Division of Intramural Research

NAEHS Council Update

September 2022

DIR RECRUITMENTS

Chief of the Epigenetics and Stem Cell Biology Laboratory
NIEHS is searching for a highly qualified, established investigator for the position of Chief of the Epigenetics and Stem Cell Biology Laboratory (ESCBL) within the Division of Intramural Research (DIR). The position was vacated by Dr. Trevor Archer when he assumed his new leadership role as the Deputy Director of NIEHS The ideal candidate will have an outstanding academic record of achievement, leadership capabilities, and broad interests in transcriptional regulation, epigenetics, chromatin architecture, RNA biology, and stem cell biology. In addition to directing his/her own independent research program, the Chief will be responsible for leading ESCBL and providing vision and directions as research in transcriptional regulation and environmental health science continue to evolve. Applicants should have a Ph.D., M.D., or equivalent doctoral degree and a strong interest and publication record in mammalian cell biology and signal transduction. Dr. Anton Jetten, Senior Investigator and Deputy Chief of the Immunity, Inflammation and Disease Laboratory serves as chair of the search committee launched June 2022 and will initiate review of applications on October 17, 2022.

Medical Director of the Clinical Research Unit
NIEHS is inviting applications for a Senior Clinician in the Clinical Research Branch (CRB), Division of Intramural Research (DIR) at the NIEHS campus in Research Triangle Park, NC to serve as Medical Director of the Clinical Research Unit (CRU) and Director of Clinical Operations for the NIEHS Personalized Environment and Genes Study (PEGS), a large cohort of over 19,000 participants, initiated in 2002 to study interaction between genes, the environment and health. PEGS offers outstanding research opportunities to intramural scientists and extramural collaborators interested in personalized environmental medicine. While it is expected that the successful candidate will be able to collaborate broadly on projects utilizing the CRU and/or PEGS cohort, resources will also be made available for conducting self-initiated research projects. The successful candidate will require evidence of strong leadership skills and significant experience in patient-oriented research, defined as research that requires direct interaction with human subjects. The individual will have a track record of national presentations and publications in respected journals in their field. Research areas may include understanding the mechanisms of human disease, genotype-phenotype studies, therapeutic interventions, and/or clinical trials. Applicants should have an M.D. or equivalent doctoral degree and 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. 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.

Chief of the Administrative and Research Services Branch
The search process has been initiated for an outstanding administrative leader to serve as Lead Administrative Officer and Chief of the Administrative and Research Services Branch (ARSB). ARSB performs program planning and resource management activities to support the intramural research programs and scientists at NIEHS. The position was vacated by J'Ingrid Mathis on July 17, 2022, when she assumed her new leadership role as the Associate Director for Management and Executive Officer at NIEHS. An advisory committee chaired by Dr. Jerrel Yakel, Chief of

the Neurobiology Laboratory, DIR has been formed to facilitate identification of a small pool of outstanding candidates to advance to the next stage of onsite interviews.

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. DIR Principal Investigators will serve on most of the 26 Stadtman subcommittees in 2022-23 representing a range of disciplines central to the NIEHS mission. Applications will be reviewed in October 2022 and outstanding candidates will be identified for interviews at NIEHS starting in November and December 2022.

DIR STAFF UPDATES

Senior Investigator
Dr. Shyamal Peddada, Chief of the Biostatistics and Bioinformatics Branch of NICHD has accepted an offer to join the Biostatistics and Computational Biology Branch (BCBB) as a Senior Investigator. His continuing research program aims to develop broadly applicable statistical methods motivated by applications in biomedical sciences aligned with the NIEHS mission, such as microbiome, genomics, toxicology and health effects of climate change. Dr. Peddada is expected to start at NIEHS in the Winder 2022.

Tenure-Track Investigator
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 early 2023.

Independent Research Scholars
Dr. Mary Diaz Santana was selected as an NIH Independent Research Scholar (IRS) and initiated her independent program at NIEHS in August 2022. Dr. Clarice Weinberg will serve as her primary mentor in BCBB. Her independent research program will focus on breast cancer risk prediction modeling, incorporating aspects of the social environment, with the goal of reducing breast cancer incidence and mortality in Hispanic women.

Dr. Francisco Alejandro (Alex) Montiel Ishino, an NIH Independent Research Scholar (IRS) joined the Epidemiology Branch (EB) at NIEHS in August 2022. His primary mentor in EB will be Dr. Chandra Jackson. His independent research program will seek to determine social environmental risk factors associated with cardiometabolic health in a U.S. Bhutanese cohort.

Deputy Chief of the Comparative Medicine Branch
Dr. Andrew Gorman has accepted an offer to join NIEHS as the Deputy Chief of the Comparative Medicine Branch (CMB). In this role, Dr. Gorman will be responsible for assisting with the management of an AAALAC International accredited animal care and use program and to support NIEHS animal research programs with a strong emphasis on rodent animal models. He will have supervisory responsibility of section heads within CMB and will serve on the NIEHS Animal Care and Use Committee (ACUC) as well as other committees. Dr. Gorman is scheduled to start at NIEHS on October 24, 2022.

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 second 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 22 FARE award winners for 2023:

FARE Winner	Mentor	Project
Ziyue Wang, Ph.D	Alison Motsinger-Reif, Ph.D.	A Novel Normalization Method for Microbiome Sequencing Count Data
Justin Collier, Pharm.D., Ph.D.	Anton Jetten, Ph.D.	PKM2 Is a Major Contributing Factor in GLIS3KO-Induced Polycystic Kidney Metabolic Reprogramming
Jasmine Mack, MPH, MS	Alison Motsinger-Reif, Ph.D.	A Multi-Ethnic Genome-Wide Association Study Identifies Novel Candidate Loci Near the RARB And LRP1B Genes Associated with Gestational Hypertension in the Personalized Environment and Genes (PEGS) Cohort
Ankit Gupta, Ph.D.	Marcos Morgan, Ph.D.	TUT4 and TUT7 Uridylate the RNA of the Mouse Coronavirus MHV and Facilitate Its Replication
Dana Al-Hasan, Ph.D.	Chandra Jackson, Ph.D.	Racial and Economic Residential Segregation and Dementia Incidence
Virginia Savy, Ph.D.	Carmen Williams, M.D. , Ph.D.	The Butterfly Effect: Abnormal Calcium Signaling at Fertilization has a Long-Term Impact on Offspring Weight
Ru Pin Chi, Ph.D	Marcos Morgan, Ph.D.	WNK1 is Indispensable for Spermatogenesis and Male Fertility Via Regulating Translation
Wan-Ning Li, Ph.D.	Francesco DeMayo, Ph.D.	The Role of Serum Response Factor in Regulating Hormonal Responsiveness in Female Reproduction
Christine Langton, Ph.D.	Donna Baird, Ph.D.	Soy-Based Infant Formula Feeding and Uterine Fibroid Development in a Prospective Ultrasound Study of African-American Women
Danielle Stevens, Ph.D.	Kelly Ferguson, Ph.D.	Early Pregnancy Phthalate and Phthalate Alternative Metabolites in Relation to Fetal Cardiac Development

