examine the joint effect of class-specific chemical mixtures on individual plasma oxylipin concentrations.
RESULTS: We found that urinary biomarkers of consumer product chemicals were positively associated with pro-inflammatory oxylipins from several biosynthetic pathways. Importantly, these associations depended upon the chemical class of exposure biomarker. We estimated positive associations between urinary phenol biomarkers and oxylipins produced from arachidonic acid by LOX enzymes, including several important pro-inflammatory hydroxyeicosatetraenoic acids (HETEs). On average, mean concentrations of oxylipin produced from the arachidonic acid/LOX pathway were 48%-71% higher per quartile increase in the phenol biomarker mixture. For example, a simultaneous quartile increase in all urinary phenols was associated with 53% higher (95% confidence interval [CI]: 11%, 111%) concentrations of 12-HETE. The positive associations among phenols were primarily driven by methyl paraben, 2,5-dichlorophenol, and triclosan. Additionally, we observed that phthalate and OPE metabolites were associated with higher concentrations of oxylipins produced from linoleic acid by CYP enzymes, including the pro-inflammatory dihydroxy-octadecenoic acids (DiHOMEs). Associations among DiHOME oxylipins were driven by metabolites of benzylbutyl and di-isodecyl phthalate, and by the metabolite of tris(1,3-dichloro-2-propyl) phosphate among OPEs. We also observed inverse associations between phthalate and OPE metabolites and oxylipins produced from other pathways; however, adjusting for a plasma indicator of dietary fatty acid intake attenuated those results.
CONCLUSIONS: Our findings support the hypothesis that consumer product chemicals may have diverse impacts on inflammation processes in pregnancy. Certain pro-inflammatory oxylipins were generally higher among participants with higher urinary chemical biomarker concentrations. Associations varied by class of chemical and by the biosynthetic pathway of oxylipin production, indicating potential specificity in the inflammatory effects of these environmental chemicals during pregnancy that warrant investigation in larger studies.

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.

Mitochondrial abnormalities have been noted in lupus, but the causes and consequences remain obscure. Autophagy-related genes ATG5, ATG7 and IRGM have been previously implicated in autoimmune disease. We reasoned that failure to clear defective mitochondria via mitophagy might be a foundational driver in autoimmunity by licensing mitochondrial DNA-dependent

induction of type I interferon. Here, we show that mice lacking the GTPase IRGM1 (IRGM homolog) exhibited a type I interferonopathy with autoimmune features. Irgm1 deletion impaired the execution of mitophagy with cell-specific consequences. In fibroblasts, mitochondrial DNA soiling of the cytosol induced cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING)-dependent type I interferon, whereas in macrophages, lysosomal Toll-like receptor 7 was activated. In vivo, Irgm1-/- tissues exhibited mosaic dependency upon nucleic acid receptors. Whereas salivary and lacrimal gland autoimmune pathology was abolished, and lung pathology was attenuated by cGAS and STING deletion, pancreatic pathology remained unchanged. These findings reveal fundamental connections between mitochondrial quality control and tissue-selective autoimmune disease.

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.

The INO80 chromatin remodeler is involved in many chromatin-dependent cellular functions. However, its role in pluripotency and cell fate transition is not fully defined. We examined the impact of Ino80 deletion in the naïve and primed pluripotent stem cells. We found that Ino80 deletion had minimal effect on self-renewal and gene expression in the naïve state but led to cellular differentiation and de-repression of developmental genes in the transition toward and maintenance of the primed state. In the naïve state, INO80 pre-marked gene promoters that would adopt bivalent histone modifications by H3K4me3 and H3K27me3 upon transition into the primed state. In the primed state, in contrast to its known role in H2A.Z exchange, INO80 promoted H2A.Z occupancy at these bivalent promoters and facilitated H3K27me3 installation and maintenance as well as downstream gene repression. Together, our results identified an unexpected function of INO80 in H2A.Z deposition and gene regulation. We showed that INO80-dependent H2A.Z occupancy is a critical licensing step for the bivalent domains, and thereby uncovered an epigenetic mechanism by which chromatin remodeling, histone variant deposition and histone modification coordinately control cell fate.

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.

