Division of Intramural Research

NAEHS Council Update

September 2023

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.

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 was formed to facilitate identification of a small pool of outstanding candidates to advance to 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 2023-24 representing a range of disciplines central to the NIEHS mission.

DIR STAFF UPDATES

New Tenure-Track Investigators

Dr. Julieta Lischinsky from the Neuroscience Institute at New York University Grossman School of Medicine has accepted an offer to join the Neurobiology Laboratory as an Earl Stadtman Tenure Track Investigator. Dr. Lischinsky will initiate an independent program focused on developing and applying innovative neuroscience approaches to elucidate how social sensory information is encoded and impacts behavior across developmental stages and how these mechanisms are disrupted during early life adversity and in psychiatric conditions, such as autism spectrum disorder (ASD). She has also been selected as a member of the NIH Distinguished Scholars Program. Dr. Lischinsky plans to start at NIEHS in October 2023.

Dr. Rajula Elango from Harvard Medical School has accepted an offer to join the Genome Integrity and Structural Biology Laboratory as a tenure-track investigator. Dr. Elango will initiate an independent research program focused on studying DNA damage and repair pathways and how environmental stressors impact these processes starting in January 2024.

New Independent Research Scholar

Dr. Mandy Goldberg was selected as an NIH Independent Research Scholar (IRS) and will initiate her independent program at NIEHS in Fall 2023. Dr. Dale Sander will serve as her primary mentor in the Epidemiology Branch. Her independent research program will focus on adolescent beauty product use and breast cancer risk in adulthood. Dr. Goldberg is also a recipient of a K99 award from NICHD (K99HD110645).

DIR COMMITMENT TO DIVERSITY, EQUITY, INCLUSION AND ACCESSIBILITY

NIH Distinguished Scholars Program

Dr. Julieta Lischinsky who will be joining DIR as an Earl Stadtman Tenure Track Investigator in the Neurobiology Laboratory in Fall 2023 was selected to participate in the NIH Distinguished Scholars Program based on her demonstrated commitment to lowering barriers to participation in science for individual traditionally underrepresented in science. Dr. Lischinsky joins 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)

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 11 FARE award winners for 2024:

FARE Winner	Mentor	Project
Dr. Yu-Ying Chen	Dr. Humphrey Yao	Somatic cell fate specification and separation in the fetal ovary
Dr. Dazhe Chen	Dr. Dale P Sandler	Ingested nitrate and nitrite and end-stage renal disease risk among licensed pesticide applicators and spouses in the Agricultural Health Study
Dr. Kathryn Dalton	Dr. Stephanie London	Occupational Farm Exposures Associated with Indoor Home Microbiota
Dr. Jennifer Ish	Dr. Alexandra White	Residential proximity to carcinogenic industrial air emissions and breast cancer incidence in a United States-wide prospective cohort
Dr. Laura Kammel	Dr. Joseph Rodriguez	Circadian disruption induces breast cancer-permissive estrogen receptor transcriptional program in hormone sensitive mammary epithelium
Dr. Suneet Kaur	Dr. Anant Parekh	Unraveling the AKAP79-Orai1 Interaction: Implications for Immune Response Regulation
Dr. Ryan Marquardt	Dr. Francesco DeMayo	The Serum Response Factor-Myocardin Pathway is Essential for Female Reproductive Function
Dr. Sookjin Moon	Dr. Michael Fessler	Flotillin-2 ablation in T cells enhances antigen sensitivity and functionality
Dr. Sukanya Saha	Dr. Guohong Cui	Bioenergetic stress triggers Amyotrophic Lateral Sclerosis-like symptoms in mice
Dr. Ziyue Wang	Dr. Alison Motsinger-Reif	Shotgun metagenomics sequencing reveals novel insights of indoor dust microbiota compared with 16S rRNA technology
Dr. Pelin Yasar	Dr. Joseph Rodriguez	Establishing Estrogen Receptor α Enriched Mouse Mammary Organoids to Investigate Transcriptional Dynamics and Heterogeneity

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

NIGMS PRAT Awards:
Dr. Adriana Alexander received a prestigious NIGMS Postdoctoral Research Associate Training (PRAT) Awards and will be mentored by Dr. Humphrey Yao in the Reproductive and Developmental Biology Laboratory with funding from NIGMS for 3 years.

2023 NIMHD Coleman Research Innovation Awards
Drs. Kaitlyn Gam, Rupsha Singh, and Jennifer Woo, postdoctoral fellows in the Epidemiology Branch have received 2023 Coleman Research Innovation Awards from NIMHD.

2023 Lalor Foundation Award from the Society for the Study of Reproduction
Drs. Yu-Ying Chen and Ryan Marquardt, postdoctoral fellows in the Reproductive and Developmental Biology Laboratory received Lalor Foundation Awards.

2023 Neuroscience Scholars Program Fellowship
Preston Siegler, IRTA Predoctoral Fellow in the Neurobiology Laboratory

2023 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

2023 Intramural AIDS Research Fellowship (IARF)

Dr. Kedar Sharma, an IRTA Postdoctoral Fellow in the Genome Integrity and Structural Biology Laboratory will be mentored by Dr. Mario Borgnia

2023 NIH Poster Day- Postbaccalaureate Fellows Outstanding Posters

Abra Granger, Genome Integrity and Structural Biology Laboratory

Stephanie Jones, Neurobiology Laboratory

Oindrila Paul, Reproductive and Developmental Biology Laboratory

DIR RESEARCH ACCOMPLISHMENTS FOR FY 2023

Structural Basis for pre-tRNA Splicing

Across all walks of life, specific tRNA genes contain intronic sequences that require splicing for these tRNAs to be functional. In humans tRNA splicing is carried out of the tRNA splicing endonuclease (TSEN) complex. All four subunits of this complex are essential and mutations within the complex are the leading cause of a group of rare neurodevelopmental disorders known as pontocerebellar hypoplasia (PCH). We determined cryo-EM structures of the human complex bound to an intron-containing pre-tRNA, revealing the overall architecture of the complex and the extensive tRNA binding interfaces. Moreover, the structure revealed atomic insight into PCH causing missense mutations.

Hayne CK, Butay KJU, Stewart ZD, Krahn JM, Perera L, Williams JG, Petrovitch RM, Deterding LJ, Matera AG, Borgnia MJ, Stanley RE. Structural basis for pre-tRNA recognition and processing by the human tRNA splicing endonuclease complex. *Nat Struct Mol Biol*. 2023 Jun;30(6):824-833. doi: 10.1038/s41594-023-00991-z. Epub 2023 May 25. PMID: 37231153.

Commentary: Hopper AK, Zhang J. Captured: the elusive eukaryotic tRNA splicing enzyme. *Nat Struct Mol Biol*. 2023 Jun;30(6):711-713. doi: 10.1038/s41594-023-00995-9. PMID: 37231155; PMCID: PMC10370254.

For determining type 2 diabetes risk, scores incorporating multiple environmental exposures show promise

Using questionnaire-based and whole-genome sequencing data from the diverse, multi-ancestry Personalized Environment and Genes Study (PEGS) cohort, we conducted an exposome-wide association study (ExWAS), analogous to a genome-wide association study, to confirm exposures known to be associated with type 2 diabetes (i.e., high BMI) and identify new associations (i.e., asbestos and coal dust exposure), including diet and lifestyle factors, occupational exposures, and household exposures. To compare the cumulative effects of genetic and environmental factors, we computed a polyexposure score (PXS) using 13 environmental variables, an overall clinical score (OCS) incorporating BMI and prediabetes, hypertension, and high cholesterol status, all of which are known to be associated with type 2 diabetes, and a multi-ancestry polygenic score (PGS) that represents disease risk due to genetics. All the scores were significantly associated with type 2 diabetes, and PXS outperformed PGS in many metrics, supporting its strong potential for use in precision medicine to target individuals for lifestyle modifications and further disease screening. Further developing methods to calculate and combine PXS with other risk scores can provide insights into the complex interactions of genetics and environmental factors in disease etiology.

Akhtari FS, Lloyd D, Burkholder A, Tong X, House JS, Lee EY, Buse J, Schurman SH, Fargo DC, Schmitt CP, Hall J, Motsinger-Reif AA. Questionnaire-Based Polyexposure Assessment Outperforms Polygenic Scores for Classification of Type 2 Diabetes in a Multiancestry Cohort. *Diabetes Care*. 2023 May 1;46(5):929-937. doi: 10.2337/dc22-0295. PMID: 36383734.