FARE Winner	Mentor	Project
Symielle Gaston Harrison, Ph.D., MPH	Chandra Jackson, Ph.D.	Racial/Ethnic Differences in Associations of Traumatic Childhood Experiences with Both Metabolic Syndrome Prevalence and Type 2 Diabetes Risk
Mandy Goldberg, Ph.D., MPH	Dale Sandler, Ph.D.	Beauty Product Use During Puberty and Breast Cancer Risk in U.S. Women
Dillon Lloyd, BS	Alison Motsinger-Reif, Ph.D.	Type 2 Diabetes Risk Prediction in a Multi-Ethnic Cohort Supports the Potential of Polyexposure Risk Scores
Adriana Alexander, Ph.D.	Humphrey Yao, Ph.D.	Sex-Specific Regulatory Networks Prime Primordial Germ Cell Fate Commitment
Chitrangda Srivastava, Ph.D.	Anton Jetten, Ph.D.	Loss of JAZF1 Modulates High-Fat Diet-Induced Gut Microbial Dysbiosis and Protects Against Nonalcoholic Fatty Liver Disease
Tanushree Mukherjee, Ph.D.	Anton Jetten, Ph.D.	Glis3 Protects Against Deregulated Osteogenesis
MyeongJin Yi, Ph.D.	Francesco DeMayo, Ph.D.	Vitamin D Regulates Uterine Stromal Cell Differentiation *in Vitro* and *in Vivo*.
Jacob Gordon, B.S.	Robin Stanley, Ph.D.	Cryo-EM Structure of The Human PELP1-WDR18 Complex Reveals Insights into the ER-PELP1 Signaling Axis
Ananda Ayyappan Jaguva Vasudevan, Ph.D	Scott Williams, Ph.D.	Biochemical and Structural Analysis of ZATT/ZNF451
Amanda Riccio, Ph.D.	William Copeland, Ph.D.	Structural Insight and Characterization of Human Twinkle Helicase in Mitochondrial Disease
Laura Kammel, Ph.D.	Joseph Rodriguez, Ph.D.	Whole Organ Immuno-Smfish Enables Spatial Gene Expression Analysis in Single Cells Within a Complex 3D Environment
Xiukun Wang, Ph.D.	Guang Hu, Ph.D.	The Histone H3.3 Chaperone HIRA Facilitates the Recruitment of the Nurd Complex to Promote the Exit from the Pluripotent State in Mouse Embryonic Stem Cells

2022 Gregory Paul Lenardo Basic Science Award
Jacob Gordon, an NIH OxCam predoctoral fellow in Robin Stanley's group (STL) received the Lenardo Basic Science Award from the International Biomedical Research Alliance

American Thoracic Society (ATS) Student Scholars Program
Gordon Smilnak, a Medical Student Research Fellow in Stephanie London's group (EB), who is completing medical school at Northwestern University was selected into this competitive program administered by the American Thoracic Society.

DIR COMMITMENT TO DIVERSITY, EQUITY, INCLUSION AND ACCESSIBILITY

NIH Distinguished Scholars Program
Dondrae Coble, D.V.M., DACLAM, Senior Scientist and Chief of the Comparative Medicine Branch (CMB) was selected to participate in the NIH Distinguished Scholars Program (DSP). This program was recently expanded to include Senior Investigators/Scientists/Clinicians with a strong commitment to enhancing diversity. Dr. Coble will join four DIR Tenure-Track Investigators previously selected to the DSP: Drs. Joe Rodriguez (ESCBL), Benedict Anchang (BCBB), Jason Watts (ESCBL) and Carlos Guardia (RDBL).

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 are expected to be provided to the Scientific Director and DIR Council in Fall 2022.

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

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

DIR RESEARCH ACCOMPLISHMENTS FOR FY 2022

NIEHS team solves 3D structure of twinkle protein, sheds light on mitochondrial diseases
Intramural researchers at the NIEHS have used cryo-electron microscopy (cryo-EM) and other techniques to solve the 3D structure of the twinkle protein, the final piece of the human minimal mitochondrial replisome to be structurally characterized. The protein, the helicase in the mitochondrial DNA replisome, helps the body use energy converted from food. Mutations to twinkle can lead to mitochondrial diseases but, working from models, researchers and clinicians were previously unable to determine the mechanistic links. By creating 3D structures of human twinkle W315L, the researchers have provided the means to show the locations of mutations and to develop targeted therapies for conditions such as progressive external ophthalmoplegia, Perrault syndrome, and hepatocerebral mitochondrial DNA depletion syndrome.

Riccio AA, Bouvette J, Perera L, Longley MJ, Krahn JM, Williams JG, Dutcher R, Borgnia MJ, Copeland WC. Structural insight and characterization of human Twinkle helicase in mitochondrial disease. *Proc Natl Acad Sci U S A*. 2022 Aug 9;119(32):e2207459119. doi: 10.1073/pnas.2207459119. Epub 2022 Aug 1. PMID: 35914129; PMCID: PMC9371709.

Highlighted through NIH Press release
Science Advisory Board highlight
News Medical
TDPel Media

Environmental conditions during initial exposure to allergens determines the severity of asthma-like responses in mice.
The frequency and severity of asthma attacks are affected by the actions of a white blood cell type known as T lymphocytes. Researchers at the NIHES have found that the longevity of asthma-like responses in mice depend on environmental conditions during initial encounters with the provoking allergen. Simultaneous exposure to allergens and bacterial endotoxin limited the pathologic actions of allergen-specific T lymphocytes and reduced the severity of asthma-like features. These findings suggest that endotoxin might be useful as part of an immunotherapeutic strategy to treat asthma.

Whitehead GS, Thomas SY, Nakano K, Royer DJ, Burke CG, Nakano H, Cook DN. A neutrophil/TGF-β axis limits the pathogenicity of allergen-specific CD4+ T cells. *JCI Insight*. 2022 Feb 22;7(4):e150251. doi: 10.1172/jci.insight.150251. PMID: 35191395; PMCID: PMC8876454.

Preterm birth more likely with exposure to phthalates
In this pooled analysis of 16 studies in the United States, phthalate metabolites were quantified in urine samples collected during pregnancy. Higher urinary metabolite concentrations for several prevalent phthalates were associated with greater odds of delivering preterm, and hypothetical interventions to reduce phthalate exposure levels were associated with fewer preterm births. In this observational study, the largest to date on this topic urinary biomarkers of common phthalates used in consumer products were a risk factor for preterm birth.

Welch BM, Keil AP, Buckley JP, Calafat AM, Christenbury KE, Engel SM, O'Brien KM, Rosen EM, James-Todd T, Zota AR, Ferguson KK; Pooled Phthalate Exposure and Preterm Birth Study Group, Alshawabkeh AN, Cordero JF, Meeker JD, Barrett ES, Bush NR, Nguyen RHN, Sathyanarayana S, Swan SH, Cantonwine DE, McElrath TF, Aalborg J, Dabelea D, Starling AP, Hauser R, Messerlian C, Zhang Y, Bradman A, Eskenazi B, Harley KG, Holland N, Bloom MS, Newman RB, Wenzel AG, Braun JM, Lanphear BP, Yolton K, Factor-Litvak P, Herbstman JB, Rauh VA, Drobnis EZ, Sparks AE, Redmon JB, Wang C, Binder AM, Michels KB, Baird DD, Jukic AMZ, Weinberg CR, Wilcox AJ, Rich DQ, Weinberger B, Padmanabhan V, Watkins DJ, Hertz-Picciotto I, Schmidt RJ. Associations Between Prenatal Urinary Biomarkers of Phthalate Exposure and Preterm Birth: A Pooled Study of 16 US Cohorts. *JAMA Pediatr*. 2022 Jul 11:e222252. doi: 10.1001/jamapediatrics.2022.2252. Epub ahead of print. PMID: 35816333; PMCID: PMC9274448.

Extrinsic proofreading improves DNA replication fidelity

DNA replication fidelity is achieved by a multistep process involving (1) the ability of all three major DNA polymerases to select the correct nucleotide for incorporation, (2) the ability of two of the three polymerases to remove mistakes made during replication, and (3) by the ability of mismatch repair to correct mismatches that escape removal and reside in double stranded DNA. This year, we provided strong evidence that the second step (proofreading) can occur either by the same DNA polymerase that originally made the mistake, or afterwards, when mistakes made by any of the three DNA polymerase can be removed, but only by one of the three, DNA polymerase delta. The extrinsic proofreading by DNA polymerase delta balances the fidelity of replication of both DNA strands, and it can partially explain differences in replication fidelity that result in cancer.

Zhou ZX, Lujan SA, Burkholder AB, St Charles J, Dahl J, Farrell CE, Williams JS, Kunkel TA. How asymmetric DNA replication achieves symmetrical fidelity. *Nat Struct Mol Biol.* 2021 Dec;28(12):1020-1028. doi: 10.1038/s41594-021-00691-6. Epub 2021 Dec 9. PMID: 34887558; PMCID: PMC8815454.

