Division of Intramural Research

NAEHS Council Update

September 2024

DIR RECRUITMENTS

Chief of the Center for Climate Change and Health Research
NIEHS is recruiting a Senior Investigator to serve as Chief of a new Center for Climate Change and Health Research (CCCHR) at NIEHS in the Division of Intramural Research (DIR). The CCCHR is a new trans-NIH center focused on advancing our understanding of the impact of climate change on human health. The goals of the CCCHR are to: 1) create a central hub that will facilitate research on the health impacts of climate change; 2) build a cadre of IRP scientists interested in Climate Change and Health (CCH) research and foster cross-cutting and convergent research partnerships; and 3) support the research and career development of both junior and experienced scientists interested in CCH research. The successful candidate will bring dynamic vision and leadership to the CCCHR while serving as a catalyst for innovation for climate change research across the NIH Intramural Research Program. The candidate will be responsible for overseeing the center's research operations, building partnerships with other NIH Institutes, Centers, and Offices, and providing scientific leadership to IRP investigators with joint appointments to the CCCHR. Applicants conducting research focused on understanding the biological mechanisms underlying the effects of climate change on health are encouraged to apply. The ideal candidate will be tenure-eligible based on an outstanding academic record of achievement, leadership capabilities, and broad interests in CCH research. The successful candidate for this position will also maintain an active independent research program. Dr. Paul Wade, Senior Investigator and Chief of the Epigenetics and Stem Cell Biology Laboratory serve as chair of the search committee which launched May 24, 2023.

Tenure-Track Investigator in the Immunity, Inflammation and Disease Laboratory
NIEHS is recruiting a Tenure-Track Investigator to study fundamental mechanisms by which immune and inflammatory responses are triggered and regulated in the lung and other organs and contribute to disease, with a particular focus on asthma, host defense/innate immunity, lung fibrosis, and cardiovascular disease. In addition to building upon current strengths, areas of special interest for future growth of IIDL include: (i) immunometabolism (programming of the immune response by changes in cellular metabolic pathways); (ii) mucosal immunity (lung, gut, other) including the heterogeneity, ontogeny, and/or function of immune, epithelial, and stromal tissue-resident cells; and (iii) systems biology of the immune response. However, we enthusiastically welcome applications from outstanding scientists in all fields of immunology. The successful candidate is expected to lead an innovative, independent research program exploring the mechanism of immune responses that enhances our understanding of the effects of the environment on human health. Applicants should have a Ph.D., M.D. and/or equivalent doctoral degree with at least 3 years of postdoctoral research experience in their field and an outstanding publication record. The emphasis will be on identifying an exceptional scientist with an innovative and productive research program. Dr. Anant Parekh, Senior Investigator and Chief of the Signal Transduction Laboratory serves as chair of the search committee which launched February 27, 2023.

Chief of the Genome Integrity and Structural Biology Laboratory
NIEHS is recruiting a Senior Investigator to serve as Chief of the Genome Integrity and Structural Biology Laboratory (GISBL) at NIEHS in the Division of Intramural Research (DIR). GISBL is currently composed of seven independent research groups that study fundamental mechanisms of genetic stability and instability, including DNA replication and repair utilizing state-of-the-art

structural biology techniques, genetics, biochemistry and cell biology to provide insights into biological processes that modulate the effects of environmental exposures on human health. The GISBL also houses four state-of-the-art core facilities that provide computational chemistry and molecular modeling, cryo-electron microscopy (cryoEM), NMR, and x-ray crystallography support to all of NIEHS and, in the case of cryoEM, for other NIH institutes. The successful candidate will be tenure-eligible based on an outstanding record of scholarly achievement, leadership capabilities, and broad interests in understanding biological processes involved in mutagenesis, genome stability, allergenicity, mitochondrial function, inflammation, and epigenetic regulation. In addition to directing an independent research program, the Chief will be responsible for leading GISBL and providing vision and directions as research in genome integrity, structural biology and environmental health science continues to evolve. Principal investigators in the NIH intramural program engage directly in high risk/high reward research with postdoctoral fellows, students, and support staff, and collaborate with colleagues to solve important scientific problems. Applicants should have a Ph.D., M.D., or equivalent doctoral degree in a relevant field, and a demonstrated interest in investigating fundamental mechanisms of genetic stability and instability. Dr. Franco DeMayo, Senior Investigator and Chief of the Reproductive and Developmental Biology Laboratory serves as chair of the search committee that launched July 2024.

Chief of the Clinical Research Branch and NIEHS Clinical Director

NIEHS is seeking applications from outstanding clinician-scientist candidates for the position of Clinical Director and Chief of the Clinical Research Branch (CRB) within the Division of Intramural Research (DIR). The Clinical Director reports to the NIEHS Director and coordinates clinical activities with the NIEHS Scientific Director. The incumbent is responsible for the development, administration, coordination and oversight of investigator-initiated clinical research; provides general advice to the Director and Scientific Director on matters relating to human and clinical studies; supervises staff in the NIEHS Clinical Research Unit (CRU) and the NIEHS Office of Human Research and Community Engagement (OHRCE); and develops policies and programs for the execution of clinical research at NIEHS. The Clinical Director is responsible for creating and maintaining a research environment in which clinical findings influence the direction of laboratory studies and laboratory findings are applied back to the clinic and clinical research communities. The incumbent will facilitate intramural clinical research by identifying opportunities for translating basic science into clinical studies and vice versa (back translation of clinical findings to basic science). The Clinical Director will ensure that Institute research reflects the highest standards of scientific excellence and ethical conduct for the protection of human subjects. The incumbent will review matters pertaining to the provision of patient care in research protocols and oversee resource allocation, scientific review, and recruitment of clinical staff. The Clinical Director will provide advice and training on the conduct of clinical studies, facilitate clinical research collaborations between intramural and extramural investigators, and develop long-range clinical research goals and objectives relevant to the mission of NIEHS and the NIEHS Strategic Plan. It is expected that the successful candidate will also oversee their own independent clinical research program that may involve some combination of outpatient-oriented studies within the NIEHS CRU, epidemiological studies, basic laboratory studies, and/or inpatient studies at the NIH Clinical Center in Bethesda. We envision that the successful candidate will primarily be engaged in clinical research; however, they will also have access to state-of-the-art NIEHS core facilities and may receive resources to support a modest basic science laboratory to facilitate translational research.

The incumbent plays a key role in creating and maintaining a nurturing clinical research environment that encourages creativity, collaboration among scientists from different disciplines, effective training of postdoctoral fellows and trainees, and efficient utilization of resources. The selected candidate will also be responsible for leading the Clinical Research Branch (CRB) whose mission is to: 1) translate basic laboratory findings to humans; 2) study interactions between genetic susceptibility and environmental factors in the pathogenesis of complex human traits and diseases; and 3) identify at-risk populations and develop novel preventative and therapeutic strategies to combat human diseases. Responsibilities will include directing the overall scientific vision of the CRB and overseeing resource allocation. The Chief will also have the opportunity to mentor investigators and clinicians at NIEHS as well as clinical fellows and medical students through affiliations with regional medical institutions.

Applicants must possess an M.D., M.D./Ph.D., or equivalent degree, and have demonstrated scientific leadership and senior-level research experience in a clinical research program of national and international standing in an area relevant to the NIEHS mission. The individual must possess a current, active, full and unrestricted license to practice medicine in the United States and be eligible to be credentialed for patient care by the NIH Clinical Center. The successful candidate will have a compelling vision for the future of the field, proven experience in managing and directing a clinical research program, and well-honed administrative and interpersonal skills. The NIEHS seeks candidates who have a commitment to scientific excellence and the energy, enthusiasm, and innovative thinking necessary to maintain the Institute's clinical research efforts at the forefront of science. Preference will be given to those known and respected within their profession, both nationally and internationally, as distinguished individuals of outstanding scientific competence and those who possess a record of achievement as a senior scientific administrator/executive leader. Applicants also must have demonstrated experience in setting, planning, implementing, and analyzing program objectives and priorities. Candidates should have the demonstrated ability to manage financial and human resources and lead a clinical research program involving extensive internal and external collaboration. Dr. Janice Lee, Clinical Director of the National Institute of Dental and Craniofacial Research (NIDCR) serves as chair of the search committee that launched April 2024.

DIR STAFF UPDATES

Medical Director of the Clinical Research Unit

Dr. Lawrence Kirschner has accepted an offer to join NIEHS as a Senior Clinician in the Clinical Research Branch (CRB) and to serve as Medical Director of the NIEHS Clinical Research Unit (CRU) and Director of Clinical Operations for the NIEHS Personalized Environment and Genes Study (PEGS) on the NIEHS campus in Research Triangle Park, North Carolina. Dr. Kirschner is a physician-scientist and clinical endocrinologist with expertise in treating patients with pituitary and adrenal tumors (including adrenal cancer and pheochromocytoma), and inherited syndromes that cause endocrine tumors or other endocrine dysfunction. Prior to joining NIEHS, he served as a Professor of Internal Medicine in the Division of Endocrinology, Diabetes and Metabolism at The Ohio State University College of Medicine in Columbus, Ohio. Dr. Kirschner has a tentative start date in August 2024.