Adolescent use of genital hygiene products may increase fibroid risk
Using data from the Sister Study cohort, researchers found that Black women who had used genital talc during ages 10-13 and also reported douching were 52% more likely to have been diagnosed with uterine fibroids before age 35 than those who did not use these products. Among non-Hispanic White women, talc use but not douching was also associated with early fibroids, with a 31% increase in the prevalence of fibroids before age 35. Early adolescence may be a window of susceptibility for fibroid development. Because fibroids are diagnosed more frequently and at an earlier age among Black women, results suggest that prevention efforts targeting the adolescent use of talc and douching may contribute to reducing this health disparity.

Ogunsina K, Sandler DP, Murphy JD, Harmon QE, D'Aloisio AA, Baird DD, O'Brien KM. Association of genital talc and douche use in early adolescence or adulthood with uterine fibroids diagnoses. *Am J Obstet Gynecol* 2023; S0002-937823)00549-5. DOI:10.1016/j.ajog.2023.08.014. PMID:3759898.

New Findings about Uterine Fibroids
The Study of Environment, Lifestyle & Fibroids [SELF] continues to provide new insights into this non-cancerous tumor of the uterine muscle - a high morbidity, but understudied condition that is the leading indication for hysterectomy in the U.S. and disproportionately affects African-American women. SELF is the first study to do standardized ultrasound screenings every 20 months for new cases of fibroids in order to identify modifiable factors that can influence fibroid development. This cohort of nearly 1700 young African-American women have been followed for over five years with a 90% retention rate. Recent new findings show a decrease in fibroid growth among participants with sufficient vitamin D. A protective effect of the active metabolite of vitamin D had been previously shown in an animal model of fibroids, and with invitro research on uterine tissues, but human data have been limited.

Harmon QE, Patchel SA, Denslow S, LaPorte F, Cooper T, Wise LA, Wegienka G, Baird DD. Vitamin D and uterine fibroid growth, incidence, and loss: a prospective ultrasound study. *Fertil Steril*. 2022 Dec;118(6):1127-1136. PMID: 36150919.

Breast cancer diagnosis and treatment increases biological aging
Breast cancer survivors have increased incidence of age-related diseases such as heart disease. Using three measures of biological aging derived from data on DNA methylation (DNAm) in blood samples collected at two time points about 8 years apart from 190 women who developed breast cancer between blood draws and 227 women who remained breast cancer free, researchers showed that women e diagnosed and treated for breast cancer had higher DNAm aging at the second time point than those who remained breast cancer free, after accounting for differences in DNAm age at the first time point. Among those with breast cancer, the strongest associations with biological aging were for those who received radiation treatments. Findings indicate that DNA methylation may play a role in the increased morbidly among breast cancer survivors and point to the need for increased medical surveillance of breast cancer survivors, especially those who received radiation.

Kresovich JK, O'Brien KM, Xu Z, Weinberg CR, Sandler DP, Taylor JA. Changes in methylation-based aging in women who do and do not develop breast cancer. *J Natl*

Cancer Inst. 2023 Jul 19:djad117. doi: 10.1093/jnci/djad117. Epub ahead of print. PMID: 37467056.

Deepwater Horizon oil spill clean-up workers exposed to volatile hydrocarbons and/or $PM_{2.5}$ from burning oil at increased risk of developing coronary heart disease

During clean-up after the 2010 Deepwater Horizon oil spill, response and clean-up workers were potentially exposed to toxic volatile components of crude oil as well as combustion products from the burning and flaring of oil done to mitigate environmental damage. In other settings, exposures to volatile organic compounds such as total hydrocarbons (THC) and BTEX-H (benzene, toluene, ethylbenzene, xylenes, and hexane) chemicals or fine particulate matter ($PM_{2.5}$) air pollution have been linked to coronary heart disease (CHD) risk. NIEHS researchers estimated exposures to THC, BTEX-H and burning-related $PM_{2.5}$ and ascertained coronary heart disease (CHD) events (heart attack or fatal CHD event) occurring after the last day of clean-up work among more than 22,000 clean-up workers who did not have CHD before the spill. Overall and in specific subgroups, higher levels of exposure to each of the measured oil spill chemicals were associated with suggestive increases in CHD risk, although there was no dose response, and few associations were statistically significant. On the other hand, **c**ompared to clean-up workers who worked on the water but not near controlled burning, those exposed to the highest level of daily average $PM_{2.5}$ from burning had 2-fold increased risk of having a CHD event and there was evidence of a dose response trend. Findings support the need for continued health surveillance of oil spill clean-up workers with the highest chemical exposures, especially those involved in burning or flaring the oil.

Chen D, Sandler DP, Keil AP, Heiss G, Whitsel EA, Pratt GC, Stewart PA, Stenzel MR, Groth CP, Banerjee S, Huynh TB, Edwards JK, Jackson WB 2nd, Engeda J, Kwok RK, Werder EJ, Lawrence KG, Engel LS. Fine particulate matter and incident coronary heart disease events up to 10 years of follow-up among Deepwater Horizon oil spill workers. *Environ Res*. 2023 Jan 15;217:114841. doi: 10.1016/j.envres.2022.114841. Epub 2022 Nov 17. PMID: 36403648; PMCID: PMC9825646.

Chen D, Sandler DP, Keil AP, Heiss G, Whitsel EA, Edwards JK, Stewart PA, Stenzel MR, Groth CP, Ramachandran G, Banerjee S, Huynh TB, Jackson WB 2nd, Blair A, Lawrence KG, Kwok RK, Engel LS. Volatile Hydrocarbon Exposures and Incident Coronary Heart Disease Events: Up to Ten Years of Follow-up among *Deepwater Horizon* Oil Spill Workers. *Environ Health Perspect*. 2023 May;131(5):57006. doi: 10.1289/EHP11859. Epub 2023 May 24. PMID: 37224072; PMCID: PMC10208425.

Structure of a Critical Molecular Scaffold

PELP1 is a large scaffolding protein that plays important roles in several biological pathways such as ribosome assembly, steroid receptor coactivation, and heterochromatin maintenance. How PELP1 coordinates its diverse cellular functions is not well understood. To begin to address this question we reconstituted a large RNA processing complex and established that PELP1 functions as the central scaffold of the mammalian Rix1 complex whose members include SENP3, TEX10, and WDR18. We determined a high resolution cryo-EM structure of PELP1 bound to WDR18 revealing that association with WDR18 directs PELP1s activity toward specific cellular functions.

Gordon J, Chapus FL, Viverette EG, Williams JG, Deterding LJ, Krahn JM, Borgnia MJ, Rodriguez J, Warren AJ, Stanley RE. Cryo-EM reveals the architecture of the PELP1-WDR18 molecular scaffold. *Nat Commun*. 2022 Nov 9;13(1):6783. doi: 10.1038/s41467-022-34610-0. PMID: 36351913; PMCID: PMC9646879.

The Vaginal Microbiota of Pregnant Women Varies with Gestational Age, Maternal Age, and Parity

There is debate regarding links between the vaginal microbiota and pregnancy complications, especially spontaneous preterm birth. Inconsistencies in results among studies are likely due to differences in sample sizes and cohort ethnicity. Ethnicity is a complicating factor because, although all bacterial taxa commonly inhabiting the vagina are present among all ethnicities, the frequencies of these taxa vary among ethnicities. Therefore, an in-depth characterization of the vaginal microbiota throughout pregnancy in the specific study population under investigation is required prior to evaluating associations between the vaginal microbiota and obstetrical disease. This initial investigation is a large longitudinal study of the vaginal microbiota throughout gestation resulting in a term delivery in a predominantly African-American cohort, a population that experiences disproportionally negative maternal-fetal health outcomes. It establishes the magnitude of associations between maternal characteristics, such as age, parity, body mass index, and self-reported Cannabis use, on the vaginal microbiota in pregnancy.