Insomnia during pregnancy has increased over time and is associated with severe maternal morbidity

Using nationally representative National Inpatient Sample data comprised of approximately 47 million hospitalizations among pregnant persons, we investigated trends in insomnia during pregnancy over a 12-year period (2006-2017) as well as the interrelationships between insomnia, maternal comorbidities, and severe maternal morbidity overall and by social determinants of health. Insomnia prevalence for both delivery and non-delivery hospitalizations increased from 2006-2017, particularly among persons with low socioeconomic status. Insomnia was associated with all investigated maternal comorbidities and severe maternal morbidity. These results support the importance of addressing and treating insomnia during pregnancy.

Kendle AM, Salemi JL, Jackson CL, Buysse DJ, Louis JM. Insomnia During Pregnancy and Severe Maternal Morbidity in the United States: Nationally Representative Data from 2006 to 2017. *Sleep*. 2022 Jul 28:zsac175. doi: 10.1093/sleep/zsac175. Epub ahead of print. PMID: 35901516.

Significance of funding and further awareness in health and prevention research for Asian Americans, Native Hawaiians, and Pacific Islanders

Between 1992 and 2018, less than half a percent of National Institutes of Health funding was dedicated to research about the health of Asian American (AsA) and Native Hawaiians, and Pacific Islanders (NHPI). Insufficient funding can create a barrier against equitable health access and prevention of health disparities that is needed among these understudied minoritized racial/ethnic groups. In March 2021, the National Heart, Lung, and Blood Institute partnered with multiple institutes within the NIH to form a multidisciplinary workshop tailored to address these issues. Upon review of current research, the workshop identified that lack of knowledge within AsA and NHPI subgroups has led to exacerbated health conditions. This workshop report provides opportunities, elucidates barriers, and suggests approaches for prevention research for AsA and NHPI groups. Specific solutions include prevention research and also tailored research efforts designed to further elucidate health among subcultures and subgroups within AsA and NHPI Americans.

Kanaya AM, Hsing AW, Panapasa SV, Kandula NR, Araneta MRG, Shimbo D, Wang P, Gomez SL, Lee J, Narayan KMV, Mau MKLM, Bose S, Daviglus ML, Hu FB, Islam N, Jackson CL, Kataoka-Yahiro M, Kauwe JSK, Liu S, Ma GX, Nguyen T, Palaniappan L, Setiawan VW, Trinh-Shevrin C, Tsoh JY, Vaidya D, Vickrey B, Wang TJ, Wong ND, Coady S, Hong Y. Knowledge Gaps, Challenges, and Opportunities in Health and Prevention Research for Asian Americans, Native Hawaiians, and Pacific Islanders: A Report From the 2021 National Institutes of Health Workshop. *Ann Intern Med*. 2022 Apr;175(4):574-589. doi: 10.7326/M21-3729. Epub 2022 Jan 4. PMID: 34978851; PMCID: PMC9018596.

Understanding the association between greenspaces and negative sleep health implications across racial/ethnic groups

Exposure to greenspaces have been associated with improved health within individuals; however, racial/ethnic groups experiencing marginalization, individuals residing in low-income neighborhoods, and individuals who have had to relocate due to gentrification are less likely to have access to greenspaces and are more likely to be exposed to pollutants. These stressors have been associated with poorer sleep outcomes. Using a community-based, mixed-methods approach along with data from the African American Sleep and Health Study, we investigated the impact of greenspace redevelopment on objectively- and subjectively-measured sleep health among African Americans experiencing marginalization due to gentrification and/or living in low-income neighborhoods. Among all participants, inequity (e.g., housing unaffordability, displacement), social stressors related to gentrification were associated with poorer sleep, which was modified by exposure to green space. Solutions including community engagement, policies aimed at eliminating structural racism, discrimination, and improvement including low-socioeconomic neighborhoods may address sleep health disparities.

Williams PC, Alhasan DM, Krafty R, Coutts C, Miles-Richardson S, Jackson CL. A mixed methods approach to understand greenspace redevelopment in relation to objectively- and subjectively-measured sleep health among Black adults in Southwest Atlanta. *Health*

Place. 2022 Jul;76:102812. doi: 10.1016/j.healthplace.2022.102812. Epub 2022 May 28. PMID: 35640375.

Racial/ethnic disparities in sleep duration that are highest among African American adults persist from 2004 to 2018

Sleep is essential for overall well-being, yet minoritized racial/ethnic groups (e.g., African Americans) are more likely to experience sleep deficiencies, which are associated with poorer health. To further elucidate trends of unrecommended short and long sleep duration within racial/ethnic groups in the United States from 2004-2018, we used a series of cross-sectional data from the nationally representative National Health Interview Survey. Among approximately 430,000 United States adults, Black adults, regardless of age and socioeconomic status, had the highest prevalence of short and long sleep duration, which persisted over time. Further, these disparities were higher among women and those with middle to high income, suggesting the importance of considering membership to multiple marginalized groups in investigations of sleep disparities.

Caraballo C, Mahajan S, Valero-Elizondo J, Massey D, Lu Y, Roy B, Riley C, Annapureddy AR, Murugiah K, Elumn J, Nasir K, Nunez-Smith M, Forman HP, Jackson CL, Herrin J, Krumholz HM. Evaluation of Temporal Trends in Racial and Ethnic Disparities in Sleep Duration Among US Adults, 2004-2018. *JAMA Netw Ope*n. 2022 Apr 1;5(4):e226385. doi: 10.1001/jamanetworkopen.2022.6385. PMID: 35389500; PMCID: PMC8990329.

Exposomic approaches and early-life interventions are necessary to address racial/ethnic disparities in sleep

There are persistent sleep and cardiovascular health disparities among minoritized racial/ethnic groups compared to non-Hispanic White people across the life course yet potential mechanisms and efficacious interventions remain to be elucidated. In response to a prior study that identified higher subclinical cardiovascular risk factors among Black and Asian adults compared to White adults who were all identified as of healthy "good sleepers", we underscored the importance of employing a life course approach given the subclinical disparities observed among health adults. Directions for future sleep disparities research adoption of a life-course perspective, adopting an exposome approach, and further research on social/environmental determinants of health as drivers of disparities in sleep and cardiovascular health.

Gaston SA, Jackson CL. Strengthening the case for early-life interventions to address racial/ethnic sleep disparities across the life-course using an exposome approach. *Sleep*. 2021 Nov 12;44(11):zsab182. doi: 10.1093/sleep/zsab182. PMID: 34272566; PMCID: PMC8598170.

Patients with congenital absence of the nose (arhinia) who have mutations in *SMCHD1* have no signs of a muscular dystrophy

Facioscapulohumeral muscular dystrophy type 2 (FSHD2) and arhinia are two distinct disorders caused by mutations in the same gene, *SMCHD1*. FSHD2 is caused by the muscle toxin, DUX4. We performed detailed neuromuscular studies, including muscle ultrasound and MRI, in 11 individuals with arhinia and observed only mild, subclinical muscle weakness, inconsistent with

FSHD2. Primary muscle cells obtained in 2 arhinia patients demonstrated only minimal DUX4 expression, suggesting that the control of DUX4 expression is different in arhinia and FSHD2.

Mohassel P, Chang N, Inoue K, Delaney A, Hu Y, Donkervoort S, Saade D, Billioux BJ, Meader B, Volochayev R, Konersman CG, Kaindl AM, Cho CH, Russell B, Rodriguez A, Foster KW, Foley AR, Moore SA, Jones PL, Bonnemann CG, Jones T, Shaw ND. Cross-sectional Neuromuscular Phenotyping Study of Patients with Arhinia with SMCHD1 Variants. *Neurology*. 2022 Mar 29;98(13):e1384-e1396. doi: 10.1212/WNL.0000000000200032. Epub 2022 Feb 4. PMID: 35121673; PMCID: PMC8967428.