DIR COMMITMENT TO DIVERSITY, EQUITY, INCLUSION AND ACCESSIBILITY

NIH Distinguished Scholars Program

Dr. Julieta Lischinsky, an Earl Stadtman Tenure Track Investigator in the Neurobiology Laboratory, and Dr. Rajula Elango, a Tenure Track Investigator in the Genome Integrity and Structural Biology Laboratory, were selected to participate in the NIH Distinguished Scholars Program based on their demonstrated commitment to lowering barriers to participation in science for individual traditionally underrepresented in science. Drs. Lischinsky and Elango join four DIR Tenure-Track Investigators previously selected to the DSP: Drs. Joseph Rodriguez (ESCBL), Benedict Anchang (BCBB), Jason Watts (ESCBL) and Carlos Guardia (RDBL) as well as Dr. Dondrae Coble (CMB Chief) who is a Senior Scientist member of the DSP cohort.

DIR Diversity, Equity, Inclusion and Accessibility (DEIA) Working Group

A voluntary working group of more than 50 members including administrative, scientific, and scientific support employees, trainees, and contractors representing all DIR Laboratories and Branches has been organized and is co-chaired by Dr. Raja Jothi, Senior Investigator in ESCBL and Dr. Steven Tuyishime, Assistant Scientific Director. This working group has been charged with proposing recommendations to the Scientific Director to improve and enhance diversity, equity, inclusion, and accessibility throughout the DIR workforce. Initial recommendations were provided to the Scientific Director and DIR Council in late 2022 and an action plan is currently being developed to prioritize and implement new policies and programs in 2023.

The working group is divided into four thematic subgroups each with two co-leaders:

Subgroup 1: Recruitment and Retention (Joe Rodriguez and Yesenia Rodriguez)
Subgroup 2: Career Development (Jackson Hoffman and Vince Guerrero)
Subgroup 3: Performance, Evaluation, and Recognition (Justin Kosak and Francesco DeMayo)
Subgroup 4: Outreach and Engagement (Anne Marie Jukic and Steve Tuyishime)

BSC REVIEW OF THE IMMUNITY, INFLAMMATION AND DISEASE LABORATORY

The NIEHS DIR Board of Scientific Counselors reviewed the Immunity, Inflammation and Disease Laboratory, June 23-25, 2024

Members of the Board of Scientific Counselors:

- Carlos A. Camargo, M.D., Dr. P.H., Professor of Emergency Medicine, Medicine and Epidemiology, Harvard Medical School and Harvard T.H. Chan School of Public Health, Boston, MA
- Fernando Camargo, Ph.D., Professor of Stem Cell and Regenerative Biology, Harvard University, Boston, MA
- Walter J. Chazin, Ph.D., Professor of Biochemistry and Chancellor's Chair in Medicine Department of Biochemistry and Chemistry, Vanderbilt University, Nashville, TN
- Dineo Khabele, M.D., Mitchell and Elaine Yanow Professor, Department of Obstetrics and Gynecology, Washington University School of Medicine, St. Louis, MO
- Ji-Yong Julie Kim, Ph.D., Susy Y. Hung Professor of Obstetrics and Gynecology and Co-Director, Center for Reproductive Science, Northwestern University, Chicago, IL
- 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
- Roland A. Owens, Ph.D., Ex-Officio BSC Member, Office of Intramural Research, NIH, Bethesda, MD
- Victor L. Schuster, M.D., BSC Chair, Ted and Florence Baumritter Chair in Medicine, Professor of Medicine (Nephrology) and Biochemistry and Senior Associate Dean, Albert Einstein College of Medicine, Bronx, NY

Ad Hoc Reviewers:

- Nabil J. Alkayed, M.D., Ph.D., James Metcalfe Chair of Cardiovascular Medicine, Professor or Anesthesiology and Perioperative Medicine, Director of Research, Knight Cardiovascular Institute, Oregon Health & Science University, Portland, OR
- Russell P. Bowler, M.D., Ph.D., Professor, Department of Medicine, Division of Pulmonary, Critical Care & Sleep Medicine, National Jewish Health, Denver, CO
- Douglas Forrest, Ph.D., Chief and Senior investigator, Nuclear Receptor Biology Section
- Laboratory of Endocrinology & Receptor Biology, National Institute of Diabetes and Digestive and Kidney Disease, NIH, Bethesda, MD
- Anthony N. Gerber, M.D., Ph.D., Professor of Medicine, Immunology and Genomic Medicine, Director of Pulmonary Research, National Jewish Health, Denver, CO
- Cory Hogaboam, Ph.D., Professor of Medicine, Division of Pulmonary and Critical Care Medicine, Cedars-Sinai Medical Center, Los Angeles, CA
- Benjamin D. Medoff, M.D., Chief, Division of Pulmonary and Critical Care, Center for Immunology and Inflammatory Diseases, Massachusetts General Hospital, Boston, MA

- Thomas O. Metz, Ph.D., Chief Science Officer, Biological Sciences Division and Director, Pacific Northwest Advanced Compound Identification Core, Pacific Northwest National Laboratory, Richland, WA
- Samuel M. Poloyac, Pharm. D., Ph.D., Dean and James T Doluisio Regents Chair, The University of Texas, Austin, TX
- Melanie A. Simpson, Ph.D., Professor and Department Head, Molecular and Structural Biochemistry, North Carolina State University, Raleigh, NC
- Hubert Tse, Ph.D., Professor, Microbiology, Molecular Genetics and Immunology, Kansas University Medical Center, The University of Kansas, Kansas City, KS

Agenda:

Closed - Sunday Evening Session - June 23, 2024 – Zoom Meeting

7:00 - 8:00 p.m.	Welcome and Discussion of Past Board Reviews, Drs. Rick Woychik, Darryl Zeldin, Michael Fessler and Victor Schuster
8:00 – end	BSC Discussion of Review, Dr. Victor Schuster and panel

Monday Morning Session - June 24, 2024 - NIEHS Rodbell Auditorium

8:30 – 8:45 (ET)	Welcome, Drs. Victor Schuster and Rick Woychik
8:45 - 9:10	Overview, Immunity, Inflammation and Disease Laboratory, Dr. Michael Fessler
9:10-10:00	Clinical Investigation of Host Defense Group, Dr. Michael Fessler
10:00 - 10:15	Break
10:15 - 11:05	Cell Biology Group, Dr. Anton Jetten
11:05 - 11:55	Environmental Cardiopulmonary Disease Group, Dr. Darryl Zeldin
11:55-12:55	Closed - Working Lunch

Monday Afternoon Session - June 24, 2024 - NIEHS Rodbell Auditorium

1:00-1:45	Closed 1:1 Sessions with Investigators Drs. Fessler, Jetten and Zeldin
1:45-2:35	Matrix Biology Group, Dr. Stavros Garantziotis
2:35-2:50	Closed 1:1 Session with Investigator, Dr. Garantziotis
2:50-3:05	Break
3:05-3:30	Immunogenetics Group, Dr. Donald Cook
3:30-4:00	Closed Meeting with Core Director, Dr. Alan Jarmusch
4:00	Return to Hotel

Tuesday Morning Sessions – June 25, 2024 - NIEHS Rodbell Auditorium

8:30-10:00	Poster Session, Rall Building C module mall
10:00-10:15	Break
10:15-10:45	Closed Session with Fellows
10:45-11:15	Closed Session with Staff Scientists, Biologists and Chemists
11:20-12:30	Closed - Working Lunch

12:30-2:00	Closed BSC Discussion and Completion of Individual Review Assignments
2:00-2:15	Break
2:15-3:15	Closed - Debriefing to NIEHS/DIR Leadership
3:15	Adjourn

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 total number of awards among all NIH Institutes and Centers and the highest success rate at NIH.