Romero R, Theis KR, Gomez-Lopez N, Winters AD, Panzer JJ, Lin H, Galaz J, Greenberg JM, Shaffer Z, Kracht DJ, Chaiworapongsa T, Jung E, Gotsch F, Ravel J, Peddada SD, Tarca AL. The Vaginal Microbiota of Pregnant Women Varies with Gestational Age, Maternal Age, and Parity. *Microbiol Spectr*. 2023 Aug 17;11(4):e0342922. doi: 10.1128/spectrum.03429-22. Epub 2023 Jul 24. PMID: 37486223; PMCID: PMC10434204.

Dietary methionine restriction impairs anti-tumor immunity through interacting with gut bacteria

Restriction of dietary methionine intake by about 80%, a dietary regimen that protects against aging and metabolic diseases, has been reported to repress cancer growth and improve cancer responses to anti-cancer therapies in mice with deficient immunity. However, how this dietary intervention impacts cancer progression in the context of the intact immune system with implications for anti-cancer immunotherapy is unknown. In this study, we demonstrate that while inhibiting cancer growth in immunocompromised mice, dietary methionine restriction reduces T cell activation, exacerbates tumor growth, and impairs tumor response to immunotherapy in immunocompetent mice. Mechanistically, dietary methionine restriction reduces gut microbial production of hydrogen sulfide, which is a sulfur-containing gas critical for immune cell survival and activation. Consistently, dietary supplementation of chemicals/nutrients that promote production of hydrogen sulfide, including methionine, stimulates anti-tumor immunity and suppresses tumor progression. Our study suggests that any possible anti-cancer benefits of MR require careful consideration of both the microbiota and the immune system.

Ji M, Xu X, Xu Q, Hsiao YC, Martin C, Ukraintseva S, Popov V, Arbeev KG, Randall TA, Wu X, Garcia-Peterson LM, Liu J, Xu X, Andrea Azcarate-Peril M, Wan Y, Yashin AI,

Anantharaman K, Lu K, Li JL, Shats I, Li X. Methionine restriction-induced sulfur deficiency impairs antitumour immunity partially through gut microbiota. *Nat Metab*. 2023 Aug 3. doi: 10.1038/s42255-023-00854-3. Epub ahead of print. PMID: 37537369.

Commentary: Joulia E, Metallo CM. Methionine and H2S alter cancer-immune dialogue. *Nat Metab*. 2023 Aug 3. doi: 10.1038/s42255-023-00862-3. Epub ahead of print. PMID: 37537368.

Associations of Pregnancy PFAS and Uterine Fibroids across Pregnancy
Fibroids (hormonally responsive benign tumors) often undergo volume changes in pregnancy. Because per- and polyfluoroalkyl substances (PFAS) disrupt hormonal signaling, they might affect fibroid growth. We assessed associations between PFAS and fibroid changes in pregnancy. Certain PFAS were associated with fibroid growth among women with small fibroids and decreases among women with medium fibroids. PFAS were not associated with fibroid prevalence or number; therefore, PFAS may influence prevalent fibroids rather than initiating fibroid development.

Mitro SD, Sundaram R, Buck Louis GM, Peddada S, Chen Z, Kannan K, Gleason JL, Zhang C, Grantz KL. Associations of Pregnancy Per- and Polyfluoroalkyl Substance Concentrations and Uterine Fibroid Changes across Pregnancy: NICHD Fetal Growth Studies - Singletons Cohort. *Environ Health Perspect*. 2023 May;131(5):57007. doi: 10.1289/EHP11606. Epub 2023 May 24. PMID: 37224071; PMCID: PMC10208432.

Amlodipine does not cause heart failure in patients
Dihydropyridines such as amlodipine are widely used as anti-hypertensive agents, being prescribed to ~70 million Americans. Dihydropyridines block voltage-gated Ca2+ channels in resistance vessels, leading to vasodilation and a reduction in blood pressure. The use of dihydropyridines has recently been called into question as these drugs appear to activate store-operated Ca2+ entry, trigger vascular remodeling, and increase heart failure, leading to the questioning of their clinical use. We show that amlodipine has marked intrinsic fluorescence which gives the erroneous impression of switching on Ca2+ entry. We find that concentrations of Ca2+ channel blockers that match therapeutic levels in serum of patients do not activate store-operated Ca2+ entry. A meta-analysis of published clinical trials and a prospective real-world analysis of patients both show that dihydropyridines are not associated with increased heart failure or other cardiovascular disorders. Removal of dihydropyridines for treatment of hypertension cannot therefore be recommended.

Bird GS, D'Agostin D, Alsanosi S, Lip S, Padmanabhan S, Parekh AB. A reappraisal of the effects of L-type Ca2+ channel blockers on store-operated Ca2+ entry and heart failure. *Function*. 2023 *in press*.

Drugs targeting purinergic receptors control COVID-like inflammation in mice
COVID-19 is associated with progressive accumulation of SARS-CoV-2-specific mRNA, which is recognized by innate immune receptors, such as TLR3. This leads to dysregulated production of multiple cytokines, including IL-6, IFN-γ, CXCL1, and TNF-α, which in turn causes acute lung injury. The current research revealed that the severity of pulmonary inflammation can be

improved by genetic deletion or pharmacologic modulation of a class of molecules known as purinergic receptors. These results suggest that pharmacologic modulation of select purinergic receptors might be therapeutically useful in treating COVID-19 and other types of pulmonary inflammation.

Whitehead GS, Karcz TP, Tosh DK, Jung YH, Wen Z, Campbell RG, Gopinatth V, Gao ZG, Jacobson KA, Cook DN. Effects of Purinergic Receptor Deletion or Pharmacologic Modulation on Pulmonary Inflammation in Mice. *ACS Pharmacol Transl Sci*. 2022 Oct 5;5(10):973-984. doi: 10.1021/acsptsci.2c00128. PMID: 36268115; PMCID: PMC9578140.

How cells achieve high accuracy of DNA replication

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

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.

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.

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.

Elucidating the role of GLIS3 in congenital hypothyroidism

Loss of function of the transcription factor GLIS3 causes congenital hypothyroidism. We demonstrated that GLIS3 does not play a major role in thyroid development but causes congenital hypothyroidism by repressing thyroid hormone biosynthesis. We demonstrated that GLIS3 regulates transcription of thyroid hormone biosynthetic genes in coordination with several other thyroid transcription factors, including PAX8, NKX2.1, and FOXE1. We further

showed that GLIS3 transcriptional activity is regulated by thyroid stimulating hormone through the activation of the protein kinase A pathway.

Kang HS, Grimm SA, Jothi R, Santisteban P, Jetten AM. GLIS3 regulates transcription of thyroid hormone biosynthetic genes in coordination with other thyroid transcription factors. *Cell Biosci*. 2023 Feb 15;13(1):32. doi: 10.1186/s13578-023-00979-8. PMID: 36793061; PMCID: PMC9930322.

Kang HS, Grimm SA, Jetten AM. Regulation of GLIS3 protein during thyroid gland development and gene expression in thyroid-specific Glis3KO mice. *Cell. Mol. Life Sci.* 2023; *In Press*.

Glucocorticoids: novel regulators of platelet production.
Steroid hormones called glucocorticoids facilitate platelet production via a novel mechanism, according to NIEHS researchers. Drs. Matias Grodzielski and John Cidlowski found that glucocorticoids stimulate the production of blood cells called platelets by directly regulating the expression of more than 1300 genes in megakaryocytes, the cells that make platelets. The study showed that the upregulation of a protein called guanine deaminase is largely responsible for glucocorticoid stimulation of platelet production. According to the authors, these findings demonstrate, for the first time, that megakaryocytes are a new target cell for glucocorticoids. Because these steroid hormones are one of the most widely prescribed medications worldwide for reducing inflammation and treating autoimmune disorders, the study could have an important clinical impact.

Grodzielski M, Cidlowski JA. Glucocorticoids regulate thrombopoiesis by remodeling the megakaryocyte transcriptome. *J Thromb Haemost*. 2023 Jun 17:S1538-7836(23)00496-8. doi: 10.1016/j.jtha.2023.06.012. Epub ahead of print. PMID: 37336437.

Why is peanut immunotherapy successful for some patients and not others?
Peanut immunotherapy to desensitize patients can increase the amount of peanut protein a patient can tolerate, but for most patients a continuous maintenance dosing will be required. For the lucky few that don't require maintenance dosing, what is different? Research by Lahood et al suggests that antibodies to specific regions of the peanut allergen Ara h 2 are required for sustained efficacy. This information may be useful in developing biomarkers of successful therapy, and developing hypoallergenic forms of Ara h 2.