NIEHS scientists develop new breast cancer risk score based on DNA methylation

NIEHS researchers have created a new breast cancer risk score based on blood DNA methylation. Using a prospective study of 2774 women who were cancer-free at enrollment and followed for years after blood draw, the researchers used machine learning to identify a set of methylation marks that predict women who would later develop breast cancer. DNA methylation plays an important role in controlling gene expression and changes with age and environmental exposure. The breast cancer risk information encoded by the methylation-based breast cancer risk score is as predictive as the risk captured by existing genetic scores based on a woman's DNA sequence, and outperforms traditional breast cancer risk factors, such as a woman's lifestyle factors and reproductive history. This research provides insight into how genetic and environmental factors combine to cause the most common cancer in American women.

Kresovich JK, Xu Z, O'Brien KM, Shi M, Weinberg CR, Sandler DP, Taylor JA. Blood DNA methylation profiles improve breast cancer prediction. *Mol Oncol*. 2022 Jan;16(1):42-53. doi: 10.1002/1878-0261.13087. Epub 2021 Nov 9. PMID: 34411412; PMCID: PMC8732352.

Investigators at NIEHS develop an approach for mining family genetic data to discover gene-by-gene interactions

Despite huge expenditures in the past two decades on genome-wide association studies, only a small fraction of the known heritability of many diseases has been explained. One important missing mechanism is genetic epistasis, interactions among genetic variants that can work together to increase risk. We developed an approach for studying epistasis based on case-parent or case-sibling designs and showed that it can find sets of synergistically acting variants by searching through the huge number of possible combinations, dramatically outperforming all previous methods for identifying those sets. We applied the method to data from families affected by the birth defect, oral clefting.

Nodzenski M, Shi M, Krahn JM, Wise AS, Li Y, Li L, Umbach DM, Weinberg CR. GADGETS: A genetic algorithm for detecting epistasis using nuclear families. *Bioinformatics*. 2021 Nov 12:btab766. doi: 10.1093/bioinformatics/btab766. Epub ahead of print. PMID: 34788792.

(Selected as a NIEHS Intramural Paper of the Month and awarded the Larry Kupper Award for the best dissertation paper of 2021 based on a dissertation in the UNC Biostatistics Department.)

Medications used for assisted reproduction do not alter signals driving development
At fertilization, calcium signals are generated in eggs and their characteristic pattern drives embryo development. Medications used for assisted reproduction help women generate multiple embryos during one treatment cycle, but it was unknown if these medications alter calcium signals and therefore impair embryo development. Using a mouse model, we show that the medications do not change the calcium oscillation patterns in the early embryo, demonstrating that these medications are unlikely to be detrimental for human embryo development.

Savy V, Stein P, Shi M, Williams CJ. Superovulation Does Not Alter Calcium Oscillations Following Fertilization. *Front Cell Dev Biol*. 2021 Nov 4;9:762057. doi: 10.3389/fcell.2021.762057. PMID: 34805168; PMCID: PMC8601230.

Levels of anti-oxidant vitamins associated with respiratory disease in U.S. adults
Oxidative stress plays a key role in the pathogenesis of respiratory diseases; however, studies on antioxidant vitamins and respiratory outcomes have been conflicting. We evaluated whether lower serum levels of vitamins A, C, D, and E are associated with respiratory morbidity and mortality in the U.S. adult population. Lower serum vitamin C increased the odds of wheeze among all participants. Among smokers, lower serum α-tocopherol vitamin E increased the odds of wheeze and chronic bronchitis/emphysema. Lower serum vitamin C was associated with increased chronic lower respiratory disease mortality in all participants, whereas lower serum 25-hydroxy vitamin D tended to increase mortality from CLRD and influenza/pneumonia among smokers. Mortality from influenza/pneumonia increased with decreasing serum vitamin A levels in all participants. In pooled analysis, vitamin C deficiency and 25-hydroxy vitamin D insufficiency were associated with increased mortality from influenza/pneumonia. Thus, lower serum levels of vitamins A, C, D, and α-tocopherol vitamin E are associated with increased respiratory morbidity and/or mortality in U.S. adults. The results underscore the importance of antioxidant vitamins in respiratory health.

Salo PM, Mendy A, Wilkerson J, Molsberry SA, Feinstein L, London SJ, Fessler MB, Thorne PS, Zeldin DC. Serum antioxidant vitamins and respiratory morbidity and mortality: a pooled analysis. *Respir Res*. 2022 Jun 9;23(1):150. doi: 10.1186/s12931-022-02059-w. PMID: 35681205; PMCID: PMC9178544.

EETs reduce macrophage phagocytosis and lung clearance of Streptococcus pneumoniae
The role of epoxyeicosatrienoic acids (EETs) and soluble epoxide hydrolase (Ephx2) in regulating macrophage function remains unknown. Lung bacterial clearance of the Gram-positive bacteria *Steptococcus pneumoniae* was impaired in Ephx2-deficient mice that have increased EET levels. sEH inhibition also reduced lung clearance of *S. pneumoniae*. In contrast, the EET receptor antagonist, EEZE, restored lung clearance of *S. pneumoniae* in Ephx2-deficient mice. Human macrophage function was similarly regulated by EETs. Defining the role of EETs and Ephx2 in macrophage function may lead to development of new therapeutic approaches for bacterial diseases.

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.

Structural Basis for Cleavage of SARS-CoV-2 dsRNA by EndoU

Viral proteins from SARS-CoV-2 use a variety of approaches to prevent activation of the host immune response. One of these proteins, EndoU, is a uridine specific nuclease that processes viral double stranded(ds)RNA intermediates, to prevent activation of host dsRNA sensors, however the mechanism of RNA cleavage is poorly understood. Through a combination of biochemical and structural approaches the Stanley lab determined the structure of EndoU bound to a dsRNA substrate. This structure reveals that EndoU can cut dsRNA though a unique base-flipping mechanism which properly positions the uridine within the active-site recognition pocket.

Frazier MN, Wilson IM, Krahn JM, Butay KJ, Dillard LB, Borgnia MJ, Stanley RE. Flipped over U: structural basis for dsRNA cleavage by the SARS-CoV-2 endoribonuclease. *Nucleic Acids Res*. 2022 Aug 12;50(14):8290-8301. doi: 10.1093/nar/gkac589. PMID: 35801916; PMCID: PMC9371922.

Communication Within a Ribosome Assembly Molecular Motor

The production of ribosomes, which are the protein making factories or the cell, requires the aid of numerous energy consuming enzymes, such as AAA-ATPases. Through a combination of biochemical and structural approaches the Stanley lab determined how the ribosome assembly AAA-ATPase Rix7 drives ribosome production through a complex communication network. The near atomic resolution cryo-EM structure of Rix7 revealed that the two AAA domains of Rix7 use a series of intricate molecular cues to coordinate inter- and intradomain communication within the large hexameric assembly.

S Kocaman, YH Lo, JM Krahn, M Sobhany, VP Dandey, ML Petrovich, SK Etigunta, JG Williams, LJ Deterding, MJ Borgnia, RE Stanley (2022) Communication Network within the essential AAA-ATPase Rix7 drives ribosome assembly. *PNAS Nexus* (In Press).

Purifying SARS-CoV-2 proteins may produce targeted therapies

NIEHS researchers have developed a simple protocol to produce pure and high quantities of two proteins required for the replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Two proteins required for the faithful replication of the SARS-CoV-2 genome are nonstructural protein 14 (NSP14) and NSP10. Lack of straightforward purification protocols for NSP10 and NSP14 has hampered biochemical and structural studies of this important SARS-CoV-2 complex. To address this need, the researchers developed a simple method for the bacterial expression and purification of NSP10 and NSP14 and for the in vitro assembly and purification of an NSP10/14 complex with high yields. These purification methods and biochemical analyses pave the way for future structural studies investigating the mechanism of SARS-CoV-2 viral synthesis

Riccio AA, Sullivan ED, Copeland WC. Activation of the SARS-CoV-2 NSP14 3'-5' exoribonuclease by NSP10 and response to antiviral inhibitors. *J Biol Chem*. 2022 Jan;298(1):101518. doi: 10.1016/j.jbc.2021.101518. Epub 2021 Dec 20. PMID: 34942146; PMCID: PMC8685350.