The NIEHS Division of Intramural Research has 15 FARE award winners for 2025:

FARE Winner	Mentor	Project
Dr. Marine Baptissart	Dr. Marcos Morgan	Revealing RNA poly(A) tail dynamic during spermiogenesis and its function to support male fertility
Dr. Niketa Bhawsinghka	Dr. Roel M Schaaper	dGTP starvation in E. coli
Dr. Dazhe Chen	Dr. Dale Sandler	Childhood and adolescent residential and farm pesticide exposures and inflammatory bowel disease incidence in a U.S. cohort of women
Mr. Jacob Gordon	Dr. Robin E Stanley	The SUMO protease SENP3 is allosterically regulated by the rixosome complex
Dr. Ji Cheng Li	Dr. Guohong Cui	Co-administration of D1 receptor PAM prevents L-DOPA-induced dyskinesia in parkinsonian mice
Dr. Wilfred Lopez Perez	Dr. Michael B Fessler	Deletion of Epithelial Membrane Protein 2 Protects from Lung Fibrosis
Dr. Mahina Monsur	Dr. Thomas A Kunkel	Whole Genome Study of Nucleotide Excision Repair and Translesion Synthesis in Saccharomyces cerevisiae
Dr. Krystal A Orlando	Dr. Paul Wade	Cooperative binding of pioneer transcription factor and co-factors depends on the transactivation domain for remodeling the enhancer landscape
Dr. Puja Sohal	Dr. Anton Jetten	GLIS3 plays a critical role in the regulation of inflammation and fibrosis in cystic kidney disease
Dr. Lenka Radonova	Dr. Carmen Williams	The power network: mitochondria-endoplasmic reticulum interactions in oocyte and egg
Dr. Danielle R Stevens	Dr. Kelly Ferguson	Gestational Exposure to Endocrine Disrupting Chemicals and Fetal Liver Development: Findings from the HPP 3D Study
Dr. Dimitrios Theofilatos	Dr. Trevor K Archer	Exposure to high temperatures alters Glucocorticoid Receptor activity

FARE Winner	Mentor	Project
Dr. Christina Wilkinson	Dr. Don Cook	CD301b+ lung dendritic cells confer tolerance to inhaled allergens
Dr. Xiaoyue Wu	Dr. Xiaoling Li	Microbiota-dependent deamidated NAD biosynthesis is important for gut resiliency under stress

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.

Ciro M. Amato III, Ph.D., received a K99 Award from NIDDK and will be mentored by Dr. Humphrey Yao in the Reproductive and Developmental Biology Laboratory

Virginia Savy, Ph.D., received a K99 Award from NICHD and will be mentored by Dr. Carmen Williams in the Reproductive and Developmental Biology Laboratory

Danielle Stevens, Ph.D., received a K99 from NIEHS and will be mentored by Dr. Kelly Ferguson in the Epidemiology Branch

Emily Werder, Ph.D., received a K99 Award from NIEHS and will be mentored by Dr. Dale Sandler in the Epidemiology Branch

Mandy Goldberg, Ph.D., received a K99 Award from NICHD and will be mentored by Dr. Dale Sandler in the Epidemiology Branch

Ayland Letsinger, Ph.D., received a K99 Award from NIDA and will be mentored by Dr. Jerry Yakel in the Neurobiology Laboratory

NIGMS PRAT Awards:
Drs. Adriana Alexander and Ryan Marquardt in the Reproductive and Developmental Biology Laboratory received prestigious NIGMS Postdoctoral Research Associate Training (PRAT) Awards and will be mentored by Drs. Humphrey Yao and Franco DeMayo, respectively. This award provides 3 years of funding from NIGMS.

2023 NIMHD Coleman Research Innovation Awards

Dr. James Murkey a postdoctoral fellow in the Epidemiology Branch received a 2024 Coleman Research Innovation Awards from NIMHD.

2024 Intramural Office of Autoimmune Diseases Research (IOADR) Fellowship

Jasmine Mack, NIH OxCam Predoctoral Fellow in the Biostatistics and Computational Biology Branch

Dr. Jennifer Woo, IRTA Postdoctoral Fellow in the Epidemiology Branch

2024 NIH Poster Day- Postbaccalaureate Fellows Outstanding Posters

John Dong	Neurobiology Laboratory
Hope Hawthorne	Epigenetics and Stem Cell Biology Laboratory
Abigail Kitakule	Reproductive and Developmental Biology Laboratory
Skylar Montague Redecke	Reproductive and Developmental Biology Laboratory
Maira Perez	Reproductive and Developmental Biology Laboratory
Elvis Quiroz	Reproductive and Developmental Biology Laboratory
Alanna Stewart	Epigenetics and Stem Cell Biology Laboratory
Tia Vierling	Neurobiology Laboratory

DIR RESEARCH ACCOMPLISHMENTS FOR FY 2024

The correction of mismatches made during DNA replication

This year we published two scientific articles on the enzymes that repair mismatches made during replication of the eukaryotic nuclear genome. The first article reports that the endonuclease activity of the Pms1 protein nicks the newly synthesized DNA strand to provide a signal for repair of mistakes present in that strand. The second article provides evidence that DNA ligase seals nicks created by repair of replication errors, thereby completing replication of lagging strand of DNA across the whole nuclear genome.

Williams JA, Lujan SA, Arana ME, Burkholder A, Tumbale P, Williams RS and Kunkel TA. High fidelity DNA ligation prevents single base insertions in the yeast genome. *Nature Communications*. 2024 in press.

Lujan S, Garbacz, M., Liberti, S., Burkholder, A. and Kunkel, T.A., (2024) Instability throughout the Saccharomyces cerevisiae genome resulting from Pms1 endonuclease deficiency. *Nucleic Acids Research*. 2024 in press.

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Accounting for reporting bias strengthens evidence for a link between talcum powder use and ovarian cancer

Using updated data on use of intimate care products such as talc and douching, NIEHS researchers showed that after accounting for possible exposure misclassification, genital talc use was positively associated with ovarian cancer incidence in the US-wide Sister Study cohort, with relative risks for frequent versus never users ranging from 1.2 to 3.3 under different scenarios. After also accounting for possible differential reporting accuracy among cases and non-cases, risk estimates were all positive, with a 40% increase in risk after accounting for a moderate level of misreporting. Frequent douching, especially during young adulthood was associated with ovarian cancer. Neither talc nor douching was associated with breast or uterine cancers. Findings support a growing body of evidence linking talc to ovarian cancer risk.

O'Brien KM, Wentzensen N, Ogunsina K, Weinberg CR, D'Aloisio AA, Edwards JK, Sandler DP. Intimate Care Products and Incidence of Hormone-Related Cancers: A Quantitative Bias Analysis. *J Clin Oncol*. 2024 Aug 1;42(22):2645-2659. doi: 10.1200/JCO.23.02037. Epub 2024 May 15. PMID: 38748950.

Role of Thromboxane in Allergic Lung Inflammation

Thromboxane A2 (TXA2) is generally considered a pro-inflammatory prostanoid. In lung, TXA2 activates the TP receptor to induce pro-inflammatory and bronchoconstrictor effects. Thus, TP receptor antagonists and TXA2 synthase inhibitors have been tested as potential asthma therapeutics in humans. Th9 cells play key roles in asthma and regulate the lung immune response to allergens. Herein, we found that TXA2 reduces Th9 cell differentiation during allergic lung inflammation. Th9 cells were decreased ~2-fold and airway hyperresponsiveness was suppressed in lungs of mice treated with TXA2 during ovalbumin (OVA)-induced allergic lung inflammation in vivo. Naïve CD4+ T cell differentiation to Th9 cells was inhibited dose-dependently by TXA2 with a concomitant increase in phosphorylation of p38 MAPK and a decrease in production of IL-9 in vitro. Consistent with these observations, TP receptor deficient

mice had a ~2-fold increase in numbers of Th9 cells in lungs in vivo after OVA exposure compared to wild type (WT) mice. Naïve CD4+ T cells from TP deficient mice exhibited increased Th9 cell differentiation, decreased phosphorylation of p38 MAPK and increased IL-9 production in vitro compared to naive CD4+ T cells from WT mice. TXA2 induced Nuclear Factor Erythroid 2 and PBX Homeobox 1 transcription factor binding to the proximal Il9 promoter to suppress IL-9 transcription. Thus, contrary to its reputation as an acute, pro-inflammatory mediator, TXA2 also has longer-lasting immunosuppressive effects that attenuate the T helper cell differentiation that drives asthma progression. These findings may explain the paradoxical failure of anti-thromboxane therapies in the treatment of asthma.

Li H, Bradbury JA, Edin ML, Gruzdev A, Li H, Graves JP, DeGraff LM, Lih FB, Feng C, Wolf ER, Bortner CD, London SJ, Sparks MA, Coffman TM, Zeldin DC. TXA2 attenuates allergic lung inflammation through regulation of Th2, Th9, and Treg differentiation. *J Clin Invest*. 2024 Mar 14;134(9):e165689. doi: 10.1172/JCI165689. PMID: 38483511; PMCID: PMC11060738.

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 studied in detail. In particular, we have discovered that the two DNA strands are not replicated with the same accuracy with lagging-strand replication being more accurate than the leading strand. We have also deciphered the entire genome sequence of an E. coli strain that is important for biotechnical applications. We have also investigated the structures of several dGTPase enzymes important for DNA replication accuracy via their effect on the DNA precursor concentrations.

Bhawsinghka N, Burkholder A, Schaaper RM. Detection of DNA replication errors and 8-oxo-dGTP-mediated mutations in E. coli by Duplex DNA Sequencing. *DNA Repair* (Amst). 2023 Mar;123:103462. doi: 10.1016/j.dnarep.2023.103462. Epub 2023 Jan 28. PMID: 36738688; PMCID: PMC9992157.