LaHood NA, Min J, Keswani T, Richardson CM, Amoako K, Zhou J, Marini-Rapoport O, Bernard H, Hazebrouck S, Shreffler WG, Love JC, Pomes A, Pedersen LC, Mueller GA, Patil SU. Immunotherapy-induced neutralizing antibodies disrupt allergen binding and sustain allergen tolerance in peanut allergy. *J Clin Invest*. 2023 Jan 17;133(2):e164501. doi: 10.1172/JCI164501. PMID: 36647835; PMCID: PMC9843057.

Gene implicated in Alzheimer's disease regulated by a molecule called AANCR
A new study has revealed how the sequences and structures of RNAs regulate transcription and disease susceptibility, according to NIEHS researchers and their collaborators.RNA is modified by hundreds of chemical reactions and folds into innumerable shapes. However, the regulatory

role of RNA sequence and structure and how dysregulation leads to diseases remain largely unknown. To address this knowledge gap, the researchers focused on RNA abasic sites, which do not contain purine or pyrimidine bases, located on three-stranded nucleic acid structures called R-loops. The results revealed how RNA abasic sites in R-loops regulate the transcription of DNA into RNA by pausing a multiprotein complex called RNA polymerase II. In addition, the researchers discovered that a molecule called APOE-activating noncoding RNA (AANCR) regulates the transcription and expression of apolipoprotein E (*APOE*) — a gene implicated in Alzheimer's disease and found that DNA sequence variants in AANCR are associated with *APOE* expression and Alzheimer's disease. Future studies can assess how variation in AANCR and *APOE* interact to affect Alzheimer's disease, potentially paving the way for novel RNA-based therapeutics.

Watts JA, Grunseich C, Rodriguez Y, Liu Y, Li D, Burdick JT, Bruzel A, Crouch RJ, Mahley RW, Wilson SH, Cheung VG. A common transcriptional mechanism involving R-loop and RNA abasic site regulates an enhancer RNA of APOE. *Nucleic Acids Res*. 2022 Nov 28;50(21):12497-12514. doi: 10.1093/nar/gkac1107. PMID: 36453989; PMCID: PMC9757052.

Low perceptions of neighborhood connectedness and solidarity associated with obesity and type 2 diabetes among US adults

Using data from the nationally representative National Health Interview Survey, we investigated the relationships between perceived neighborhood social cohesion, defined as connectedness and solidarity between neighbors, and both obesity and type 2 diabetes. We also investigated whether relationships varied by age, sex, and race and ethnicity. Low social cohesion was associated with a higher prevalence of both obesity and type 2 diabetes. Further, associations with obesity were stronger among non-Hispanic White compared to Hispanic/Latino and Black adults, among women compared to men, and among adults aged 50 years and older compared to adults aged younger than 50 years. Associations between perceived neighborhood social cohesion varied also by age as well as race and ethnicity. Tailored neighborhood-level interventions that consider lived experiences across complex, intersectional identities related to belonging to multiple sociodemographic groups (e.g., older, minoritized women) may address cardiometabolic health disparities.

Alhasan DM, Gaston SA, Gullett L, Jackson WB 2nd, Stanford FC, Jackson CL. Neighborhood Social Cohesion and Obesity in the United States. *Endocr Metab Sci*. 2023 Jun 30;11:100129. doi: 10.1016/j.endmts.2023.100129. Epub 2023 Apr 27. PMID: 37396161; PMCID: PMC10310065.

Williams PC, Alhasan DM, Gaston SA, Henderson KL, Braxton Jackson W 2nd, Jackson CL. Perceived neighborhood social cohesion and type 2 diabetes mellitus by age, sex/gender, and race/ethnicity in the United States. *Prev Med*. 2023 May;170:107477. doi: 10.1016/j.ypmed.2023.107477. Epub 2023 Mar 12. PMID: 36918070; PMCID: PMC10106280.

Lack of access to sufficient, adequate food associated with poor sleep among US adults

Access to sufficient food of adequate quality will likely decrease, particularly among vulnerable populations, due to indicators of climate change, including, for instance, severe weather and

droughts that disrupt food production. Diet has been previously linked to sleep health. Therefore, we sought to investigate associations between food insecurity and sleep health among US adults, overall and by race and ethnicity, given marginalization among minoritized adults. Using National Health Interview Survey data, we found that very low versus high food security was associated with a higher prevalence of short sleep duration as well as sleep disturbances. Results differed by race and ethnicity and suggested stronger relative associations among Asian and non-Hispanic White participants compared to associations among non-Hispanic Black and Hispanic/Latino adults. Intervention and mitigation strategies addressing food access and quality may aid in improving sleep health among US adults.

Alhasan DM, Riley NM, Jackson II WB, Jackson CL. Food insecurity and sleep health by race/ethnicity in the United States. *J Nutr Sci*. 2023 May 18;12:e59. doi: 10.1017/jns.2023.18. PMID: 37252683; PMCID: PMC10214135.

Relationships between reported financial hardship during COVID-19 and higher sleep disturbances were strongest among women and minoritized racial and ethnic groups

Financial hardship can impact sleep by activating biological and psychological stress response pathways that can make it difficult to engage in adequate, uninterrupted sleep. Data suggest that the financial statuses of women and minoritized racial and ethnic groups were disproportionately negatively impacted by the COVID-19 pandemic compared to men and non-Hispanic White people. Both women and minoritized racial ethnic groups have displayed poorer sleep health compared to men and White people prior to the pandemic. However, few prior studies investigated financial hardship during the pandemic in relation to sleep health disparities. Further, few studies included multiethnic populations including American Indian/Alaska Native, Asian, Black/African American, Hispanic/Latino, multiracial, Native Hawaiian/Pacific Islander, and non-Hispanic White adults. Using data from the nationally representative, racially and ethnically diverse COVID-19's Unequal Racial Burden (CURB) survey, we found that prevalence of both financial hardship and sleep disturbances were higher among women compared to men and among certain minoritized racial and ethnic groups (e.g., Native Hawaiian/Pacific Islander) compared to non-Hispanic White adults. Financial hardship was associated with a higher prevalence of moderate to severe sleep disturbances. While these associations did not differ by gender, associations were strongest among Black/African American adults. Interventions supporting financial security across racial and ethnic groups in the US my address and reduce the likelihood of the exacerbation of previously observed sleep health disparities subsequent to the COVID-19 pandemic.

Gaston SA, Strassle PD, Alhasan DM, Pérez-Stable EJ, Nápoles AM, Jackson CL. Financial hardship, sleep disturbances, and their relationship among men and women in the United States during the COVID-19 pandemic. *Sleep Health*. 2023 Jun 4:S2352-7218(23)00086-4. doi: 10.1016/j.sleh.2023.04.007. Epub ahead of print. PMID: 37280141; PMCID: PMC10239652.

Studying effects of exposures on human fertility

Investigators at NIEHS have now developed a computationally-straightforward new approach to assessing effects of reproductive toxicants on human fertility.

Couples trying for a pregnancy vary considerably in their probability of conception, and methods based on the number of menstrual cycles required must account for that couple-to-couple biologic heterogeneity. The semi-parametric new approach enables estimation of the ratio of mean conception rates for exposed versus unexposed couples.

Shi M, Weinberg CR. Approaches for Assessing Effects of Exposures on Human Fertility. *Epidemiology*. 2023 Mar 1;34(2):230-237. doi: 10.1097/EDE.0000000000001575. Epub 2022 Dec 1. PMID: 36722805; PMCID: PMC9896569.

Black women are disproportionately exposed to indoor light at night: Implications for sleep health disparities

Exposure to light at night is a pervasive pollutant and known sleep disruptor. However, few studies previously investigated exposure to indoor light at night in relation to multiple dimensions of sleep among racially and ethnically diverse populations. Further, few studies assess the population attributable risk (PAR) by race and ethnicity, which provides information on the change in proportion of the population that would be affected by, in our work, poor sleep health dimensions if the exposure of light at night were removed from the entire population. The PAR provides information that can be used by public health practitioners to prioritize intervention strategies. Using data from the Sister Study, we found that both sleeping with light from the television and multiple poor sleep dimensions were most prevalent among non-Hispanic Black women compared to non-Hispanic White and Hispanic/Latina women. In the overall population, sleeping with light from the television versus no light was associated with a higher prevalence of multiple sleep dimensions, including short sleep duration. Further, the PARs were often higher among Black women compared to the remaining racial and ethnic groups, suggesting that interventions aimed at reducing indoor light at night may be most efficacious among Black women, implicating the importance of interventions aimed at reducing exposure to light at night for eliminating sleep health disparities.