Molecular Basis DNA repair activity by Apn2/APE2
Apn2/APE2 nucleases resolve chemically diverse DNA damage including endogenous DNA lesions created by Topoisomerase 1 (Top1). In this work we report structure and functional characterization of yeast Apn2-DNA complexes showing how the enzyme wedges and frays DNA ends. Our data further demonstrate how inactivation of Apn2 function causes novel forms of mutagenesis in budding yeast.

Williams JS, Wojtaszek JL, Appel DC, Krahn J, Wallace BD, Walsh E, Kunkel TA, and Williams RS. Molecular Basis for Processing of Topoisomerase 1-Triggered DNA damage by Apn2/APE2. *Cell Reports* (in press)

Oil spill cleanup workers twice as likely to have asthma symptoms
Gulf Long-Term Follow-up (GuLF STUDY) is a prospective cohort study of long-term health effects of cleanup workers and non-workers following the 2010 Deepwater Horizon disasters. Researchers analyzed data from 19,018 oil spill response and cleanup workers and 5,585 non-workers who did not have asthma prior to the spill. The nonworkers were people who completed the mandatory worker safety training but were not hired to do the cleanup work. Primary findings showed that workers involved in cleaning up the nation's largest oil spill were twice as likely to be diagnosed with asthma or experience asthma symptoms one to three years after the spill than non-workers. Researchers also found that the relative risk for asthma symptoms increased with increasing levels of exposure to individual BTEX-H chemicals as well as with the BTEX-H mixture. This is the largest study of oil spill workers to date and the first to consider exposure to specific oil spill chemicals.

Lawrence KG, Niehoff NM, Keil AP, Braxton Jackson W 2nd, Christenbury K, Stewart PA, Stenzel MR, Huynh TB, Groth CP, Ramachandran G, Banerjee S, Pratt GC, Curry MD, Engel LS, Sandler DP. Associations between airborne crude oil chemicals and symptom-based asthma. *Environ Int*. 2022 Sep;167:107433. doi: 10.1016/j.envint.2022.107433. Epub 2022 Jul 27. PMID: 35921771; PMCID: PMC9378681.

Vitamin D may protect against breast cancer in Black/African American and Hispanic/Latin American women Prior studies of largely non-Hispanic white women have unsuggested that low levels of vitamin D may be associated with increased breast cancer risk. Black/African American women and Hispanic/Latina women have lower circulating vitamin D levels than non-Hispanic White women, but few studies have examined the association between vitamin D and breast cancer within these racial/ethnic groups. In a case-cohort sample of self-identified Black/African American and non-Black Hispanic/Latina women participating in the US-wide Sister Study cohort, circulating 25-hydroxyvitamin D (25(OH)D) and 24,25-dihydroxyvitamin D (24,25(OH)2D) levels in blood samples collected at study enrollment from 415 women who developed breast cancer were compared to concentrations in samples from 1084 women randomly selected from the cohort. Over a mean follow-up of 9.2 years, women with

circulating 25(OH)D concentrations above the clinical cut point for deficiency (20.0 ng/mL) had lower breast cancer rates than women with concentrations below this level (HR, 0.79; 95% CI, 0.61-1.02). The inverse association was strongest among Hispanic/Latina women (HR, 0.52; 95% CI, 0.29-0.93). This prospective study supports the hypothesis that vitamin D may be protective against breast cancer incidence in women, including non-Black Hispanic/Latina and Black/African American women.

O'Brien KM, Harmon QE, Jackson CL, Diaz-Santana MV, Taylor JA, Weinberg CR, Sandler DP. Vitamin D concentrations and breast cancer incidence among Black/African American and non-Black Hispanic/Latina women. *Cancer*. 2022 Jul 1;128(13):2463-2473. doi: 10.1002/cncr.34198. Epub 2022 Apr 25. PMID: 35466399; PMCID: PMC9177687.

Oil spill cleanup workers at risk for hypertension

Workers who cleaned up after the *Deepwater Horizon* oil spill were exposed to a range of chemicals that may increase risk of developing cardiovascular diseases. Among 6,846 adults who had worked on the oil spill cleanup (workers) and 1,505 others who had completed required safety training but did not do cleanup work (nonworkers) who did not have diagnosed hypertension before the spill, workers who did cleanup on water or response work near the wellhead were 34% and 51% more likely to have newly detected hypertension up to three years after the spill than nonworkers. Increased risk of hypertension was associated with increasing levels of cumulative hydrocarbon exposure (a marker of exposure to the crude oil) and with exposure to burning and/or flaring of oil and gas during cleanup.

Kwok RK, Jackson WB 2nd, Curry MD, Stewart PA, McGrath JA, Stenzel M, Huynh TB, Groth CP, Ramachandran G, Banerjee S, Pratt GC, Miller AK, Zhang X, Engel LS, Sandler DP. Association of Deepwater Horizon Oil Spill Response and Cleanup Work With Risk of Developing Hypertension. *JAMA Netw Open*. 2022 Feb 1;5(2):e220108. doi: 10.1001/jamanetworkopen.2022.0108. Erratum in: *JAMA Netw Open*. 2022 Mar 1;5(3):e226792. PMID: 35195699; PMCID: PMC8867245.

New therapeutic approach to treating nonalcoholic fatty liver disease.
Obesity and obesity-induced metabolic dysfunctions are significant risk factors for nonalcoholic fatty liver disease and cardiovascular diseases that represent an economic and social burden in developed countries. Blocking the synthesis of inositol pyrophosphates by inositol hexakisphosphate kinase (IP6K) has been identified as a potential therapeutic strategy for obesity and related diseases. We have developed a novel and potent IP6K inhibitor; its intraperitoneal injection into diet-induced obese mice improved glycemic profiles, ameliorated hepatic steatosis, and reduced weight gain without altering food intake. This novel inhibitor has therapeutic relevance in treating obesity and related diseases.

Zhou Y, Mukherjee S, Huang D, Chakraborty M, Gu C, Zong G, Stashko MA, Pearce KH, Shears SB, Chakraborty A, Wang H, Wang X. Development of Novel IP6K Inhibitors for the Treatment of Obesity and Obesity-Induced Metabolic Dysfunctions. *J Med Chem*.

2022 May 12;65(9):6869-6887. doi: 10.1021/acs.jmedchem.2c00220. Epub 2022 Apr 25. PMID: 35467861; PMCID: PMC9383042.

New atomic level understanding of oncogenic protein tyrosine phosphatases
Structural snapshots of protein/ligand complexes are a prerequisite for gaining atomic level insight into enzymatic reaction mechanisms. An important group of enzymes has been deprived of this analytical privilege: members of the protein tyrosine phosphatase (PTP) superfamily with catalytic WPD-loops lacking the indispensable general-acid/base within a tryptophan-proline-aspartate/glutamate context. Here, we provide the first ligand/enzyme crystal complexes for one such PTP outlier (AtPFA-DSP1), and thereby demonstrate an unprecedented substrate-driven intramolecular proton donation that substitutes for the absent aspartate/glutamate general-acid. This substantial mechanistic insight into adaptability of the conserved PTP structural elements is applicable to the human PTEN oncogene.

Wang H, Perera L, Jork N, Zong G, Riley AM, Potter BVL, Jessen HJ, Shears SB. A structural exposé of noncanonical molecular reactivity within the protein tyrosine phosphatase WPD loop. *Nat Commun*. 2022 Apr 25;13(1):2231. doi: 10.1038/s41467-022-29673-y. PMID: 35468885; PMCID: PMC9038691.