Klemm BP, Singh D, Smith CE, Hsu AL, Dillard LB, Krahn JM, London RE, Mueller GA, Borgnia MJ, Schaaper RM. Mechanism by which T7 bacteriophage protein Gp1.2 inhibits Escherichia coli dGTPase. *Proc Natl Acad Sci U S A*. 2022 Sep 13;119(37):e2123092119. doi: 10.1073/pnas.2123092119. Epub 2022 Sep 6. PMID: 36067314; PMCID: PMC9478638.

Klemm BP, Sikkema AP, Hsu AL, Horng JC, Hall TMT, Borgnia MJ, Schaaper RM. High-resolution structures of the SAMHD1 dGTPase homolog from Leeuwenhoekiella blandensis reveal a novel mechanism of allosteric activation by dATP. *J Biol Chem*. 2022 Jul;298(7):102073. doi: 10.1016/j.jbc.2022.102073. Epub 2022 May 26. PMID: 35643313; PMCID: PMC9257424.

New Tool Enhances Understanding of Complex Biological Data

Researchers at NIEHS have developed a groundbreaking computational tool called MIBCOVIS, designed to improve the visualization and interpretation of complex biological datasets. This innovative approach addresses the challenge of analyzing intricate patterns in data that change over time or space, which are often difficult to simplify and interpret. By enabling easy comparisons of various data reduction methods, MIBCOVIS helps scientists gain deeper insights into biological processes, particularly in fields like developmental biology. This tool promises to enhance the accuracy and interpretability of high-dimensional data, paving the way for advancements in multiple scientific disciplines.

Atitey K, Motsinger-Reif AA, Anchang B. Model-based evaluation of spatiotemporal data reduction methods with unknown ground truth through optimal visualization and interpretability metrics. *Brief Bioinform*. 2023 Nov 22;25(1):bbad455. doi: 10.1093/bib/bbad455. PMID: 38113074; PMCID: PMC10729792.

How disordered regions of proteins regulate RNA binding

Intrinsically disordered regions (IDRs) help to mediate interactions between partner proteins to control RNAs, according to NIEHS researchers and their collaborators. By determining a crystal structure of a roundworm protein called fem-3 binding factor-2 (FBF-2) and through biochemical studies, the researchers discovered that an IDR at the C-terminus of FBF-2 autoinhibits its RNA-binding affinity. The findings also suggest that LST-1 enhances FBF-2 RNA-binding affinity by displacing its C-terminus, thereby alleviating autoinhibition.

Qiu C, Zhang Z, Wine RN, Campbell ZT, Zhang J, Hall TMT. Intra- and inter-molecular regulation by intrinsically-disordered regions governs PUF protein RNA binding. *Nat Commun.* 2023 Nov 13;14(1):7323. doi: 10.1038/s41467-023-43098-1. PMID: 37953271; PMCID: PMC10641069.

The steroid hormones estrogen and progesterone work together to regulate uterus function

Steroid hormones are key regulators of female reproductive function but our understanding of how these hormones work was based mainly on experiments done using either cultured cells or animals lacking ovaries. We tested how the estrogen and progesterone receptors control uterine gene expression in normal cycling female mice. We discovered unexpectedly that almost all estrogen receptor binding to DNA is accompanied by the progesterone receptor to regulate cyclic uterine gene expression. These studies are relevant to our understanding of how endocrine disrupting chemicals could impact human reproduction.

Jefferson WN, Wang T, Padilla-Banks E, Williams CJ. Unexpected nuclear hormone receptor and chromatin dynamics regulate estrous cycle dependent gene expression. *Nucleic Acids Res*. 2024 Aug 21:gkae714. doi: 10.1093/nar/gkae714. Epub ahead of print. PMID: 39166489.

Improving the Synthesis of Synthetic Heparin

Heparosan Synthase 2 from Pasteurella multocida (PmHS2) is utilized in the chemoenzymatic synthesis of heparin and heparan sulfate that provides therapeutic benefits over the porcine purified form currently used in the clinic. NIEHS researchers in collaboration with UNC School

of Pharmacy researchers determined the structure of PmHS2 and used this information to engineer PmHS2 to be more suitable for large scale industrial production.

Stancanelli, E, Krahn, JA, Viverette, E, Dutcher, R., Pagadala, V., Borgnia, MJ, Liu, J, Pedersen, LC. Structural and Functional Analysis of Heparosan Synthase 2 from Pasteurella multocida to Improve the Synthesis of Heparin. *ACS Catal*. 2024; 9:6577-6588. doi.org/10.1021/acscatal.4c00677

How the mitochondria deal with diseased DNA polymerase gamma partially elucidated The replicative mitochondrial DNA polymerase, Polγ, and its protein regulation are essential for the integrity of the mitochondrial genome. The intricacies of Polγ regulation and its interactions with regulatory proteins, which are essential for fine-tuning polymerase function, remain poorly understood. Misregulation of the Polγ heterotrimer, consisting of PolG, the polymerase catalytic subunit, and PolG2, the accessory subunit, ultimately results in mitochondrial diseases. The researchers used single particle cryo-electron microscopy to resolve the structure of PolG. Chemical crosslinking mass spectrometry and site-directed mutagenesis uncovered the region where a protein called LonP1 engages with PolG, promoting proteolysis and regulation of PolG protein levels. PolG2 clinical variants, which disrupted a stable Polγ complex, led to enhanced LonP1-mediated PolG degradation. Overall, this insight into Polγ aids in an understanding of mitochondrial DNA replication and characterizes how machinery of the replication fork may be targeted for proteolytic degradation when improperly functioning. According to the authors, the spectrum of the downstream implications of LonP1 targeting PolG is currently unknown. However, future work could explore targeting the interaction sites of PolG and PolG2 as a potential therapeutic in pancreatic cancer.

Riccio AA, Brannon AJ, Krahn JM, Bouvette J, Williams JG, Borgnia MJ, Copeland WC. Coordinated DNA polymerization by Polγ and the region of LonP1 regulated proteolysis. *Nucleic Acids Res*. 2024 Jul 22;52(13):7863-7875. doi: 10.1093/nar/gkae539. PMID: 38932681; PMCID: PMC11260448.

The structure of the mitochondrial single-stranded DNA binding protein, mtSSB, with DNA helps to explain disease mutations in the mtSSB gene

Description (3-5 sentences): The apo structure of the human mitochondrial single stranded DNA binding protein, mtSSB, was solved more than 25 years ago. But the structure with single strand DNA has eluded researchers until now. Here, researchers in the Copeland lab at the NIEHS has solved a high-resolution structure of the human mtSSB with DNA. This structure illuminates the consequences of many of the recently discovered disease mutations in the gene for mtSSB and how they interact with the environment. This new structure points to a clear understanding of the pathogenesis of these mitochondrial diseases, opening doors to therapies.

Riccio AA, Brannon AJ, Krahn JM, Bouvette J, Williams JG, Borgnia MJ, Copeland WC. Coordinated DNA polymerization by Polγ and the region of LonP1 regulated proteolysis. *Nucleic Acids Res*. 2024 Jul 22;52(13):7863-7875. doi: 10.1093/nar/gkae539. PMID: 38932681; PMCID: PMC11260448.

Lung fibroblasts are important for the maintenance of the lung stem cell niche
We discovered that while fibroblasts in injured lung acquire a potentially reversible fibrogenic profile, which alters the kinetics of epithelial regeneration and potentially contributes to dysregulated repair, leading to fibrosis.

Trempus CS, Papas BN, Sifre MI, Bortner CD, Scappini E, Tucker CJ, Xu X, Johnson KL, Deterding LJ, Williams JG, Johnson DJ, Li JL, Sutton D, Ganta C, Mahapatra D, Arif M, Basu A, Pommerolle L, Cinar R, Perl AK, Garantziotis S. Functional Pdgfra fibroblast heterogeneity in normal and fibrotic mouse lung. *JCI Insight*. 2023 Nov 22;8(22):e164380. doi: 10.1172/jci.insight.164380. PMID: 37824216; PMCID: PMC10721331.

Higher outdoor air pollutant levels associated with a higher risk of breast cancer
We evaluated the relationship between historic concentrations of fine particulate matter (PM2.5) and incident breast cancer in a large, geographically spread U.S. cohort which included 196,905 female participants enrolled between 1995-1996. Residential outdoor exposure to a five-year average PM2.5 concentrations at their baseline residence was estimated between 1980 and 1984 and women were followed for cancer diagnoses through 2017. Living in areas with greater than the average levels of PM2.5 was associated with an 8% higher incidence of breast cancer overall. This association was particularly evident for women with estrogen receptor–positive tumors, which may be more likely to be influenced by endocrine disrupting compounds compared to other tumor subtypes.

White AJ, Fisher JA, Sweeney MR, Freedman ND, Kaufman JD, Silverman DT, Jones RR. Ambient fine particulate matter and breast cancer incidence in a large prospective US cohort. *J Natl Cancer Inst*. 2024 Jan 10;116(1):53-60. doi: 10.1093/jnci/djad170. PMID: 37691174; PMCID: PMC11045029.