BACKGROUND: Poor sleep may contribute to chronic kidney disease (CKD) through several pathways, including hypoxia-induced systemic and intraglomerular pressure, inflammation, oxidative stress and endothelial dysfunction. However, few studies have investigated the association between multiple objectively measured sleep dimensions and CKD.
METHODS: We investigated the cross-sectional association between sleep dimensions and CKD among 1895 Multi-Ethnic Study of Atherosclerosis Sleep Ancillary Study participants who completed in-home polysomnography, wrist actigraphy and a sleep questionnaire. Using Poisson regression models with robust variance, we estimated separate prevalence ratios (PR) and 95% CIs for moderate-to-severe CKD (glomerular filtration rate <60 mL/min/1.73 m2 or albuminuria >30 mg/g) among participants according to multiple sleep dimensions, including

very short (≤5 hours) sleep, Apnoea-Hypopnoea Index and sleep apnoea-specific hypoxic burden (SASHB) (total area under the respiratory event-related desaturation curve divided by total sleep duration, %min/hour)). Regression models were adjusted for sociodemographic characteristics, health behaviours and clinical characteristics.
RESULTS: Of the 1895 participants, mean age was 68.2±9.1 years, 54% were women, 37% were white, 28% black, 24% Hispanic/Latino and 11% Asian. Several sleep metrics were associated with higher adjusted PR of moderate-to-severe CKD: very short versus recommended sleep duration (PR=1.40, 95% CI 1.06 to 1.83); SASHB (Box-Cox transformed SASHB: PR=1.06, 95% CI 1.02 to 1.12); and for participants in the highest quintile of SASHB plus sleep apnoea: PR=1.28, 95% CI 1.01 to 1.63.
CONCLUSIONS: Sleep apnoea associated hypoxia and very short sleep, likely representing independent biological mechanisms, were associated with a higher moderate-to-severe CKD prevalence, which highlights the potential role for novel interventions.

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.

Chronically elevated intraocular pressure (IOP) is the major risk factor of primary open-angle glaucoma, a leading cause of blindness. Dysfunction of the trabecular meshwork (TM), which controls the outflow of aqueous humor (AqH) from the anterior chamber, is the major cause of elevated IOP. Here, we demonstrate that mice deficient in the Krüppel-like zinc finger transcriptional factor GLI-similar-1 (GLIS1) develop chronically elevated IOP. Magnetic resonance imaging and histopathological analysis reveal that deficiency in GLIS1 expression induces progressive degeneration of the TM, leading to inefficient AqH drainage from the anterior chamber and elevated IOP. Transcriptome and cistrome analyses identified several glaucoma- and extracellular matrix-associated genes as direct transcriptional targets of GLIS1. We also identified a significant association between GLIS1 variant rs941125 and glaucoma in humans ($P = 4.73 \times 10\text{-}6$), further supporting a role for GLIS1 into glaucoma etiology. Our study identifies GLIS1 as a critical regulator of TM function and maintenance, AqH dynamics, and IOP.

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.

Histone crotonylation is a non-acetyl histone lysine modification that is as widespread as acetylation. However, physiological functions associated with histone crotonylation remain almost completely unknown. Here we report that histone crotonylation is crucial for endoderm differentiation. We demonstrate that key crotonyl-coenzyme A (CoA)-producing enzymes 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. 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 for therapeutic strategies against a number of human diseases.

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.

The mosquito protein AEG12 is up-regulated in response to blood meals and flavivirus infection though its function remained elusive. Here, we determine the three-dimensional structure of AEG12 and describe the binding specificity of acyl-chain ligands within its large central hydrophobic cavity. We show that AEG12 displays hemolytic and cytolytic activity by selectively delivering unsaturated fatty acid cargoes into phosphatidylcholine-rich lipid bilayers. This property of AEG12 also enables it to inhibit replication of enveloped viruses such as Dengue and Zika viruses at low micromolar concentrations. Weaker inhibition was observed against more distantly related coronaviruses and lentivirus, while no inhibition was observed against the nonenveloped virus adeno-associated virus. Together, our results uncover the mechanistic understanding of AEG12 function and provide the necessary implications for its use as a broad-spectrum therapeutic against cellular and viral targets.

Park YM, Bookwalter DB, O'Brien KM, Jackson CL, Weinberg CR, Sandler DP. A prospective study of type 2 diabetes, metformin use, and risk of breast cancer. *Ann Oncol*. 2021 Mar;32(3):351-359. doi: 10.1016/j.annonc.2020.12.008. Epub 2021 Jan 29. PMID: 33516778; PMCID: PMC7995619.