Disease Flares following COVID-19 Vaccination among Adults with Systemic Rheumatic Disease
Vaccines have been of concern in patients with systemic rheumatic diseases, as the potential for disease increase or flare following vaccination has been documented with several vaccines, including influenza. In collaboration with the COIVD-19 Global Rheumatology Alliance, an international online survey study was conducted of 5619 adults with systemic rheumatic diseases to examine adverse events following COVID-19 vaccination, including flares of disease requiring a change in treatment. Flares requiring a change in treatment following COVID-19 vaccination were reported by 4.9% of patients. Compared with rheumatoid arthritis, certain systemic rheumatic diseases, including systemic lupus erythematosus, psoriatic arthritis, and polymyalgia rheumatica were associated with higher odds of flare, while idiopathic inflammatory myopathies were associated with lower odds for flare. The Oxford-AstraZeneca vaccine was associated with higher flare frequencies relative to the Pfizer-BioNTech vaccine, as were a prior reaction to a non-COVID-19 vaccine and female sex. Systemic rheumatic disease flares requiring changes in treatment following COVID-19 vaccination were uncommon in this large international study. Several potential risk factors, as well as differences by disease type, warrant further examination in prospective cohorts.

Rider LG, Parks CG, Wilkerson J, Schiffenbauer AI, Kwok RK, Noroozi Farhadi P, Nazir S, Ritter R, Sirotich E, Kennedy K, Larche MJ, Levine M, Sattui SE, Liew JW, Harrison CO, Moni TT, Miller AK, Putman M, Hausmann J, Simard JF, Sparks JA, Miller FW; COVID-19 Global Rheumatology Alliance Vaccine Survey Group. Baseline factors associated with self-reported disease flares following COVID-19 vaccination among adults with systemic rheumatic disease: results from the COVID-19 global rheumatology

alliance vaccine survey. *Rheumatology* (Oxford). 2022 Jun 28;61(SI2):SI143-SI150. doi: 10.1093/rheumatology/keac249. PMID: 35460240; PMCID: PMC9248066.

RNA processing requirements for male fertility.
Spermatogenesis is a multi-step process by which spermatogonial stem cells differentiate to become sperm. In this review, we discuss RNA processing requirements at different stages of this complex transformation. Failure to process RNA efficiently leads to spermatogenesis arrest and male infertility.

Morgan M, Kumar L, Li Y, Baptissart M. Post-transcriptional regulation in spermatogenesis: all RNA pathways lead to healthy sperm. *Cell Mol Life Sci*. 2021 Dec;78(24):8049-8071. doi: 10.1007/s00018-021-04012-4. Epub 2021 Nov 8. PMID: 34748024; PMCID: PMC8725288.

Intestinal epithelial stress hormone signaling have a dual role in regulation of intestinal inflammation and cancer
Synthetic immunosuppressive glucocorticoids are widely used to control inflammatory bowel disease (IBD). However, the impact of this stress signaling on intestinal tumorigenesis remains controversial. In collaboration with Dr. John Cidlowski's group at the NIEHS and Dr. Shuang Tang's group at Fudan University Cancer Center, we recently report that intestinal epithelial glucocorticoid receptor (GR) signaling promotes chronic intestinal inflammation associated colorectal cancer in both humans and mice. In colorectal cancer patients, GR is enriched in intestinal epithelial cells and high epithelial GR is associated with poor prognosis. In mice, intestinal epithelium-specific deletion of GR (GR iKO) increases macrophage infiltration, improves tissue recovery, and enhances antitumor response, and suppresses tumor formation in a chronic inflammation-associated colorectal cancer model. Furthermore, oral GC administration in the early phase of tissue injury delays recovery and accelerates the formation of aggressive colorectal cancers. Our study suggests that colorectal epithelial GR could serve as a predictive marker for colorectal cancer risk and prognosis. Our findings further suggest that although synthetic glucocorticoid treatment for IBD should be used with caution in colorectal cancer patients, there is a therapeutic window for glucocorticoid therapy during colorectal cancer development.

Tang S, Zhang Z, Oakley RH, Li W, He W, Xu X, Ji M, Xu Q, Chen L, Wellman AS, Li Q, Li L, Li JL, Li X, Cidlowski JA, Li X. Intestinal epithelial glucocorticoid receptor promotes chronic inflammation-associated colorectal cancer. *JCI Insight*. 2021 Dec 22;6(24):e151815. doi: 10.1172/jci.insight.151815. PMID: 34784298; PMCID: PMC8783679.

A role for the locus coeruleus in the modulation of feeding
Noradrenergic neurons of the locus coeruleus (LC-NE neurons) are known to play an important role in arousal, emotion, memory, and cognition. Expanding upon these functions, NIEHS researchers led by Patricia Jensen, Ph.D., uncovered the role of endogenous LC-NE activity in natural, homeostatic feeding. Dr. Jensen’s group found that natural activity of LC-NE neurons is suppressed during feeding and influenced by nutritional state, and that experimental activation of these neurons reduces food intake. In addition, they found that activation of the LC-to-lateral

hypothalamus neural pathway suppresses feeding and enhances avoidance and anxiety-like responding, suggesting that LC-NE neurons modulate feeding by integrating both external information (e.g., anxiety-inducing environmental cues) and internal drives (e.g., satiety).

Sciolino NR, Hsiang M, Mazzone CM, Wilson LR, Plummer NW, Amin J, Smith KG, McGee CA, Fry SA, Yang CX, Powell JM, Bruchas MR, Kravitz AV, Cushman JD, Krashes MJ, Cui G, Jensen P. Natural locus coeruleus dynamics during feeding. *Sci Adv*. 2022 Aug 19;8(33):eabn9134. doi: 10.1126/sciadv.abn9134. Epub 2022 Aug 19. PMID: 35984878; PMCID: PMC9390985.

SIRT1 regulates cardiomyocyte alignment during maturation

Cardiomyocytes, cells responsible for generating contractile force in the heart, require elongation and alignment during maturation around birth (perinatal stage). This morphological remodeling is crucial for formation of the highly organized intra- and inter-cellular structures for spatially and temporally ordered contraction in adult cardiomyocytes. However, control of cardiomyocyte alignment remains elusive. Here we report that SIRT1, the most conserved NAD+-dependent protein deacetylase highly expressed in perinatal heart, plays an important role in regulating cardiomyocyte remodeling during development. SIRT1 deficiency impairs alignment of cardiomyocyte and disrupts normal beating patterns at late developmental stages in an in vitro differentiation system from human embryonic stem cells. Consistently, deletion of SIRT1 at a late developmental stage in mouse embryos induces the irregular distribution of cardiomyocytes and misalignment of myofibrils and reduces the heart size. At the molecular level, we found that the expression of several genes involved in cell movement in response to chemical stimulus is dramatically blunted during maturation of SIRT1 deficient cardiomyocytes. Pharmacological inhibition of these signaling suppresses cardiomyocyte alignment. Our study identifies a regulatory factor that modulates cardiomyocyte alignment at the inter-cellular level during maturation.

Fang Y, Fan W, Xu X, Janoshazi AK, Fargo DC, Li X. SIRT1 regulates cardiomyocyte alignment during maturation. *J Cell Sci*. 2022 Apr 1;135(7):jcs259076. doi: 10.1242/jcs.259076. Epub 2022 Apr 1. PMID: 35260907; PMCID: PMC9016619.

Cryo-electron microscopy views of the catalytic cycle reveal how Dicer-1 selects authentic pre-microRNA substrates

A series of six cryo-electron microscopy structures illustrates how the Drosophila melanogaster Dicer-1 enzyme collaborates with its partner protein Loquacious to process authentic pre-microRNA substrates. These structures are the first to trace an entire catalytic cycle and the first to show the catalytically competent conformation of any animal Dicer. Both Dicer-1 and Loquacious undergo rearrangements to recognize the characteristic features of pre-microRNAs. Furthermore, the RNA conformation adjusts to allow correct positioning at the active sites. These data provide a structural and mechanistic rationale to explain two decades of research on pre-microRNA processing by Dicer enzymes.

Jouravleva K, Golovenko D, Demo G, Dutcher RC, Hall TMT, Zamore PD and Korostelev AA. Structural Basis of MicroRNA Biogenesis by Dicer-1 and Its Partner Protein Loqs-PB, *Mol. Cell* (2022), in press.