Effects of Soluble Epoxide Hydrolase Inhibition during SARS-CoV-2 Infection
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection involves an initial viral infection phase followed by a host-response phase that includes an eicosanoid and cytokine storm, lung inflammation and respiratory failure. While vaccination and early anti-viral therapies are effective in preventing or limiting the pathogenic host response, this latter phase is poorly understood with no highly effective treatment options. Inhibitors of soluble epoxide hydrolase (sEH) increase levels of anti-inflammatory molecules called epoxyeicosatrienoic acids (EETs). This study aimed to investigate the impact of sEH inhibition on the host response to SARS-CoV 2 infection in a mouse model with human angiotensin-converting enzyme 2 (ACE2) expression. Mice were infected with SARS-CoV-2 and treated with either vehicle or the sEH inhibitor 1-trifluoromethoxyphenyl-3-(1-propionylpiperidin-4-yl) urea (TPPU). At day 5 post-infection, SARS-CoV-2 induced weight loss, clinical signs, a cytokine storm, an eicosanoid storm, and severe lung inflammation with ~50% mortality on days 6-8 post-infection. SARS-CoV-2 infection induced lung expression of phospholipase A2 (PLA2), cyclooxygenase (COX) and lipoxygenase (LOX) pathway genes, while suppressing expression of most cytochrome P450 genes. Treatment with the sEH inhibitor TPPU delayed weight loss but did not alter clinical signs, lung cytokine expression or overall survival of infected mice. Interestingly, TPPU

treatment significantly reversed the eicosanoid storm and attenuated viral-induced elevation of 39 fatty acids and oxylipins from COX, LOX and P450 pathways, which suggests effects at the level of PLA2 activation. The suppression of the eicosanoid storm by TPPU without corresponding changes in lung cytokines, lung inflammation or mortality reveals a surprising dissociation between systemic oxylipin and cytokine signaling pathways during SARS-CoV-2 infection and suggests that the cytokine storm is primarily responsible for morbidity and mortality in this animal model.

Edin ML, Gruzdev A, Graves JP, Lih FB, Morisseau C, Ward JM, Hammock BD, Bosio CM, Zeldin DC. Effects of sEH inhibition on the eicosanoid and cytokine storms in SARS-CoV-2-infected mice. *FASEB J*. 2024 May 31;38(10):e23692. doi: 10.1096/fj.202302202RR. PMID: 38786655; PMCID: PMC11141730.

Job and Other Forms of Everyday Racial and Ethnic Discrimination Linked to Higher Hypertension Risk, Especially among Black Women with Higher Education

Two longitudinal studies from the Sister Study cohort highlight the significant impact of discrimination on hypertension risk among U.S. women, particularly Black women. In one study, Black women with higher educational attainment had the highest burdens of everyday racial and ethnic discrimination across all racial and ethnic and educational attainment groups. Black women with high educational attainment also had a higher risk of racial and ethnic discrimination-related hypertension risk. Another study demonstrated that perceived job discrimination was associated with an increased risk of hypertension across all participants, yet Black women had among the highest burdens of job discrimination. The findings emphasize the need for interventions to address multiple forms of discrimination to improve cardiovascular health and promote health equity.

Gaston SA, Forde AT, Green M, Sandler DP, Jackson CL. Racial and Ethnic Discrimination and Hypertension by Educational Attainment Among a Cohort of US Women. *JAMA Netw Open*. 2023 Nov 1;6(11):e2344707. doi: 10.1001/jamanetworkopen.2023.44707. PMID: 37991758; PMCID: PMC10665977.

Designing a hypoallergenic form of the major peanut allergen Ara h 2 for safer immunotherapy

Peanut allergy is a potentially life-threatening condition, which rarely resolves. Current therapy is occasionally accompanied by severe reactions that discourage continuing treatment and are potentially dangerous. In this study we examined the molecular interactions of patient antibodies with the major peanut allergen Ara h 2 and designed a hypoallergenic form. We demonstrated that this molecule is less likely to cause severe reactions, and may also be used as a diagnostic for the development of certain antibodies linked to therapeutic success. A patent application was filed for this invention.

Min J, Keswani T, LaHood NA, Lytle IR, Marini-Rapoport O, Andrieux L, Sneed SL, Edwards LL, Petrovich RM, Perera L, Pomés A, Pedersen LC, Patil SU, Mueller GA. Design of an Ara h 2 hypoallergen from conformational epitopes. *Clin Exp Allergy*. 2024 Jan;54(1):46-55. doi: 10.1111/cea.14433. Epub 2024 Jan 2. PMID: 38168500; PMCID: PMC10843581.

A tool for prediction of moderate to severe obstructive sleep apnea-hypopnea
Sleep apnea is a common sleep disorder. The availability of an easy-to-use sleep apnea predictor would provide a public health benefit by promoting early diagnosis and treatment. NIEHS computational biologists developed a prediction tool that uses commonly available variables and can be accessed through a public web site. Our tool employs only seven widely available predictor variables: age, sex, weight, height, pulse oxygen saturation, heart rate and respiratory rate. This easy-to-use tool will serve as a screening vehicle that enables more patients to be clinically diagnosed and treated for OSA.

Talukder A, Li Y, Yeung D, Shi M, Umbach DM, Fan Z, Li L. OSApredictor: A tool for prediction of moderate to severe obstructive sleep apnea-hypopnea using readily available patient characteristics. *Comput Biol Med*. 2024 Aug;178:108777. doi: 10.1016/j.compbiomed.2024.108777. Epub 2024 Jun 19. PMID: 38901189; PMCID: PMC11265974.

Vitamin D receptor (VDR) or retinoid-related receptor (ROR) are required for the anti-fibrotic effect of Vitamin D metabolites
Treatment of skin fibroblasts with vitamin D or its metabolites inhibit fibrosis and proliferation. This inhibition was abrogated in skin fibroblasts deficient in vitamin D receptor (VDR) or retinoid-related receptor (ROR) suggesting that both VDR and ROR are necessary for this inhibitory effect. Vitamin D metabolites maybe be useful in the treatment of fibrosis.

Janjetovic Z, Qayyum S, Reddy SB, Podgorska E, Scott SG, Szpotan J, Mobley AA, Li W, Boda VK, Ravichandran S, Tuckey RC, Jetten AM, Slominski AT. Novel Vitamin D3 Hydroxymetabolites Require Involvement of the Vitamin D Receptor or Retinoic Acid-Related Orphan Receptors for Their Antifibrogenic Activities in Human Fibroblasts. *Cells*. 2024 Jan 26;13(3):239. doi: 10.3390/cells13030239. PMID: 38334631; PMCID: PMC10854953.

Protein kinase A (PKA) regulates the activity and function of the transcriptional regulator GLIS3.
Loss of transcriptional regulator GLI-Similar 3 (GLIS3) function in mice and humans causes congenital hypothyroidism (CH). GLIS3-deficiency does not cause major changes in prenatal thyroid gland development but inhibits thyroid hormone (TH) biosynthesis (referred to as dyshormonogenesis) by repressing several genes critical for TH biosynthesis. Activation of PKA by thyroid stimulating hormone (TSH) signaling was found to regulate GLIS3 activity and consequently its regulation of TH biosynthetic genes.

. Kang HS, Grimm SA, Liao XH, Jetten AM. GLIS3 expression in the thyroid gland in relation to TSH signaling and regulation of gene expression. *Cell Mol Life Sci.* 2024 Jan 28;81(1):65. doi: 10.1007/s00018-024-05113-6. PMID: 38281222; PMCID: PMC10822819.

GLIS2: a potential therapeutic target for treating autosomal dominant polycystic kidney disease (ADPKD)

Deficiency in the transcriptional regulator GLI-Similar 2 (GLIS2) causes nephronophthisis, an end-stage cystic kidney disease characterized by renal atrophy, inflammation and fibrosis. Loss of GLIS2 functions was found to suppress the progression of ADPKD in a mouse model. These findings suggest that GLIS2 may be a potential therapeutic target for treating ADPKD.

Zhang C, Rehman M, Tian X, Pei SLC, Gu J, Bell TA 3rd, Dong K, Tham MS, Cai Y, Wei Z, Behrens F, Jetten AM, Zhao H, Lek M, Somlo S. Glis2 is an early effector of polycystin signaling and a target for therapy in polycystic kidney disease. *Nat Commun*. 2024 May 1;15(1):3698. doi: 10.1038/s41467-024-48025-6. PMID: 38693102; PMCID: PMC11063051.