Sweeney MR, Nichols HB, Jones RR, Olshan AF, Keil AP, Engel LS, James P, Sandler DP, White AJ, Jackson CL. Exposure to indoor light at night in relation to multiple dimensions of sleep health: Findings from the Sister Study. *Sleep*. 2023 Apr 5:zsad100. doi: 10.1093/sleep/zsad100. Epub ahead of print. PMID: 37018759.

All countries on the planet need to promote sleep health, which has an important role in climate change adaptation, mitigation, and resiliency

As we observe increasing evidence of climate change and aim to address its impacts, it is important to consider the human health consequences that may result from natural disasters and hazards as well as the psychological impacts related to the threat of climate change. Sleep health is especially important to consider since inadequate sleep is now a well-established risk factor for overall health and wellbeing. To emphasize this important point, we published two commentaries. We summarized the limited literature to date that suggests climate change may disrupt sleep health though several pathways such as, for instance, through temperature extremes negatively impacting quality as well as sleep disruption after experiencing natural disasters. We emphasize that additional research of climate change in relation to sleep is warranted, particularly among vulnerable populations, including children, individuals of lower socioeconomic status, and other groups experiencing marginalization. A health equity lens is

required since such groups will be disproportionately impacted by climate change, and it is important to assess cumulative exposures over the life course. Since climate change is a global problem, it will be important for all countries throughout the world to consider climate change as well as sleep health, in general, in public health agendas. Most countries – especially developing countries – do not adequately include sleep health in public health policy. We recommend several equitable strategies to accomplish this goal, such as sleep health education and awareness, standardization and centralization of global sleep-related data, and development of sleep health policy.

Lim DC, Najafi A, Afifi L, Bassetti CLA, Buysee DJ, Han F, Högl B, Melaku YA, Morin CM, Pack AI, Poyares D, Somers VK, Eastwood PR, Zee PC, Jackson CL on behalf of the World Sleep Society Global Sleep Health Task Force. The urgent need for all countries to promote sleep health. *Lancet Public Health* 2023; *In Press*.

Gaston SA, Singh R, Jackson CL. The need to study the role of sleep in climate change adaptation, mitigation, and resiliency strategies across the life course. *Sleep*. 2023 Jul 11;46(7):zsad070. doi: 10.1093/sleep/zsad070. PMID: 36913312; PMCID: PMC10334480.

Structural racism is a fundamental cause of racial/ethnic disparities in sleep health and access to sleep health care

Throughout the life course, racially and ethnically minoritized individuals generally have poorer sleep health (e.g., short sleep duration, poor sleep quality) compared to non-Hispanic White counterparts. Structural racism, which disadvantages minoritized groups by reinforcing economic, environmental, and social inequities, is a fundamental determinant of sleep health disparities. Therefore, in a commentary, we underscore the need to study racism as an upstream driver of observed sleep health disparities. By focusing on racism and its manifestations, research can go beyond the social construct of race to identify institutions and structures in which actionable interventions can be implemented. To advance sleep disparities research, we offer several recommendations, strategies, and best practices related to the measurement and interdisciplinary study of structural racism. Relatedly, in a separate commentary, we provide an illustrative example of how inequities related to structural racism, namely differential access to care, may promote sleep health disparities. Using data from the Health Resources & Services Administration (HRSA), we discuss the dire, low percentage of sleep medicine physicians in the HRSA grant, loan repayment, or scholarship program, each of which support the mission of providing equitable healthcare to under-resourced communities with the highest needs. Specifically, no sleep medicine specialists practice in Health Professional Shortage Areas or Medically Underserved Areas/Populations, and one specialist practices in a rural area. These data demonstrate a major disparity in access to care, illuminating the urgent need for the sleep field to address the lack of sleep medicine specialists in programs designed to address access to care gaps among underserved populations.

Johnson DA, Reiss B, Cheng P, Jackson CL. Understanding the role of structural racism in sleep disparities: a call to action and methodological considerations. *Sleep*. 2022 Oct 10;45(10):zsac200. doi: 10.1093/sleep/zsac200. PMID: 35999030; PMCID: PMC9548670.

Singh R, Juarez PD, Redline S, Jackson CL. Shortage of sleep medicine specialists in federally qualified health centers: an illustrative example of differential access to care. *J Clin Sleep Med*. 2023 Jun 14. doi: 10.5664/jcsm.10688. Epub ahead of print. PMID: 37312564.

Transcriptomic and Proteomic Pathways in Dermatomyositis

The myositis syndromes are rare systemic autoimmune diseases with characteristic muscle inflammation, weakness, photosensitive skin rashes, and significant morbidity. We examined transcript and protein expression data in the peripheral blood of active adult and juvenile dermatomyositis (DM) patients, and used a novel multi-enrichment analysis to examine gene expression and protein expression together, which enabled discovery of a number of novel activated pathways. A subset of interferon-stimulated genes was found, but broad upregulation of innate immune markers specific to neutrophil granules and neutrophil extracellular traps were up-regulated in both adult and juvenile dermatomyositis. in addition, several key intracellular signaling pathways were broadly upregulated in adult DM, including PI3K/AKT, ERK, and p38 MAP kinase signaling, and peripheral upstream and downstream components were differentially regulated in both adult and juvenile-onset DM. Up-regulated components shared by DM and JDM included cytokine:receptor pairs, several cell death components, and numerous glycolytic enzymes. Pathways unique to DM included aryl hydrocarbon receptor signaling, an environmental sensor pathway, as well as sirtuin signaling, protein ubiquitination, and granzyme B signaling. In this study, the combination of proteomics and transcript expression by multi-enrichment analysis broadened the identification of up- and down-regulated pathways among active adult and juvenile DM patients. These pathways, particularly those which include PI3K/AKT and MAP kinase signaling and neutrophil degranulation, may be potential therapeutic targets.

Ward J, Ambatipudi M, O'Hanlon TP, Smith MA, de Los Reyes M, Schiffenbauer A, Rahman S, Zerrouki K, Miller FW, Sanjuan MA, Li JL, Casey KA, Rider LG. Shared and Distinctive Transcriptomic and Proteomic Pathways in Adult and Juvenile Dermatomyositis. *Arthritis Rheumatol*. 2023 May 25. doi: 10.1002/art.42615. Online ahead of print. PMID: 37229703

New Response Criteria for Clinical Trials Developed for Juvenile and Adult Dermatomyositis and Polymyositis

The ACR-EULAR myositis response criteria were developed as a composite measure using absolute percentage change in six core set measures. We aimed to further validate the response criteria by assessing the contribution of each core set measure, frequency of strength versus extramuscular activity improvement, representation of patient-reported outcome measures, and frequency of core set measure worsening. In two reports, we have now validated these criteria in adult dermatomyositis and polymyositis and juvenile dermatomyositis, using data from several large natural history studies and therapeutic trials. In both adult and juvenile myositis studies, the number of improving core set measures and absolute percentage change in all core set measures increased by improvement level. Of patients with at least minimal improvement, almost all patients had improvement in muscle-related measures and 84 - 95% had improvement in patient-reported outcome measures. Patients with minimal improvement had worsening in a

median of 0- 1 core set measure, and most patients with moderate-major improvement had no worsening core set measures. Physician assessment of change generally agreed with myositis response criteria improvement categories. The ACR-EULAR myositis response criteria perform consistently across multiple studies, further supporting its use as an efficacy end point in future myositis therapeutic trials.