Geospatial Distribution of Myositis Cases in the United States Suggests Environmental Influences

The myositis syndromes are rare systemic autoimmune diseases with characteristic muscle inflammation, weakness, and organ damage, including lung disease. From a national myositis patient registry of nearly 1200 patients enrolled throughout the United States, we examined the geospatial distribution of the major clinical subgroups, including dermatomyositis (DM, the form with photosensitive rashes), polymyositis (PM, with primary immune attack on the skeletal muscles), and inclusion body myositis (IBM, a slowly progressive form primarily in older men). We found a higher density of myositis cases in the Northeast. DM, IBM, and cases with lung disease were more common in the East, whereas PM cases were more common in the Southeast. One area in the West had a significant excess of DM cases relative to PM, and one area in the South had an excess of cases with lung disease relative to those without lung disease. There was a trend of a higher prevalence of myositis and its major phenotypes among people living closer to large roadways. This study suggests clustering of myositis in some regions of the United States and a possible association of proximity to roadways, suggesting environmental influences in these diseases.

Hossain MM, Wilkerson J, McGrath JA, Farhadi PN, Brokamp C, Khan MTF, Goldberg B, Brunner HI, Macaluso M, Miller FW, Rider LG. The Geospatial Distribution of Myositis and Its Phenotypes in the United States and Associations With Roadways: Findings From a National Myositis Patient Registry. *Front Med* (Lausanne). 2022 Mar 16;9:842586. doi: 10.3389/fmed.2022.842586. PMID: 35372396; PMCID: PMC8966380.

Phage Display of Protein Toxins and Microbes Reveals Antibody Responses

Lifelong exposures to microbes and their protein products are crucial environmental factors that impact human health by sculpting the immune system. Antibody profiling via Phage ImmunoPrecipitation Sequencing (PhIP-Seq) provides a high-throughput approach for detecting exposure and antibody response to more than 14,000 toxin and microbial protein products. This study examined antibody responses of healthy volunteers and patients with autoimmune diseases, finding that that serum antibody bindings to these ToxScan peptides are unique and stable in adulthood. The major histocompatibility class II locus influences the antibody selection. Flagellin antibodies were found in patients with Crohn's disease and juvenile dermatomyositis, suggesting gut microbe exposures may be involved in the pathogenesis of both autoimmune diseases.

Angkeow JW, Monaco DR, Chen A, Venkataraman T, Jayaraman S, Valencia C, Sie BM, Liechti T, Farhadi PN, Funez-dePagnier G, Sherman-Baust CA, Wong MQ, Ruczinski I, Caturegli P, Sears CL, Simner PJ, Round JL, Duggal P, Laserson U, Steiner TS, Sen R, Lloyd TE, Roederer M, Mammen AL, Longman RS, Rider LG, Larman HB. Phage display of environmental protein toxins and virulence factors reveals the prevalence, persistence, and genetics of antibody responses. *Immunity*. 2022 Jun 14;55(6):1051-1066.e4. doi: 10.1016/j.immuni.2022.05.002. Epub 2022 May 31. PMID: 35649416; PMCID: PMC9203978.

Characterizing novel allergens from peanuts and walnuts helps to understanding the comorbidity of peanut and walnut allergies

Peanut and walnut allergies are frequently comorbid for reasons not completely understood. Usually, allergen sources that are close in evolutionary time (like rye grass and northern grass) have allergens that look similar, and patients generate antibodies that react to both sources. However, peanuts are legumes and walnuts are from deciduous trees and the allergens appear quite different, hence would not be expected to be so frequently comorbid. In studies by the Mueller lab, 3D molecular characterizations of peanut and walnut allergens revealed unexpected similarities that may help explain the comorbidity. This information could be used to improved diagnostics and therapies for nut allergies.

Foo ACY, Nesbit JB, Gipson SAY, Cheng H, Bushel P, DeRose EF, Schein CH, Teuber SS, Hurlburt BK, Maleki SJ, Mueller GA. Structure, Immunogenicity, and IgE Cross-Reactivity among Walnut and Peanut Vicilin-Buried Peptides. *J Agric Food Chem*. 2022 Feb 23;70(7):2389-2400. doi: 10.1021/acs.jafc.1c07225. Epub 2022 Feb 9. PMID: 35139305; PMCID: PMC8959100.

Evaluation of Diagnostic Criteria for Canine Glioma

Glioma tumors occur in the brain and spinal cord. While human diagnostic criteria for glioma have been established for quite some time, canine diagnostic glioma standards for glioma were not established until 2018 when the Comparative Brain Tumor Consortium (CBTC) created a set of diagnostic criteria to aid veterinary pathologists in diagnostic consensus. Histopathologic evaluation of tumors is a subjective process, and pathologist diagnoses frequently do not achieve 100% agreement even with detailed diagnostic criteria. Using statistical measures of agreement, the CBTC system produced a statistically moderate agreement among five veterinary pathologist raters evaluating 85 samples from dogs with previous diagnosis of intracranial glioma. This result is similar to pathologist agreement found in most human glioma studies and other established diagnostic systems in veterinary medicine, indicating that the CBTC system is likely sufficient for routine diagnostic pathology.

Krane GA, Shockley KR, Malarkey DE, Miller AD, Miller CR, Tokarz DA, Jensen HL, Janardhan KS, Breen M, Mariani CL. Inter-pathologist agreement on diagnosis, classification and grading of canine glioma. *Vet Comp Oncol*. 2022 Jul 20. doi: 10.1111/vco.12853. Epub ahead of print. PMID: 35856268.

Scientists discover new model for understanding sex differences in anxiety

Women are disproportionately affected by anxiety disorders and neurodegenerative conditions like Alzheimer's disease. The reasons for this are not well understood because of long-standing failure to include female subjects in basic science research. In an effort to overcome this, researchers at NIEHS carefully examined behavioral differences between male and female mice. They found that female mice reacted more cautiously to novel sounds, and this had a significant impact on how we have traditionally measured learning and memory. They found ways to reduce this by more carefully handling the mice during the behavioral studies and suggest that a better understanding of what causes this difference may provide better treatments for medical conditions that are more common in women.

Stevanovic KD, Fry SA, DeFilipp JMS, Wu N, Bernstein BJ, Cushman JD. Assessing the importance of sex in a hippocampus-dependent behavioral test battery in C57BL/6NTac mice. *Learn Mem*. 2022 Jul 26;29(8):203-215. doi: 10.1101/lm.053599.122. PMID: 35882502; PMCID: PMC9374270.

Developing improved heparan sulfate therapeutics by understanding mechanism and products of the 3-O-sulfotransferase isoform 5 enzyme.
Specific sulfation of Heparan sulfate (HS) on the 3-O-poisition can regulate coagulation as well as contribute to cancer pathogenesis, neural development, and regulation. Using crystal structures of HS bound to 3-O-sulfotransferase isoform 5, researchers have learned how this enzyme distinguishes its substrates compared to other 3-O-sulfotransfease isoforms. Researchers were able to utilize this enzyme to develop an oligosaccharide with improved binding affinity to antithrombin that suggests it would require less compound with a longer half-life than a current oligosaccharide that is approved as an anticoagulant.

Wander R, Kaminski AM, Wang Z, Stancanelli E, Xu Y, Pagadala V, Li J, Krahn JM, Pham TQ, Liu J, Pedersen LC. Structural and substrate specificity analysis of 3-O-sulfotransferase isoform 5 to synthesize heparan sulfate. *ACS Catal*. 2021 Dec 17;11(24):14956-14966. doi: 10.1021/acscatal.1c04520. Epub 2021 Nov 30. PMID: 35223137; PMCID: PMC8865405.

Spatial transcriptomics identifies the communication between the embryo and compartments of the uterus in pregnant mice.
We utilized spatial transcriptomics which combines histological sectioning and next generation sequencing to identify gene expression in the uterus. Using this approach, we were able to identify the molecular signatures of the cells in the uterus in conjunction with their spatial localization. We were also able to infer the growth factor communication between these compartments. This has implications in understanding how the embryo interacts with the different cells in the uterus during pregnancy.