Personal care product use during puberty may influence breast cancer risk

Personal care product use often starts in adolescence, when rapidly developing pubertal breast tissue may be more vulnerable to the endocrine-disrupting chemicals that many personal care products contain. Patterns of product use vary by race and ethnicity, as do the chemical constituents of products marketed to different racial and ethnic groups. Using self-reported data on the use of 37 “everyday” personal care products (e.g., make-up, body creams and lotions, shampoo, conditioner) during the ages of 10 to 13 years from the NIEHS Sister Study cohort, we characterized patterns of personal care product use during puberty among Black, Hispanic/Latina, and White women and examined associations of product use with breast cancer incidence. Although patterns of product use during puberty were not clearly associated with breast cancer diagnosis, we found that frequent use of some products, such as lipstick, pomade, and nail products, during puberty was associated with higher incidence of breast cancer in at least one racial or ethnic group. This was the first study to examine the use of these “everyday” personal care products during puberty in relation to breast cancer incidence, and the findings add to a growing body of literature supporting that environmental exposures around the time of puberty may influence breast cancer risk.

Goldberg M, Chang CJ, Ogunsina K, O'Brien KM, Taylor KW, White AJ, Sandler DP. Personal Care Product Use during Puberty and Incident Breast Cancer among Black, Hispanic/Latina, and White Women in a Prospective US-Wide Cohort. *Environ Health Perspect*. 2024 Feb;132(2):27001. doi: 10.1289/EHP13882. Epub 2024 Feb 2. PMID: 38306193; PMCID: PMC10836586.

Myositis Associated Autoantibodies are Associated with Refractory Disease and Mortality in Patients with Juvenile Myositis

The myositis syndromes are rare systemic autoimmune diseases with characteristic muscle inflammation, weakness, photosensitive skin rashes, and significant morbidity. From prior studies utilizing a national registry of juvenile myositis patients, myositis specific autoantibodies have been found in up to 60% of patients and each autoantibody is associated with unique phenotypic features and distinct outcomes. The frequency and significance of myositis associated autoantibodies, which are also present in patients with other systemic autoimmune diseases, have not been adequately studied in juvenile myositis. Among 550 patients with juvenile myositis, 36% were found to have a myositis associated autoantibody and 13% had more than one of these

autoantibodies. Myositis associated autoantibodies were frequently seen in patients with overlap myositis (myositis co-occurring with another autoimmune disease), as well as with certain clinical features, including Raynaud phenomenon and interstitial lung disease. Some of these autoantibodies were associated with skin inflammation and with cardiac disease, among other features. Patients with a myositis associated autoantibody had a higher odds of a chronic disease course and higher mortality. Myositis associated autoantibodies define subgroups of patients with more severe illness and increased mortality. Prospective studies are needed to determine whether early detection of these autoantibodies may lead to improved outcomes for patients with juvenile myositis.

Sherman MA, Noroozi Farhadi P, Pak K, Trieu EP, Sarkar K, Targoff IN, Neely ML, Mammen AL, Rider LG; Childhood Myositis Heterogeneity Collaborative Study Group. Myositis-Associated Autoantibodies in Patients With Juvenile Myositis Are Associated With Refractory Disease and Mortality. *Arthritis Rheumatol*. 2024 Jun;76(6):963-972. doi: 10.1002/art.42813. Epub 2024 Mar 12. PMID: 38272842; PMCID: PMC11136598.

Clinical Features and Immunogenetic Risk Factors Associated with Additional Autoantibodies in Anti-Transcriptional Intermediary Factor 1γ Juvenile-Onset Dermatomyositis

Novel autoantibody specificities, including anti-CCAR1 autoantibodies, were recently discovered in adult patients with anti-transcriptional intermediary factor (TIF1)-positive dermatomyositis (DM) and were associated with attenuated cancer emergence. Anti-TIF1 autoantibodies are the more frequent myositis-specific autoantibody present in juvenile-onset myositis patients. The aims of the present study were to examine whether these autoantibodies also occur in patients with juvenile-onset DM (JDM) and to determine their associated features. In the sera of anti-TIF1 autoantibody positive JDM, any one of the anti-TIF1γ-associated autoantibodies was present in 29% of JDM patients overall, including 17% with anti-Sp4, 15% with anti-TBL1XR1, 9% with anti-CCAR1, and 1% each with anti-C1Z1 and anti-IMMT autoantibodies. These anti-TIF1γ-associated autoantibodies frequently co-occurred. Patients with any of the anti-TIF1γ-associated autoantibodies had less frequent falling episodes and lower peak muscle enzymes. Patients with these autoantibodies had less severe muscle disease and were not enriched for HLA-DRB1*03, the primary HLA risk factor for JDM. None of the children with these autoantibodies had cancer. In summary, additional autoantibodies in JDM patients with anti-TIF1γ autoantibodies appear to contribute to the heterogeneity of the anti-TIF1γ serologic subgroup.

Sherman MA, Yang Q, Gutierrez-Alamillo L, Pak K, Flegel WA, Mammen AL, Rider LG, Casciola-Rosen LA; Childhood Myositis Heterogeneity Collaborative Study Group. Clinical Features and Immunogenetic Risk Factors Associated With Additional Autoantibodies in Anti-Transcriptional Intermediary Factor 1γ Juvenile-Onset Dermatomyositis. *Arthritis Rheumatol*. 2024 Apr;76(4):631-637. doi: 10.1002/art.42768. Epub 2024 Jan 30. PMID: 38059274; PMCID: PMC10965375.

Mutations related to stress response may induce antibiotic resistance

Pseudomonas aeruginosa is a Gram-negative bacterium that is a major cause of nosocomial infections, including burn infections, urinary tract infection, and pneumonia. It is also the leading

cause of chronic lung infections in cystic fibrosis and chronic obstructive pulmonary disease patients. Antibiotic treatment remains challenging because P. aeruginosa is resistant to high concentrations of antibiotics and has a remarkable ability to acquire mutations conferring resistance to antimicrobial agents. Paul Doetsch and colleagues discovered a previously overlooked mechanism by which P. aeruginosa may acquire resistance to ciprofloxacin (cipro), an antibiotic commonly prescribed for the treatment of chronic P. aeruginosa infections. The results indicate that most P. aeruginosa cipro-resistant mutants in non-dividing or slow-dividing bacterial cultures owe their resistance to mutations that activate genes related to the Stringent Response. The Stringent Response is a stress response triggered by amino acid starvation, fatty acid limitation, iron limitation, heat shock and other challenging conditions. These findings may offer clinically - relevant clues on preventing acquisition of antibiotic resistance.

García-Villada L, Degtyareva NP, Brooks AM, Goldberg JB, Doetsch PW. A role for the stringent response in ciprofloxacin resistance in Pseudomonas aeruginosa. *Sci Rep*. 2024 Apr 13;14(1):8598. doi: 10.1038/s41598-024-59188-z. PMID: 38615146; PMCID: PMC11016087.

How long-term memories are created during sleep

A brain region called the entorhinal cortex (EC) plays a critical role in forming long-term memories during sleep by generating synchronous neural activity, according to NIEHS researchers and their collaborators. Together, the findings demonstrated that delta oscillations of temporoammonic pathway neurons are critical for the consolidation of newly encoded memory.

Haam J, Gunin S, Wilson L, Fry S, Bernstein B, Thomson E, Noblet H, Cushman J, Yakel JL. Entorhinal cortical delta oscillations drive memory consolidation. *Cell Rep*. 2023 Oct 31;42(10):113267. doi: 10.1016/j.celrep.2023.113267. Epub 2023 Oct 14. PMID: 37838945; PMCID: PMC10872950.

Pesticides may be linked to risk of inflammatory bowel disease

Inflammatory bowel disease (IBD) is an autoimmune disease characterized by chronic intestinal inflammation and includes Crohn's disease and ulcerative colitis. There are few known risk factors for IBD. NIEHS researchers have found evidence for a link between use of pesticides and the incidence of IBD. In one study, use of specific pesticides was associated with higher IBD incidence among farmers participating in the prospective Agricultural Health Study. Ever vs. never use of dieldrin, toxaphene, parathion and terbufos had the strongest associations, with about 50% increases in the relative risk of developing IBD during follow-up. A second study found that women whose childhood homes were regularly treated with pesticides, especially those who personally applied pesticides, were about 1.26 times as likely to be diagnosed with IBD as those without exposure. Among women who lived on farms during childhood, those who reported being in the fields during pesticide use were twice as likely to develop IBD as those who were not exposed. These findings contribute to a small but growing body of evidence indicating pesticide exposure is a contributor to IBD development and establishes childhood and adolescence as a potential window of susceptibility. Practices that reduce pesticide exposure during early life may help reduce the burden of IBD.

Chen D, Woo JMP, Parks CG, Lawrence KG, O'Brien KM, Sandler RS, Sandler DP. Childhood and adolescent residential and farm pesticide exposures and inflammatory bowel disease incidence in a U.S. cohort of women. *Sci Total Environ*. 2024 Oct 10;946:174475. doi: 10.1016/j.scitotenv.2024.174475. Epub 2024 Jul 2. PMID: 38964382; PMCID: PMC11296211.

Chen D, Parks CG, Hofmann JN, Beane Freeman LE, Sandler DP. Pesticide use and inflammatory bowel disease in licensed pesticide applicators and spouses in the Agricultural Health Study. *Environ Res.* 2024 May 15;249:118464. doi: 10.1016/j.envres.2024.118464. Epub 2024 Feb 12. PMID: 38354883; PMCID: PMC11065595.