BACKGROUND: Type 2 diabetes (T2D) has been associated with increased breast cancer risk, but commonly prescribed antidiabetic medications such as metformin may reduce risk. Few studies have investigated T2D and medications together in relation to breast cancer.
PATIENTS AND METHODS: Data came from 44 541 Sister Study participants aged 35 to 74 years at enrollment (2003-2009) who satisfied eligibility criteria, followed through 15 September 2017. Information on time-varying, self-reported, physician-diagnosed, prevalent and incident T2D, use of antidiabetic medications, and covariates was obtained from baseline and follow-up questionnaires. Incident breast cancers were confirmed with medical records. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated.
RESULTS: During follow-up (median, 8.6 years), 2678 breast cancers were diagnosed at least 1 year after enrollment. There were 3227 women (7.2%) with prevalent and 2389 (5.3%) with incident T2D, among whom 61% (n = 3386) were ever treated with metformin. There was no overall association between T2D and breast cancer risk (HR 0.99; 95% CI, 0.87-1.13). However, T2D was associated with increased risk of triple-negative breast cancer (HR 1.40; 95% CI, 0.90-2.16). Compared with not having T2D, T2D with metformin use was not

associated with overall breast cancer risk (HR 0.98; 95% CI, 0.83-1.15), but it was associated with decreased risk of estrogen receptor (ER)-positive breast cancer (HR 0.86; 95% CI 0.70-1.05) and increased risk of ER-negative (HR 1.25; 95% CI, 0.84-1.88) and triple-negative breast cancer (HR 1.74; 95% CI, 1.06-2.83). The inverse association with ER-positive cancer was stronger for longer duration (≥10 year) metformin use (HR 0.62; 95% CI, 0.38-1.01; P for trend = 0.09). Results were supported by sensitivity analyses.
CONCLUSION: Our findings suggest that associations between T2D and breast cancer may differ by hormone receptor status and that associations between T2D and ER-positive breast cancer may be reduced by long-term metformin use.

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.

Nsp15, a uridine specific endoribonuclease conserved across coronaviruses, processes viral RNA to evade detection by host defense systems. Crystal structures of Nsp15 from different coronaviruses have shown a common hexameric assembly, yet how the enzyme recognizes and processes RNA remains poorly understood. Here we report a series of cryo-EM reconstructions of SARS-CoV-2 Nsp15, in both apo and UTP-bound states. The cryo-EM reconstructions, combined with biochemistry, mass spectrometry, and molecular dynamics, expose molecular details of how critical active site residues recognize uridine and facilitate catalysis of the phosphodiester bond. Mass spectrometry revealed the accumulation of cyclic phosphate cleavage products, while analysis of the apo and UTP-bound datasets revealed conformational dynamics not observed by crystal structures that are likely important to facilitate substrate recognition and regulate nuclease activity. Collectively, these findings advance understanding of how Nsp15 processes viral RNA and provide a structural framework for the development of new therapeutics.

Jamsen JA, Sassa A, Perera L, Shock DD, Beard WA, Wilson SH. Structural basis for proficient oxidized ribonucleotide insertion in double strand break repair. *Nat Commun*. 2021 Aug 20;12(1):5055. doi: 10.1038/s41467-021-24486-x. PMID: 34417448; PMCID: PMC8379156.

Reactive oxygen species (ROS) oxidize cellular nucleotide pools and cause double strand breaks (DSBs). Non-homologous end-joining (NHEJ) attaches broken chromosomal ends together in mammalian cells. Ribonucleotide insertion by DNA polymerase (pol) μ prepares breaks for end-joining and this is required for successful NHEJ in vivo. We previously showed that pol μ lacks discrimination against oxidized dGTP (8-oxo-dGTP), that can lead to mutagenesis, cancer, aging and human disease. Here we reveal the structural basis for proficient oxidized ribonucleotide (8-oxo-rGTP) incorporation during DSB repair by pol μ. Time-lapse crystallography snapshots of structural intermediates during nucleotide insertion along with computational simulations reveal substrate, metal and side chain dynamics, that allow oxidized ribonucleotides to escape polymerase discrimination checkpoints. Abundant nucleotide pools, combined with inefficient sanitization and repair, implicate pol μ mediated

oxidized ribonucleotide insertion as an emerging source of widespread persistent mutagenesis and genomic instability.