Saygin D, Kim H, Douglas C, Erman B, Wilkerson J, McGrath JA, Oddis CV, Lundberg IE, Amato AA, García-De La Torre I, Chinoy H, Fiorentino D, Chung L, Song YW, Miller FW, Ruperto N, Vencovsky J, Aggarwal R, Rider LG; International Myositis Assessment and Clinical Studies Group (IMACS). Performance of the 2016 ACR-EULAR myositis response criteria in adult dermatomyositis/polymyositis therapeutic trials and consensus profiles. *Rheumatology* (Oxford). 2023 Mar 17:kead110. doi: 10.1093/rheumatology/kead110. Online ahead of print. PMID: 36929923

Kim H, Saygin D, Douglas C, Wilkerson J, Erman B, Pistorio A, McGrath JA, Reed AM, Oddis CV, Bracaglia C, van Royen-Kerkhof A, Bica B, Dolezalova P, Ferriani VPL, Flato B, Bernard-Medina AG, Herlin T, Miller FW, Vencovsky J, Ruperto N, Aggarwal R, Rider LG; International Myositis Assessment and Clinical Studies Group (IMACS) and Paediatric Rheumatology INternational Trials Organization (PRINTO). Performance of the 2016 ACR-EULAR myositis response criteria in juvenile dermatomyositis therapeutic trials and consensus profiles. *Rheumatology* (Oxford). 2023 Mar 17:kead111. doi: 10.1093/rheumatology/kead111. Epub ahead of print. PMID: 36929918.

A small epoxide causes mutations in humans through lifetime

Mutagens often prefer oligonucleotide motifs that can be revealed by studying the hypermutation spectra. This work revealed a mutational motif caused by glycidamide - a simple epoxide formed endogenously in humans from the environmental toxicant acrylamide. This mutational motif is ubiquitous in human cancers and in non-cancerous somatic cells. Mutation load with this motif strongly correlated with age of individuals. The data suggest that this mutational motif reflects mutagenic lesions from a potentially broad range of endogenous and exogenous agents.

Hudson KM, Klimczak LJ, Sterling JF, Burkholder AB, Kazanov MD, Saini N, Mieczkowki PA, Gordenin, DA Glycidamide-induced hypermutation in yeast single-stranded DNA reveals a ubiquitous clock-like mutational motif in humans. *Nucleic Acids Res*. 2023. Epub 20230720. doi: 10.1093/nar/gkad611, PubMed PMID: 37471042.

The three RNA recognition domains of Glorund are functionally interchangeable in control of nanos mRNA translation

The RNA regulatory protein Glorund regulates the translation of the nanos mRNA in Drosophila melanogaster eggs and embryo. This regulation is critical for proper embryonic development. Glorund contains three RNA-binding domains that can recognize two different RNA features: a short stretch of guanine nucleotides or a stem-loop that is rich in uracil and adenosine base pairs. Both of these RNA features are found in nanos RNA. Studies with purified proteins and RNA or in Drosophila showed that any two of the RNA-binding domains can combine to recognize nanos RNA and control its translation.

Warden MS, DeRose EF, Tamayo JV, Mueller GA, Gavis ER, Hall TMT. The translational repressor Glorund uses interchangeable RNA recognition domains to recognize Drosophila nanos. *Nucleic Acids Res*. 2023 Jul 10:gkad586. doi: 10.1093/nar/gkad586. Epub ahead of print. PMID: 37427795.

Machine learning methods and complex survey data

Despite the prominent use of complex survey data and the growing popularity of machine learning methods in epidemiologic research, few machine learning software implementations offer options for handling complex samples. A major challenge impeding the broader incorporation of machine learning into epidemiologic research is incomplete guidance for analyzing complex survey data, including the importance of sampling weights for valid prediction in target populations. Using data from 15,820 participants in the 1988-1994 National Health and Nutrition Examination Survey cohort, we determined whether ignoring weights in gradient boosting models of all-cause mortality affected prediction. In simulations, we additionally assessed the impact of sample size, weight variability, predictor strength, and model dimensionality. We found that failing to account for sampling weights may limit generalizability for data from complex surveys, dependent on sample size and other analytic properties. In the absence of software for configuring weighted algorithms, post-hoc re-calculations of unweighted model performance using weighted observed outcomes may more accurately reflect model prediction in target populations than ignoring weights entirely.

MacNell N, Feinstein L, Wilkerson J, Salo PM, Molsberry SA, Fessler MB, Thorne PS, Motsinger-Reif AA, Zeldin DC. Implementing machine learning methods with complex survey data: Lessons learned on the impacts of accounting sampling weights in gradient boosting. *PLoS One*. 2023 Jan 13;18(1):e0280387. doi: 10.1371/journal.pone.0280387. PMID: 36638125; PMCID: PMC9838837.

Disruption of Ephx2 in cardiomyocytes improves functional recovery after ischemia-reperfusion

Cytochromes P450 metabolize arachidonic acid to epoxyeicosatrienoic acids (EETs) which have numerous effects. After cardiac ischemia, EET-induced coronary vasodilation increases delivery of oxygen/nutrients to the myocardium, and EET-induced signaling protects cardiomyocytes against postischemic mitochondrial damage. Soluble epoxide hydrolase 2 (EPHX2) diminishes the benefits of EETs through hydrolysis to less active dihydroxyeicosatrienoic acids. EPHX2 inhibition or genetic disruption improves recovery of cardiac function after ischemia. Immunohistochemical staining revealed EPHX2 expression in cardiomyocytes and some endothelial cells but little expression in cardiac smooth muscle cells or fibroblasts. To determine specific roles of EPHX2 in cardiac cell types, we generated mice with cell-specific disruption of Ephx2 in endothelial cells ($Ephx2^{fx/fx}$/Tek-cre) or cardiomyocytes ($Ephx2^{fx/fx}$/Myh6-cre) to compare to global Ephx2-deficient mice (global $Ephx2^{-/-}$) and WT ($Ephx2^{fx/fx}$) mice in expression, EET hydrolase activity, and heart function studies. Most cardiac EPHX2 expression and activity is in cardiomyocytes with substantially less activity in endothelial cells. $Ephx2^{fx/fx}$/Tek-cre hearts have similar EPHX2 expression, hydrolase activity, and postischemic cardiac function as control $Ephx2^{fx/fx}$ hearts. However, $Ephx2^{fx/fx}$/Myh6-cre hearts were similar to global $Ephx2^{-/-}$ hearts with significantly diminished EPHX2 expression, decreased hydrolase activity, and enhanced postischemic cardiac function compared to $Ephx2^{fx/fx}$ hearts. During

reperfusion, Ephx2$^{fx/fx}$/Myh6-cre hearts displayed increased ERK activation compared to Ephx2$^{fx/fx}$ hearts, which could be reversed by EEZE treatment. EPHX2 did not regulate coronary vasodilation in this model. We conclude that EPHX2 is primarily expressed in cardiomyocytes where it regulates EET hydrolysis and postischemic cardiac function, whereas endothelial EPHX2 does not play a significant role in these processes.

Edin ML, Gruzdev A, Bradbury JA, Graves JP, Lih FB, DeGraff LM, Fleming I, Zeldin DC. Disruption of Ephx2 in cardiomyocytes but not endothelial cells improves functional recovery after ischemia-reperfusion in isolated mouse hearts. *J Biol Chem*. 2023 Apr;299(4):103049. doi: 10.1016/j.jbc.2023.103049. Epub 2023 Feb 22. PMID: 36822325; PMCID: PMC10040734.

CYP eicosanoid pathway mediates colon cancer-promoting effects of dietary linoleic acid
Human and animal studies support that consuming a high level of linoleic acid (LA), an essential fatty acid and key component of the human diet, increases the risk of colon cancer. However, results from human studies have been inconsistent, making it challenging to establish dietary recommendations for optimal LA intake. Given the importance of LA in the human diet, it is crucial to better understand the molecular mechanisms underlying its potential colon cancer-promoting effects. Using LC-MS/MS-based targeted lipidomics, we found that the cytochrome P450 (CYP) monooxygenase pathway is a major pathway for LA metabolism in vivo. Furthermore, CYP monooxygenase is required for the colon cancer-promoting effects of LA, since the LA-rich diet fails to exacerbate colon cancer in CYP monooxygenase-deficient mice. Finally, CYP monooxygenase mediates the pro-cancer effects of LA by converting LA to epoxy octadecenoic acids (EpOMEs), which have potent effects on promoting colon tumorigenesis via gut microbiota-dependent mechanisms. Overall, these results support that CYP monooxygenase-mediated conversion of LA to EpOMEs plays a crucial role in the health effects of LA, establishing a unique mechanistic link between dietary fatty acid intake and cancer risk. These results could help in developing more effective dietary guidelines for optimal LA intake and identifying subpopulations that may be especially vulnerable to LA's negative effects.