Breakthrough in protein N-glycosylation: stability of acceptors key to efficient modification
We have discovered that the stability of proteins significantly affects their modification through N-glycosylation, a process crucial for proper protein function in cells. By studying a series of engineered proteins, we found that less stable proteins are more efficiently glycosylated. This insight reveals the importance of protein stability in cellular processes and may lead to better understanding and treatment of diseases linked to glycosylation abnormalities.

Couto PM, Guardia CMA, Couto FL, Labriola CA, Labanda MS, Caramelo JJ. Acceptors stability modulates the efficiency of post-translational protein N-glycosylation. *FASEB J*. 2024 Jul 15;38(13):e23782. doi: 10.1096/fj.202302267R. PMID: 38934375; PMCID: PMC11307252.

Socioeconomic disadvantage in childhood contributes to adult obesity
We used data from the Sister Study, a prospective U.S. cohort of women aged 35-74 years (N = 50,884; enrollment: 2003-2009) to examine the associations between measures of socioeconomic position (SEP) in childhood and obesity in adulthood. Lower childhood SEP – estimated using a latent variable that incorporated multiple factors - was associated with a 16% greater risk of being obese in adulthood. Associations persisted in analyses that accounted for SEP in adulthood.

Woo JMP, Bookwalter DB, Green GY, Sandler DP. Early life socioeconomic position contributes to adult obesity independent of adult socioeconomic factors: Findings from the sister study cohort. *SSM Popul Health*. 2023 Nov 10;24:101556. doi: 10.1016/j.ssmph.2023.101556. PMID: 38053627; PMCID: PMC10694340.

High pesticide exposures linked to shingles risk in older adults
We studied the possible link between pesticide exposure and shingles using Medicare linked data in a study of 22,753 licensed pesticide applicators (mostly farmers) who enrolled in the NIEHS and NCI sponsored Agricultural Heath Study in 1993-1997. Included participants were over age 65 and had more than a year of Medicare fee-for-service hospital and outpatient coverage between 1999 and 2016. Over more than 192,000 person-years of follow-up, 2,396 applicators were diagnosed with shingles. Applicators who were hospitalized for a pesticide-related illness, high pesticide exposure event, or poisoning were from 20% to 70% more likely to have developed shingles. These novel findings suggest that acute, high-level, and clinically impactful

pesticide exposures may increase the risk of shingles in subsequent years – sometimes as much as decades following exposure.

Parks CG, Leyzarovich D, Love SA, Long S, Hofmann JN, Beane Freeman LE, Sandler DP. High pesticide exposures events, pesticide poisoning, and shingles: A medicare-linked study of pesticide applicators in the agricultural health study. *Environ Int*. 2023 Nov;181:108251. doi: 10.1016/j.envint.2023.108251. Epub 2023 Oct 7. PMID: 37862860; PMCID: PMC10836588.

Soluble Epoxide Hydrolase and Post-Ischemic Heart Function

Cytochromes P450 can metabolize endogenous fatty acids, such as arachidonic acid, to bioactive lipids such as epoxyeicosatrienoic acids (EETs) that have beneficial effects. EETs protect hearts against ischemic damage, heart failure or fibrosis; however, their effects are limited by hydrolysis to less active dihydroxy oxylipins by soluble epoxide hydrolase (sEH), encoded by the epoxide hydrolase 2 gene (EPHX2, EC 3.3.2.10). Pharmacological inhibition or genetic disruption of sEH/EPHX2 have been widely studied for their impact on cardiovascular diseases. Less well studied is the role of increased EPHX2 expression, which occurs in a substantial human population that carries the EPHX2 K55R polymorphism or after induction by inflammatory stimuli. Herein, we developed a mouse model with cardiomyocyte-selective expression of human EPHX2 (Myh6-EPHX2) that has significantly increased total EPHX2 expression and activity. Myh6-EPHX2 hearts exhibit strong, cardiomyocyte-selective expression of EPHX2. EPHX2 mRNA, protein, and epoxide hydrolysis measurements suggest that Myh6-EPHX2 hearts have 12-fold increase in epoxide hydrolase activity relative to wild type (WT) hearts. This increased activity significantly decreased epoxide:diol ratios in vivo. Isolated, perfused Myh6-EPHX2 hearts were not significantly different from WT hearts in basal parameters of cardiac function; however, compared to WT hearts, Myh6-EPHX2 hearts demonstrated reduced recovery of heart contractile function after ischemia and reperfusion (I/R). This impaired recovery after I/R correlated with reduced activation of PI3K/AKT and GSK3β signaling pathways in Myh6-EPHX2 hearts compared to WT hearts. In summary, the Myh6-EPHX2 mouse line represents a novel model of cardiomyocyte-selective overexpression of EPHX2 that has detrimental effects on cardiac function.

Edin ML, Gruzdev A, Bradbury JA, Graves JP, Muse GW, Goulding DR, Lih FB, DeGraff LM, Zeldin DC. Overexpression of soluble epoxide hydrolase reduces post-ischemic recovery of cardiac contractile function. *Biochem Pharmacol*. 2024 Apr 26:116237. doi: 10.1016/j.bcp.2024.116237. Epub ahead of print. PMID: 38679211.

Living in areas prone to natural disasters is associated with poor mental health

Mental health effects are frequently reported after manmade and natural disasters. We studied the impact of living through multiple disasters in a study of over 9,000 persons participating the Gulf Long-term Follow-up Study who lived in one of the 5 states adjacent to the Gulf of Mexico. Using geocoded residence addresses linked to census tract-level natural hazard risk scores estimated using FEEMA's National Risk Index (NRI), we found that living in areas prone to hurricanes and coastal flooding was associated with increased risk of PTSD, anxiety, and depression assessed using standardized scales. Associations were strongest for PTSD with relative risk estimates of 2.30 and 1.59 for highest versus lowest quartile of hurricane and coastal

flooding risks. Heatwaves were associated with increased anxiety and depression. Results indicate that living in areas prone to natural disasters contributes to poor mental health status.

Lawrence KG, Sweeney MR, Werder EJ, Zuzak C, Gall M, Emrich CT, Cochran FV, Deng X, Christenbury KE, Buller ID, Braxton Jackson Ii W, Engel LS, Sandler DP. Residential natural hazard risk and mental health effects. *Am J Epidemiol*. 2024 Jul 19:kwae200. doi: 10.1093/aje/kwae200. Epub ahead of print. PMID: 39038796.

Prenatal Exposure to a Stress Hormone Blocker Disrupts Brain Development and Behavior in Mice

In both mice and humans, a stress hormone receptor (mineralocorticoid receptors; MR; Nr3c2), is enriched in a part of the brain called the hippocampus, specifically in area CA2. Because knockout of MR disrupted many features of mouse CA2 neurons, we tested whether prenatal exposure to an MR antagonist, spironolactone, would cause similar disruptions. We found that spironolactone treatment caused a significant reduction of CA2 neuron output (axons) in its target, CA1, and that at least one major synaptic input to CA2 was decreased as well. Mice that were treated prenatally with spironolactone also showed an increased reactivity to novel objects, an effect similar to what is seen with embryonic or postnatal CA2-targeted MR knockout. These findings do indicate that developmental disruption in MR signaling can have persistent effects on hippocampal circuitry and behavior.

Jones SM, Sleiman SJ, McCann KE, Jarmusch AK, Alexander GM, Dudek SM. Prenatal Exposure to the Mineralocorticoid Receptor Antagonist Spironolactone Disrupts Hippocampal Area CA2 Connectivity and Alters Behavior in Mice. *Neuropsychopharmacology*. 2024 in press

Amlodipine is safe and effective for treatment of hypertension

Amlodipine has been taken for decades to treat high blood pressure and is currently used by over 500 million people globally. Recently, its mechanism of action and safety was questioned with the claim it increased heart failure , leading to prominent news stories in the media. We have investigated the actions of amlodipine and find it works through inhibition of voltage-gated calcium channels, does not cause heart failure or has associated cardiovascular risks. The research was reported globally to reassure patients on amlodipine to keep taking it.

Bird GS, D'Agostin D, Alsanosi S, Lip S, Padmanabhan S, Parekh AB. A Reappraisal of the Effects of L-type Ca^{2+} Channel Blockers on Store-Operated Ca^{2+} Entry and Heart Failure. *Function (Oxf).* 2023 Oct 12;4(6):zqad047. doi: 10.1093/function/zqad047. PMID: 37841523; PMCID: PMC10568199.