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.

Birth defects of the external genitalia are among the most common in the world. Proper formation of the external genitalia requires a highly orchestrated process that involves special cell populations and sexually dimorphic hormone signaling. It is clear what the end result of the sexually dimorphic development is (a penis in the male versus clitoris in the female); however, the cell populations involved in the process remain poorly defined. Here, we used single-cell messenger RNA sequencing in mouse embryos to uncover the dynamic changes in cell populations in the external genitalia during the critical morphogenetic window. We found that overall, male and female external genitalia are largely composed of the same core cellular components. At the bipotential stage of development (embryonic day or E14.5), few differences in cell populational composition exist between male and female. Although similar in cell population composition, genetic differences in key sexual differentiation developmental pathways arise between males and females by the early (E16.5) and late (E18.5) differentiation stages. These differences include discrete cell populations with distinct responsiveness to androgen and estrogen. By late sexual differentiation (E18.5), unique cell populations in both male and female genitalia become apparent and are enriched with androgen- and estrogen-responsive genes, respectively. These data provide insights into the morphogenesis of the external genitalia that could be used to understand diseases associated with defects in the external genitalia.

Li H, Bradbury JA, Edin ML, Graves JP, Gruzdev A, Cheng J, Hoopes SL, DeGraff LM, Fessler MB, Garantziotis S, Schurman SH, Zeldin DC. sEH promotes macrophage phagocytosis and lung clearance of Streptococcus pneumoniae. *J Clin Invest*. 2021 Nov 15;131(22):e129679. doi: 10.1172/JCI129679. PMID: 34591792; PMCID: PMC8592545.

Epoxyeicosatrienoic acids (EETs) have potent antiinflammatory properties. Hydrolysis of EETs by soluble epoxide hydrolase/ epoxide hydrolase 2 (sEH/EPHX2) to less active diols attenuates their antiinflammatory effects. Macrophage activation is critical to many inflammatory responses; however, the role of EETs and sEH in regulating macrophage function remains unknown. Lung bacterial clearance of Streptococcus pneumoniae was impaired in Ephx2-deficient (Ephx2-/-) mice and in mice treated with an sEH inhibitor. The EET receptor antagonist EEZE restored lung clearance of S. pneumoniae in Ephx2-/- mice. Ephx2-/- mice had normal lung Il1b, Il6, and Tnfa expression levels and macrophage recruitment to the lungs during S. pneumoniae infection; however, Ephx2 disruption attenuated proinflammatory cytokine induction, Tlr2 and Pgylrp1 receptor upregulation, and Ras-related C3 botulinum toxin substrates 1 and 2 (Rac1/2) and cell division control protein 42 homolog (Cdc42) activation in PGN-stimulated macrophages. Consistent with these observations, Ephx2-/- macrophages displayed reduced phagocytosis of S. pneumoniae in vivo and in vitro. Heterologous overexpression of TLR2 and peptidoglycan recognition protein 1 (PGLYRP1) in Ephx2-/- macrophages restored macrophage activation and phagocytosis. Human

macrophage function was similarly regulated by EETs. Together, these results demonstrate that EETs reduced macrophage activation and phagocytosis of S. pneumoniae through the downregulation of TLR2 and PGLYRP1 expression. Defining the role of EETs and sEH in macrophage function may lead to the development of new therapeutic approaches for bacterial diseases.

AWARDS AND HONORS

Scientific Awards

Dr. Benedict Anchang (Biostatistics and Computational Biology Branch) was awarded a prestigious grant from the Chan Zuckerberg Initiative (CZI) to create a Nigeria Maternal Atlas to Improve Birth Outcomes using single-cell analysis as part of the Ancestry Networks for the Human Cell Atlas project.

Dr. Dondrae Coble (Chief, Comparative Medicine Branch) received the 2021 George R. Collins Education and Training Award by the American Association for Laboratory Animal Science (AALAS) for his outstanding contributions in the field of Laboratory Animal Technician Training.

Dr. R. Scott Williams (Genome Integrity and Structural Biology Laboratory) received the Southeast Regional Collaborative Access Team (SER-CAT) Outstanding Science Award from Argonne National Laboratory of the U.S. Department of Energy.