Zhang J, Yang J, Duval C, Edin ML, Williams A, Lei L, Tu M, Pourmand E, Song R, Graves JP, DeGraff LM, Wong JJ, Wang Y, Sun Q, Sanidad KZ, Wong S, Han Y, Zhang Z, Lee KSS, Park Y, Xiao H, Liu Z, Decker EA, Cui W, Zeldin DC, Zhang G. CYP eicosanoid pathway mediates colon cancer-promoting effects of dietary linoleic acid. FASEB J. 2023 Jul;37(7):e23009. doi: 10.1096/fj.202300786R. PMID: 37273180; PMCID: PMC10283155. (Co-Corresponding Author).

DUX4 toxicity leads to congenital absence of the nose
Arhinia is a severe congenital malformation characterized by an absent nose. It is caused by mutations in the gene *SMCHD1*. In the current studies, Inoue et al. demonstrate that when the *SMCHD1* gene doesn't function properly, a toxin called DUX4 is produced by the precursors of the nose, leading to cell death.

Inoue K, Bostan H, Browne MR, Bevis OF, Bortner CD, Moore SA, Stence AA, Martin NP, Chen SH, Burkholder AB, Li JL, Shaw ND. DUX4 double whammy: The transcription factor that causes a rare muscular dystrophy also kills the precursors of the human nose.

Sci Adv. 2023 Feb 17;9(7):eabq7744. doi: 10.1126/sciadv.abq7744. Epub 2023 Feb 17. PMID: 36800423; PMCID: PMC9937577.

Mutational motif of redox stress are heterogenous and some of them are found in human cancer genomes

We found that the mutational signatures of redox stress are heterogeneous and mirror metabolic changes caused by different types of redox stress agents. We were able to identify some of the mutational motifs of redox stress in human cancer genomes. One of the unexpected, counterintuitive observations was that an oxidative chemical used in the baking industry, potassium bromate, is activated by several thiol-containing antioxidants. Some of them (glutathione and N-acetylcysteine) are used as dietary supplements.

Degtyareva NP, Placentra VC, Gabel SA, Klimczak LJ, Gordenin DA, Wagner BA, Buettner GR, Mueller GA, Smirnova TI, Doetsch PW. Changes in metabolic landscapes shape divergent but distinct mutational signatures and cytotoxic consequences of redox stress. *Nucleic Acids Res*. 2023 Jun 9;51(10):5056-5072. doi: 10.1093/nar/gkad305. PMID: 37078607; PMCID: PMC10250236.

Computer-based reanalysis of published studies of COVID-19 pneumonia reveals new insights into how SARS-CoV-2 damages the deep airspaces of the lung

Over the past few years, researchers have sequenced the RNA in cells washed out from the lungs of COVID-19 patients in order to learn which genes are turned on by SARS-CoV-2 in the human lung; however, insights have been greatly limited due to the small numbers of patients in individual studies. Scientists at NIEHS accessed raw data from several such published single-cell RNA-sequencing reports from COVID-19 pneumonia and used computer-based methods to harmonize and pool the data across these studies to expand the overall dataset and enrich for novel insights. Of interest, this meta-analysis provided evidence that the flat, gas-exchanging cells of the deep airspaces (alveolar epithelial type I cells) may undergo changes during COVID-19 pneumonia similar to those that occur in the outermost layers of skin when it undergoes toughening, so called ‘cornification’. These findings suggest new ways in which the SARS-CoV-2 may damage the lung, and new potential avenues for the development of therapeutics.

Karmaus PWF, Tata A, Meacham JM, Day F, Thrower D, Tata PR, Fessler MB. Meta-Analysis of COVID-19 Bronchoalveolar Lavage scRNA-Seq Reveals Alveolar Epithelial Transitions and Unique Alveolar Epithelial Cell Fates. *Am J Respir Cell Mol Biol*. 2023 Jul 31. doi: 10.1165/rcmb.2023-0077OC. Epub ahead of print. PMID: 37523502.

Higher air pollution associated with an increased risk of breast cancer

In one of the largest studies to date looking at the relationship between air pollution and breast cancer risk, researchers found that women living in areas with higher fine particulate matter ($PM_{2.5}$) levels had a higher risk of going on to develop breast cancer. The researchers found an 8% increase in breast cancer risk for a 10 microgram per cubic meter (10 μg/m3) increase in particulate matter concentrations 10-15 years before enrolling in a large national study. In particular, $PM_{2.5}$ was associated with estrogen receptor-positive tumors, which are the most commonly diagnosed breast cancers in the U.S.

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*. 2023. *In press.*

Host Enzymes TUT4/7 Identified as Key Regulators in Coronavirus RNA Decay and Replication Inhibition

Our recent research has unveiled a cellular mechanism employed against coronaviruses, specifically the mouse hepatitis virus. Within the host cells, enzymes termed TUT4/7 have been identified to uridylate the virus's RNA. This uridylation acts as a marker, earmarking the viral RNA for subsequent degradation, thereby curtailing the virus's replication capabilities. Experimental depletion of TUT4/7 activity led to increased viral replication, underscoring the critical role of these enzymes in viral RNA regulation. Such findings offer valuable insights with potential ramifications for therapeutic interventions against related viruses.

Gupta A, Li Y, Chen SH, Papas BN, Martin NP, Morgan M. TUT4/7-mediated uridylation of a coronavirus subgenomic RNAs delays viral replication. *Commun Biol*. 2023 Apr 21;6(1):438. doi: 10.1038/s42003-023-04814-1. PMID: 37085578; PMCID: PMC10119532.

Researchers at the NIEHS in collaboration with NC State define a novel structure and role of the mitochondrial DNA polymerase accessory subunit

Intramural researchers from the Copeland and Williams group in the Genome Integrity and Structural Biology Laboratory at the NIEHS in collaboration with NC State investigators solved the three dimensional structure of the human mitochondrial DNA polymerase accessory subunit, called POLG2, when bound to DNA. The structure identifies a novel binding mode that is independent of its normal function in mitochondrial DNA replication. Using X-ray crystallography, atomic force microscopy and biochemistry, the researchers identify a novel timer of dimer protein structure with DNA and define the specific DNA binding motifs in the protein subunit. This unique binding suggests a novel role in binding and maintaining the D-loop in the human mitochondrial genome and paves the way for further research in the regulation of DNA replication of mitochondrial DNA.

Wojtaszek JL, Hoff KE, Longley MJ, Kaur P, Andres SN, Wang H, Williams RS, Copeland WC. Structure-specific roles for PolG2-DNA complexes in maintenance and replication of mitochondrial DNA. *Nucleic Acids Res*. 2023 Aug 18:gkad679. doi: 10.1093/nar/gkad679. Epub ahead of print. PMID: 37592734.

Protection against COVID19 can be predicted by antibody levels

In a year-long observational study of 629 subjects, 82% of breakthrough infections in vaccinees occurred when their anti-spike antibody titers were below 3,000 AU/mL. Our findings suggest that there may be an antibody threshold associated with breakthrough infections and that this threshold could possibly be used to aid decision-making regarding booster vaccinations. In addition, the use of anti-nucleocapsid antibody titers significantly underestimated the prevalence of breakthrough infections in vaccinated individuals, because they did not mount an anti-nucleocapsid antibody response.

McGee C, Shi M, House J, Drude A, Gonzalez G, Martin N, Chen SH, Rogers H, Njunge A, Hodge X, Mosley B, George M, Agrawal R, Wild C, Smith C, Brown A, Barber L, Garantziotis S. Longitudinal Serological Surveillance for COVID-19 Antibodies after Infection and Vaccination. *Microbiol Spectr*. 2022 Oct 26;10(5):e0202622. doi: 10.1128/spectrum.02026-22. Epub 2022 Sep 19. PMID: 36121258; PMCID: PMC9603261.

Too much calcium at fertilization impairs offspring growth

At fertilization, sperm-induced oscillations in egg calcium levels initiate embryo development. Using a mouse model, we found that when eggs are exposed to prolonged elevation in calcium at fertilization, the offspring have abnormal growth trajectories. These findings provide guidance for appropriate design of culture media and laboratory procedures used during human assisted reproduction.