Li R, Wang TY, Xu X, Emery OM, Yi M, Wu SP, DeMayo FJ. Spatial transcriptomic profiles of mouse uterine microenvironments at pregnancy day 7.5†. *Biol Reprod*. 2022 Aug 9;107(2):529-545. doi: 10.1093/biolre/ioac061. PMID: 35357464; PMCID: PMC9382390.

The generation of a novel mouse model to investigate gene expression in the post implantation mouse uterus.
Cre recombinase was inserted into the mouse Prolactin A2 gene. The mouse generated allows for gene editing in the decidual cells of the post implantation mouse uterus. This will allow the dissection of the molecular mechanisms governing the ability of the uterus to maintain fetal development.

Dickson MJ, Oh Y, Gruzdev A, Li R, Balaguer N, Kelleher AM, Spencer TE, Wu SP, DeMayo FJ. Inserting Cre recombinase into the Prolactin 8a2 gene for decidua-specific recombination in mice. *Genesis*. 2022 May;60(4-5):e23473. doi: 10.1002/dvg.23473. Epub 2022 Apr 27. PMID: 35475540; PMCID: PMC9422316.

Uterine epithelial organoids reflect a subset of progesterone responsive genes when compared to normal human endometrium.
This report investigated the gene expression and chromatin structure as well as sites bound by the progesterone in human endometrial organoids. Here we found that human endometrial organoids only reflect a subset of progesterone responsive genes. Analysis of the chromatin structure demonstrate that many of the progesterone binding sites in organoid culture may reside in silent regions of the chromatin. This research determines the utility of the in vitro approach to investigate hormone responsiveness in the human uterine epithelial cells.

Hewitt SC, Wu SP, Wang T, Young SL, Spencer TE, DeMayo FJ. Progesterone Signaling in Endometrial Epithelial Organoids. *Cells*. 2022 May 27;11(11):1760. doi: 10.3390/cells11111760. PMID: 35681455; PMCID: PMC9179553.

The identification of Estrogen Receptor binding sites in the human endometrium during the early menstrual cycle.
The binding sites of the estrogen receptor to human endometrial cells isolated from endometrial biopsies was identified. Here we determined the gene directly regulated by estrogen. This analysis is important because it helps understand how estrogen regulates normal uterine function and how environmental estrogens may disrupt uterine function.

Hewitt SC, Wu SP, Wang T, Ray M, Brolinson M, Young SL, Spencer TE, DeCherney A, DeMayo FJ. The Estrogen Receptor α Cistrome in Human Endometrium and Epithelial Organoids. *Endocrinology*. 2022 Sep 1;163(9):bqac116. doi: 10.1210/endocr/bqac116. PMID: 35895287; PMCID: PMC9368022.

Timing of Progesterone stimulation of the uterus is critical for the establishment of pregnancy.
We demonstrated that alteration of progesterone receptor signaling in the uterus will cause infertility in mice. We demonstrate that the altered progesterone receptor expression inhibits embryo implantation in part by preventing the estrogen receptor from regulationg critical genes governing implantation. This is of critical importance in understanding how endocrine disruptors with progesterone action may impact pregnancy.

Li R, Wang TY, Xu X, Emery OM, Yi M, Wu SP, DeMayo FJ. Spatial transcriptomic profiles of mouse uterine microenvironments at pregnancy day 7.5†. *Biol Reprod*. 2022 Aug 9;107(2):529-545. doi: 10.1093/biolre/ioac061. PMID: 35357464; PMCID: PMC9382390.

Researchers at the NIEHS have used molecular dynamics to understand disease mutation in mitochondrial DNA binding protein
Several mutations in the gene for the mitochondrial single stranded DNA binding protein (SSBP1) have recently been implicated in human disease, but initial reports are insufficient to explain the molecular mechanism of disease, including the possible role of SSBP1 heterotetramers in heterozygous patients. NIEHS researchers employed molecular simulations to model the dynamics of wild type and 31 disease SSBP1 tetramer systems, including 7 variant

homotetramer and 24 representative heterotetramer systems. These simulations indicate that all variants are stable and most have stronger intermonomer interactions, reduced solvent accessible surface areas, and a net loss of positive surface charge. Overall, the findings identify subtle changes to DNA binding, wrapping, or release that can cause rare but consequential failures of mtDNA maintenance.

Gustafson MA, Perera L, Shi M, Copeland WC. Mechanisms of SSBP1 variants in mitochondrial disease: Molecular dynamics simulations reveal stable tetramers with altered DNA binding surfaces. *DNA Repair* (Amst). 2021 Nov;107:103212. doi: 10.1016/j.dnarep.2021.103212. Epub 2021 Aug 17. PMID: 34464898; PMCID: PMC8526412.

Studying genotoxicity of the Sudan I and Sudan II azo dyes and their metabolites using molecular modeling

Sudan I and Sudan II are synthetic azo dyes that have been used as coloring agents. Although animal toxicity studies suggested that Sudan dyes are mutagenic, their molecular mechanism of action is unknown. This makes it challenging to understand how these molecules could be modified to ameliorate toxicity. Additionally, their metabolites such as azobiphenyl and 4-aminobiphenyl have been correlated with epigenetic alterations. Using molecular dynamics simulations, we observed that the DNA adducts of these dyes and their metabolites cause significant perturbations to the DNA conformation and structure, potentially interfering with the repair mechanisms.

Bienstock RJ, Perera L, Pasquinelli MA. Molecular Modeling Study of the Genotoxicity of the Sudan I and Sudan II Azo Dyes and Their Metabolites. *Front Chem*. 2022 Jun 23;10:880782. doi: 10.3389/fchem.2022.880782. PMID: 35815205; PMCID: PMC9261194.

Use of injectable contraceptive Depo-Provera reduces uterine fibroid incidence and growth

Uterine fibroids develop in up to 80% of women and can cause heavy menstrual bleeding and pain and may require surgical intervention. We followed a cohort of young (23–35-year-old) African American or Black women from the Detroit Michigan area for 5 years with a standardized ultrasound protocol to detect and measure uterine fibroids. In this cohort we found that use of Depo-Provera within 2 years of a visit resulted in a 40% reduction in fibroid incidence and 42% lower fibroid growth. In keeping with the reduced growth, we also observed that use of Depo-Provera within 2 years also increased the likelihood that a fibroid would be lost. Use of Depo-Provera for contraception may delay fibroid symptom onset and reduce the need for invasive treatment.

Harmon QE, Patchel SA, Zhao S, Umbach DM, Cooper TE, Baird DD. Depot Medroxyprogesterone Acetate Use and the Development and Progression of Uterine Leiomyoma. *Obstet Gynecol*. 2022 May 1;139(5):797-807. doi: 10.1097/AOG.0000000000004745. Epub 2022 Apr 5. PMID: 35576339; PMCID: PMC9015023.

In non-diabetic women a measure of blood sugar in mid-pregnancy may help predict infant size and the risk of preterm birth and preeclampsia

High blood sugar which results in gestational diabetes is a risk factor for pregnancy complications, however not as much is known about measures of blood sugar in pregnancies without gestational diabetes. We examined pregnancy and infant outcomes in almost 3,000 pregnancies with measured glycated hemoglobin (HbA1c, a marker of long-term blood sugar) at 18 weeks' gestation. All the pregnancies were a part of the Norwegian Mother, Father and Child Cohort Study (MoBa), and none had HbA1c measures which would result in a diagnosis of gestational diabetes. Although all the measures of HbA1c were within the "normal" range, higher measures of HbA1c were associated with larger infant size at birth and an increased risk of delivering a large for gestational age infant. Those with the highest measures of HbA1c also had an increased risk of preterm birth and preeclampsia. Although HbA1c is not routinely measured in pregnancy, it may be a useful predictor of pregnancy complications even within the "normal range".

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