Named Professorships/Lectures

Dr. Chandra Jackson (Epidemiology Branch) was invited as the Keynote Speaker at the 2021 Reproductive Science and Medicine Summit organized by the Northwestern University Center for Reproductive Science on May 7, 2021.

Dr. Geoffrey Mueller (Genome Integrity and Structural Biology Laboratory) was selected to present the 2022 John W. Yunginger Memorial Lectureship at the American Academy of Allergy, Asthma and Immunology (AAAAI) Annual Meeting.

Dr. Lisa Rider (Clinical Research Branch) was invited to present the 9th Annual Kennedy Lectureship at the University of Alabama Department of Pediatrics on November 11, 2021.

Dr. Stephen Shears (Signal Transduction Laboratory) has been invited to present the Keynote Address at the 2022 International Inositol Phosphate Meeting.

Advisory/Editorial Boards

Dr. Trevor Archer (NIH Distinguished Investigator and Chief, Epigenetics and Stem Cell Biology Laboratory) served on the Board of Reviewing Editors of *Science*.

Dr. Dondrae Coble (Chief, Comparative Medicine Branch) served as a member of the Board of Directors for the National Association of Black Veterinarians; Chairperson for the American College of Laboratory Animal Medicine Equity and Inclusion Task Force; and Certification and Registry Board Member for the American Association for Laboratory Animal Science.

Dr. William Copeland (Chief, Genome Integrity and Structural Biology Laboratory) served as Chair for the 25th anniversary meeting of the United Mitochondrial Disease Foundation held June 2021 in Charlotte, NC.

Dr. Francesco DeMayo (Chief, Reproductive and Developmental Biology Laboratory) served as Past President and Board Member of Society for the Study of Reproduction.

Dr. Paul Doetsch (Deputy Scientific Director and Genome Integrity and Structural Biology Laboratory) served on the Department of Defense Programmatic Panel (Grants Council)

for Cancer Research Program. He also served as an Academic Editor for *BioMed Research International, Biochemistry Research International* and on the editorial boards *Nucleic Acids Research* and *DNA Repair*.

Dr. Kelly Ferguson (Epidemiology Branch) served on the Editorial Board of *Environmental Research*.

Dr. Michael Fessler (Chief, Immunity, Inflammation and Disease Laboratory) served as an Associate Editor for the *American Journal of Respiratory Cell and Molecular Biology*

Dr. Stavros Garantziotis (Immunity, Inflammation and Disease Laboratory) served on the Editorial Board of *Matrix Biology*, *American Journal of Respiratory Cell and Molecular Biology* and the *American Journal of Physiology – Lung Cellular and Molecular Physiology*. He served as an Associate Editor for *Lung.*

Dr. Dmitry Gordenin (Genome Integrity and Structural Biology Laboratory) served as Associate Editor for *PLoS Genetics* and on the Editorial Board of *Mutation Research, Fundamental and Molecular Mechanisms of Mutagenesis*.

Dr. Chandra Jackson (Epidemiology Branch) was elected to the Board of Directors of the Sleep Research Society.

Dr. Patricia Jensen (Neurobiology Laboratory) served as a member of the External Advisory Committee for the Metabolic Basis of Disease Center for the Pennington Biomedical Research Center. She is also served on the Editorial Board of *Brain Research.*

Dr. Anton Jetten (Immunity, Inflammation and Disease Laboratory) served on the Editorial Boards for *Nuclear Receptor Research*, *Stem Cell Investigation* and *Cells*

Dr. Anne Marie Jukic (Epidemiology Branch) served on the Editorial Board of *Environmental Health Perspectives.*

Dr. Kathy Laber (Comparative Medicine Branch) served as an Emeritus Council Member for AAALAC.

Dr. Alison Motsinger-Reif (Chief, Biostatistics and Computational Biology Branch) served as a Statistical Associate Editor for *Exposome* and on the Statistical Board of Reviewing Editors (sBORE) for *Science*.

Dr. Geoffrey Mueller (Genome Integrity and Structural Biology Laboratory) served as a review editor for *Frontiers in Allergy*. He also served on the World Health Organization / International Union of Immunological Societies Allergen Nomenclature Subcommittee.

Dr. Anant Parekh (Chief, Signal Transduction Laboratory) served as Executive Editor of *Function* and served on the Editorial Board of *Cells*.