Savy V, Stein P, Shi M, Williams CJ. PMCA1 depletion in mouse eggs amplifies calcium signaling and impacts offspring growth. *Biol Reprod*. 2022 Dec; 107(6): 1439-1451. doi: 10.1093/biolre/ioac180. PMID: 36130203. PMCID: PMC10144700.

ESCBL scientists establish new method for genome-wide assessment of DNA methylation

This paper describes use of a new tool, a commercial bead-chip array, for assessing DNA methylation levels in mice. ESCBL scientists compared this technology to the gold standard in the field, whole-genome bisulfite sequencing, finding that the bead chip technology faithfully recapitulates the more expensive and cumbersome methodology. The validation of this technology provides researchers with a new, rapid, low cost, highly validated tool for DNA methylation measurements in mice.

Martin EM, Grimm SA, Xu Z, Taylor JA, Wade PA. Beadchip technology to detect DNA methylation in mouse faithfully recapitulates whole-genome bisulfite sequencing. *Epigenomics*. 2023 Feb;15(3):115-129. doi: 10.2217/epi-2023-0034. Epub 2023 Apr 5. PMID: 37020391; PMCID: PMC10131490.

Gene Expression Responses to Pentabrominated Diphenyl Ether Across Rat Life Cycle Stages are Associated with Carcinogenesis

Pentabrominated Diphenyl Ether (PBDE) is a known rat chemical carcinogen. This study integrated recently published PBDE transcriptomics data to examine and compare how PBDE exposure affected rats at different lifetime stages in the rat, including neonate, young, and adult animals. Here, gene expression changes in response to PBDE upregulated liver transcriptomic changes at all three life stages. These changes included the induction of transcripts involved in cancer, metabolic, membrane function, and Nrf2 antioxidant pathways, a signal which is characteristic of chemical carcinogens. This study illustrates the utility of performing a combined analysis of previously published data from separate studies and suggests the possibility that a similar transcriptomic assessment might be useful for providing toxic and chemical hazard information for other chemicals.

Shockley KR, Dunnick JK. Gene expression profiling after exposure to a chemical carcinogen, Pentabrominated Diphenyl Ether, at different life stages. *Front Toxicol*. 2023

Jan 4;4:1028309. doi: 10.3389/ftox.2022.1028309. PMID: 36687508; PMCID: PMC9847571.

Statistical Tests to Account for Sibling Correlation in Fetal Defect Data
Laboratory animal studies to investigate differences in fetal defect incidence upon chemical exposure often involve treatment groups containing multiple pups from the same litter which can lead to correlated responses among siblings. However, increased false positive rates can result if the statistical approaches do not account for these correlated responses. This project used simulation studies to evaluate the performance of various statistical methods to analyze fetal defect data and compared the results from these methods after analysis of a common and a rare defect from two prenatal developmental toxicology studies. This work introduces a modification to the Rao-Scott Cochran-Armitage test which compares favorably with other litter-based statistical methods and is robust across background defect rates (included zero or near-zero incidence rates in control groups) and litter size distributions.

Harris SF, McBride SJ, Smith MV, Cunny HC, Shockley KR. Analysis of incidence data in developmental toxicity studies: Statistical tests to account for litter effects in fetal defect data. Birth Defects Res. 2023 Feb 1;115(3):327-337. doi: 10.1002/bdr2.2120. Epub 2022 Nov 8. PMID: 36345811; PMCID: PMC9898081.

DNASE1L3 enhances antitumor immunity and suppresses tumor progression
DNASE1L3 is a DNA hydrolyzing enzyme highly expressed in dendritic cells, a type of professional antigen-presenting immune cells. It is functionally important for regulating autoimmune responses to self-DNA and chromatin, as deficiency of DNASE1L3 leads to development of autoimmune diseases in both humans and mice. In collaboration with Dr. Leping Li, we recently identified DNASE1L3 as a new regulator of anti-tumor immunity and a tumor suppressor in colon cancer. In humans, DNASE1L3 is reduced in tumor-infiltrating dendritic cells, and this reduction is associated with poor patient survival and reduced tumor immune cell infiltration in many cancer types. In mice, Dnase1l3 deficiency in the tumor microenvironment enhances tumor formation and growth in several colon cancer models. Notably, the increased tumor formation and growth in Dnase1l3-deficient mice are associated with impaired anti-tumor immunity. Collectively, our study unveils a previously unknown link between DNASE1L3 and anti-tumor immunity, and further suggests that restoration of DNASE1L3 activity may represent a potential therapeutic approach for anti-cancer therapy.

Li W, Nakano H, Fan W, Li Y, Sil P, Nakano K, Zhao F, Karmaus PW, Grimm SA, Shi M, Xu X, Mizuta R, Kitamura D, Wan Y, Fessler MB, Cook DN, Shats I, Li X, Li L. DNASE1L3 enhances antitumor immunity and suppresses tumor progression in colon cancer. *JCI Insight*. 2023 Aug 15:e168161. doi: 10.1172/jci.insight.168161. Epub ahead of print. PMID: 37581941.

Brain connections get depressed too! How synapses weaken in a one part of the brain
Neurons in the mouse hippocampal area CA2, which have recently been implicated in social behavior, are now known for their lack of synaptic plasticity. In this study, however, researchers discovered that in fact these connections between neurons can be changed, just that the plasticity

involves the weakening of the synapses, not strengthening. Using electrophysiology in mouse brain slices, they found that activation of a certain type of glutamate receptor led to a robust synaptic depression of the synaptic responses, an effect that relied on other molecules that are highly enriched in CA2. Scientists hope to eventually determine whether this feature of CA2 synapses is what makes it so important for social cognition.

Samadi M, Hales CA, Lustberg DJ, Farris S, Ross MR, Zhao M, Hepler JR, Harbin NH, Robinson ESJ, Banks PJ, Bashir ZI, Dudek SM. Mechanisms of mGluR-dependent plasticity in hippocampal area CA2. *Hippocampus*. 2023 Jun;33(6):730-744. doi: 10.1002/hipo.23529. Epub 2023 Mar 27. PMID: 36971428; PMCID: PMC10213158.

Methods for genetic and epidemiological studies and research investigating molecular and environmental factors for human diseases

We developed machine-learning methods for studying gene-gene and gene-environment interactions using genetic data from a case and his/her parents, performed simulation studies to assess the beta-geometric statistical models in time-to-pregnancy studies, and designed a method that can be used in pooled sample analysis for a popular epidemiological study design. The collaborative research elucidated environmental factors and molecular mechanisms for an array of human diseases.

Ajayi T, Rai P, Shi M, Gabor KA, Karmaus PWF, Meacham JM, Katen K, Madenspacher JH, Schurman SH, Fessler MB. Race-specific association of an IRGM risk allele with cytokine expression in human subjects. *Sci Rep*. 2023 Aug 9;13(1):12911. doi: 10.1038/s41598-023-40313-3. PMID: 37558924; PMCID: PMC10412543.

Hurson AN, Pal Choudhury P, Gao C, Hüsing A, Eriksson M, Shi M, Jones ME, Evans DGR, Milne RL, Gaudet MM, Vachon CM, Chasman DI, Easton DF, Schmidt MK, Kraft P, Garcia-Closas M, Chatterjee N; B-CAST Risk Modelling Group. Prospective evaluation of a breast-cancer risk model integrating classical risk factors and polygenic risk in 15 cohorts from six countries. *Int J Epidemiol*. 2022 Jan 6;50(6):1897-1911. doi: 10.1093/ije/dyab036. Epub 2021 Mar 23. PMID: 34999890; PMCID: PMC8743128.

Kana MA, Shi M, Ahmed J, Ibrahim JM, Ashir AY, Abdullahi K, Bello-Manga H, Taingson M, Mohammed-Durosinlorun A, Shuaibu M, Tabari AM, London SJ. Biomass fuel use and birth weight among term births in Nigeria. *PLOS Glob Public Health*. 2022 Jun 10;2(6):e0000419. doi: 10.1371/journal.pgph.0000419. PMID: 36962417; PMCID: PMC10022098.

Li L, Umbach DM, Li Y, Halani P, Shi M, Ahn M, Yeung DSC, Vaughn B, Fan ZJ. Sleep apnoea and hypoventilation in patients with five major types of muscular dystrophy. *BMJ Open Respir Res*. 2023 Apr;10(1):e001506. doi: 10.1136/bmjresp-2022-001506. PMID: 37072321; PMCID: PMC10124300.