Novel Insight into the Role of Norepinephrine in Context-Dependent Learning and Memory

Using two new mouse models of altered norepinephrine (NE) synthesis, together with NE and dopamine (DA) sensors, and in vivo fiber photometry we demonstrated the precise temporal dynamics of NE and DA release in the hippocampus during contextual encoding and memory retrieval. We found that both NE and DA release is increased in the dorsal hippocampus when animals are presented with an aversive stimulus and decreased during recall of the fear memory. In addition, we found that short term memory retrieval was sensitive to both partial and complete

loss NE synthesis throughout prenatal and postnatal development. In contrast, long term memory retrieval was compromised only by complete loss of locus coeruleus–NE synthesis beginning prenatally. The findings from this study provide novel insights into the role of NE in context-dependent learning and memory and highlight complex relationships between genotype, sex, and NE signaling.

Wilson LR, Plummer NW, Evsyukova IY, Patino D, Stewart CL, Smith KG, Konrad KS, Fry SA, Deal AL, Kilonzo VW, Panda S, Sciolino NR, Cushman JD, Jensen P. Partial or Complete Loss of Norepinephrine Differentially Alters Contextual Fear and Catecholamine Release Dynamics in Hippocampal CA1. *Biol Psychiatry Glob Open Sci*. 2023 Oct 12;4(1):51-60. doi: 10.1016/j.bpsgos.2023.10.001. PMID: 38058990; PMCID: PMC10695841.

Maternal History of Uterine Fibroids is Associated with Increased Risk in Daughters The Study of Environment, Lifestyle and Fibroids followed nearly 1700 African American participants over 5 years with ultrasound examinations at approximately 20-month intervals to identify new cases of fibroids and measure fibroid growth. Participant's mothers who were available (~90%) reported their own medical history of fibroids. New fibroid development during the study among those fibroid-free at baseline was more common among those with a maternal history of fibroid, with a stronger association observed among those whose mothers were diagnosed at a younger age. Fibroid growth was about 8% faster among participants with maternal history, regardless of the age when a mother was diagnosed. Further study of environmental and genetic factors that can be passed from one generation to the next are needed to better understand this common under-studied women's health condition; however, clinicians can encourage patients to learn about their family history and monitor symptoms that could indicate fibroid development, thus promoting patient self-advocacy.

Langton CR, Harmon QE, Baird DD. Family History and Uterine Fibroid Development in Black and African American Women. *JAMA Netw Open*. 2024 Apr 1;7(4):e244185. doi: 10.1001/jamanetworkopen.2024.4185. PMID: 38568693; PMCID: PMC10993075.

Phthalate exposure may contribute to racial disparities in preterm birth
In a pooled study of 16 US cohorts, including 6,045 pregnancies, we investigated racial and ethnic disparities in prenatal phthalate exposure and how those disparities might contribute to the concurrent racial and ethnic disparities in rates of preterm birth. After adjusting for factors associated with race and ethnicity as well as phthalate exposure, we observed large disparities in exposure. Black and Hispanic/Latina participants had 23-148% and 4-94% higher urinary concentrations of phthalate metabolites compared to non-Hispanic White participants, respectively. Using a statistical model that simulates an intervention, we showed that reducing phthalate exposure among Black and Hispanic/Latina participants to the same levels observed among non-Hispanic White participants would result in fewer preterm births within those groups.

Welch BM, Keil AP, Buckley JP, Engel SM, James-Todd T, Zota AR, Alshawabkeh AN, Barrett ES, Bloom MS, Bush NR, Cordero JF, Dabelea D, Eskenazi B, Lanphear BP, Padmanabhan V, Sathyanarayana S, Swan SH, Aalborg J, Baird DD, Binder AM,

Bradman A, Braun JM, Calafat AM, Cantonwine DE, Christenbury KE, Factor-Litvak P, Harley KG, Hauser R, Herbstman JB, Hertz-Picciotto I, Holland N, Jukic AMZ, McElrath TF, Meeker JD, Messerlian C, Michels KB, Newman RB, Nguyen RHN, O'Brien KM, Rauh VA, Redmon B, Rich DQ, Rosen EM, Schmidt RJ, Sparks AE, Starling AP, Wang C, Watkins DJ, Weinberg CR, Weinberger B, Wenzel AG, Wilcox AJ, Yolton K, Zhang Y, Ferguson KK. Racial and Ethnic Disparities in Phthalate Exposure and Preterm Birth: A Pooled Study of Sixteen U.S. Cohorts. *Environ Health Perspect.* 2023 Dec;131(12):127015. doi: 10.1289/EHP12831. Epub 2023 Dec 20. PMID: 38117586; PMCID: PMC10732302.

New statistical method for analysis of microbiome composition

Many microbiome studies involve more than two groups, sometimes even ordered groups such as stages of a disease. Standard methods are inefficient in terms of power and false discovery rates. In this Article, we propose a general framework, ANCOM-BC2, for performing a wide range of multigroup analyses with covariate adjustments and repeated measures. The methodology is illustrated using two real datasets. The first example explores the effects of aridity on the soil microbiome, and the second example investigates the effects of surgical interventions on the microbiome of patients with inflammatory bowel disease.

Lin H, Peddada SD. Multigroup analysis of compositions of microbiomes with covariate adjustments and repeated measures. *Nat Methods*. 2024 Jan;21(1):83-91. doi: 10.1038/s41592-023-02092-7. Epub 2023 Dec 29. PMID: 38158428; PMCID: PMC10776411.

Gut microbiome changes linked HIV infection

Pathogenic changes in gut microbial composition precede the onset of HIV-1 infection in men who have sex with men (MSM). This process is associated with increased levels of systemic inflammatory biomarkers and risk for AIDS development. Using the biospecimens obtained from MSM, before they were HIV-1 infected, we demonstrated high risk sexual behavior among men who have sex with men is linked to changes in gut microbiome and systemic inflammation leading to HIV-1 infection.

Lin, H, Chen Y, Abror G, Price M, Morris A, Sun J, Palella F, Chew KW, Brown TT, Rinaldo CR, Peddada SD. The effect of sexual behavior on primary HIV-1 infection is mediated by the gut microbiome and proinflammatory cytokines. *Nature Communications Biology*. 2024. accepted for publication

Environmental triggers of early puberty identified in a high-throughput screen of environmental compounds using mouse and human brain cells

There has been an alarming trend toward earlier puberty in girls, suggesting the influence of an unknown environmental factor(s). We used GnRH receptor (GnRHR) or kisspeptin receptor (KISS1R)-expressing cells to screen the Tox21 10K compound library, a compendium of pharmaceuticals and environmental compounds, for GnRHR and KISS1R activation. Musk ambrette was identified as a KISS1R agonist, and treatment with musk ambrette led to increased expression of *Gnrh1* in murine and human hypothalamic cells, and expansion of GnRH neuronal area in developing zebrafish larvae. A group of cholinergic agonists with structures similar to

methacholine was identified as GnRHR agonists. In summary, utilizing a Tox21 10K compound library screen combined with cellular and molecular techniques, we identified novel environmental agents that may activate the human KISS1R or GnRHR.

Yang S, Zhang L, Khan K, Travers J, Huang R, Jovanovic V, Veeramacheni R, Sakamuru S, Tristan C, Davis EE, Klumpp-Thomas C, Witt KL, Simeonov A, Xia M, and Shaw ND. Identification of environmental compounds that may trigger early female puberty by activating human GnRHR and KISS1R. *Endocrinology*. 2024. accepted for publication

Environmental Management of Asthma

The National Asthma Education and Prevention Program guidelines emphasize environmental control as an integral part of asthma management; however, limited national-level data exist on how clinicians implement environmental control recommendations. We analyzed data on clinicians' self-reported use of recommended environmental control practices in a nationally representative sample of primary care physicians, asthma specialists, and advanced practice providers from the National Asthma Survey of Physicians, a supplemental questionnaire to the 2012 National Ambulatory Medical Care Survey. We examined clinician and practice characteristics as well as clinicians' decisions and strategies regarding environmental trigger assessment and environmental control across provider groups. Regression modeling was used to identify clinician and practice characteristics associated with implementation of guideline recommendations. A higher percentage of specialists assessed asthma triggers at home, school, and/or work than primary care or advanced practice providers. Almost all clinicians recommended avoidance of secondhand tobacco smoke, whereas recommendations regarding cooking appliances (e.g., proper ventilation) were infrequent. Although assessment and recommendation practices differed between clinician groups, Modeling results showed that clinicians who reported almost always assessing asthma control were more likely to assess environmental asthma triggers. Use of asthma action plans was also strongly associated with implementation of environmental control recommendations. Environmental assessment and recommendations to patients varied among asthma care providers. High adherence to other key guideline components, such as assessing asthma control, was associated with environmental assessment and recommendation practices on environmental control.

Salo PM, Akinbami LJ, Cloutier MM, Wilkerson JC, Elward KS, Mazurek JM, Diette GB, Mitchell TA, Williams S, Zeldin DC. Environmental management of asthma in clinical practice: Results from the 2012 National Ambulatory Medical Care Survey. *J Allergy Clin Immunol Glob*. 2023 Nov 22;3(1):100192. doi: 10.1016/j.jacig.2023.100192. PMID: 38187868; PMCID: PMC10770720.