Dr. Lalith Perera (Genome Integrity and Structural Biology Laboratory) served on the Editorial Board of *International Journal of Molecular Sciences* and as an Associate Editor of *Frontiers in Chemistry*.

Dr. Lisa Rider (Clinical Research Branch) served as an Associate Editor for *Autoimmune and Autoinflammatory Disorders, Frontiers in Immunology*, and served on the Editorial Boards of *Journal of Neuromuscular Diseases* and *Clinical Experimental Rheumatology.* She also served as an uncompensated Medical Advisor to Alexion, Pfizer and Argenx and as Chair of the Cure JM Foundation Medical Advisory Committee.

Dr. Keith Shockley (Biostatistics and Computational Biology Branch) served on the editorial boards of *Toxicologic Pathology*, *Frontiers in Toxicogenomics*, *Frontiers in Computational Toxicology and Informatics*. He also appointed as Associate Editor for *Toxigenomics*.

Dr. Carmen Williams (Reproductive and Developmental Biology Laboratory) was appointed as Associate Editor of *Biology of Reproduction* served as Academic Editor for *PLoS Biology*.

Dr. R. Scott Williams (Genome Integrity and Structural Biology Laboratory) served on the Editorial Board of the *Journal of Biological Chemistry.*

Dr. Humphrey Yao (Reproductive and Developmental Biology Laboratory) served on the Editorial Board for *Sexual Development* and on the Board of Reviewing Editors for *Biology of Reproduction.* Dr. Yao was also selected as a regular member of the Cellular, Molecular and Integrative Reproduction Study Session for the NIH.

Dr. Darryl Zeldin (Scientific Director and Immunity, Inflammation and Disease Laboratory) served as an Associate Editor for *Pharmacology and Therapeutics* and on the Editorial or Reviewer Boards of *Journal of Allergy and Clinical Immunology, Journal of Biological Chemistry*, the *American Journal of Physiology: Lung Cellular and Molecular Biology*, *American Journal of Respiratory Cell and Molecular Biology*, *Prostaglandins and Other Lipid Mediators*, *Open Environmental Research Journal, Molecular and Cellular Pharmacology* and the *Journal of Lipid Research.* He also served on the National Asthma Education and Prevention Program Federal Advisory Committee.

Dr. Shanshan Zhao (Biostatistics and Computational Biology Branch) served as an Associate Editor of *Biometrics* and as an academic advisor for *PLoS One*.

Training and Mentoring

NIEHS Trainee Alumni

From January 1, 2021, through December 31, 2021, 2 predoctoral trainees left NIEHS to continue their doctoral studies in their universities. 24 postbaccalaureate trainees left NIEHS. The majority of them went to either medical school or graduate school. And 29 postdoctoral trainees left NIEHS. Below is a summary of the analysis of where the postbaccalaureate and postdoctoral trainees have gone upon completing their training, what they are doing and the level of the positions they took.

Summary for the 24 departed postbaccalaureate trainees:

What are they doing?

Graduate School	**11**
Medical School	**8**
Veterinary Medicine School	**1**
Remained at NIEHS as contractor	**1**
Additional Postbaccalaureate training	**1**
Job in Industry	**1**
Other	**1**
TOTAL	**24**

Summary for the 29 departed postdoctoral trainees:

What are they doing?

Additional postdoctoral training	2
Internship	0
Additional advanced degree	0
Primarily teaching	2
Primarily basic research	7
Primarily clinical research	2
Primarily clinical practice	0
Primarily applied research	6
Primarily patient care	0
Regulatory affairs	0
Science administration/project management	0
Intellectual property/ licensing and patenting	1
Consulting	0
Public policy	0
Science writing or communications	1
Grants management	0
Business development or Operations	1
Computation/informatics	1
Sales/marketing	0
Technical/customer support	1
Unknown or Undecided	3
Other	1
Unemployed	1
TOTAL	29

Where did they go?

Academic institution	11
Government agency	4
For-profit company	8
Non-profit organization	1
Private medical practice	0
Independent/self-employed	1
Unknown or Undecided	3
Unemployed	1
TOTAL	29

What is the level of their position?

Tenure track faculty	6
Non-tenure track faculty	3
Professional staff	13
Support staff	0
Management	0
Trainee	3
Unknown or Undecided	3
Unemployed	1
TOTAL	29