Division of Intramural Research

NAEHS Council Update

September 2018

DIR RECRUITMENTS

Chief of the Immunity, Inflammation and Disease Laboratory
The National Institute of Environmental Health Sciences (NIEHS) is recruiting outstanding candidates to serve as Chief of the Immunity, Inflammation and Disease Laboratory (IIDL) within the Division of Intramural Research. The ideal candidate will be tenure-eligible based on an outstanding academic record of achievement, leadership capabilities, and broad interests in immunology, inflammation, and disease biology. In addition to directing his/her own independent research program, the Chief will have responsibility for leading IIDL in new directions as research in environmental health science continually evolves. Applicants should have a Ph.D., M.D., or equivalent doctoral degree in a related field, and a strong interest in immunology, inflammation, and disease biology. Dr. Franceso DeMayo, Chief of the Reproductive and Developmental Biology Laboratory serves as Chair of the Search Committee.

Tenure-Track Investigator in Neurobiology
The National Institute of Environmental Health Sciences (NIEHS) is seeking an exceptional individual as a Tenure-Track Investigator in the Neurobiology Laboratory within the Division of Intramural Research. The successful candidate is expected to lead an innovative, independent research program and will have a strong record of accomplishments in the field of neuroscience. Preference will be given to candidates who utilize innovative methodological approaches to investigate basic mechanisms underlying neuroinflammation and neurodegeneration. 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. Emphasis will be on identifying an exceptional scientist with an innovative and productive research program. Dr. Michael Fessler, Acting Chief of the Immunity, Inflammation and Disease Laboratory serves as Chair of the Search Committee.

NEW HIRES

Chief of the Biostatistics and Computational Biology Branch
Dr. Alison Motsinger-Reif has accepted an offer to become the Chief of the Biostatistics and Computational Biology Branch (BCBB) in DIR. She is coming from North Carolina State University where she is a Full Professor in the Department of Statistics and Director of the Bioinformatics Consulting and Service Core and the Statistical Consulting Core within the Bioinformatics Research Center. At NIEHS Dr. Motsinger-Reif will focus on development of statistical and bioinformatics methods and applying these to interesting environmental health problems with specific focus on developing methods for gene-gene interactions, dose response modeling, pharmacogenomics and toxicogenomics applications, and methods development for quantifying response to chemical mixtures. Dr. Motsinger-Reif is expected to start in December 2018.

New Tenure-Track Investigators
Dr. Joseph Rodriguez started as a Tenure Track Investigator in the Epigenetic and Stem Cell Biology Laboratory and member of the NIH Distinguished Scholars Program in July 2018. He was previously a Postdoctoral Fellow in the Laboratory of Receptor Biology and Gene Expression at NCI. Dr. Rodriguez will initiate an independent research program at NIEHS focused on developing biophysical methods to study dynamic action of Estrogen Receptors and other transcription factors in living cells.

Dr. Anne Marie Jukic started as a Tenure Track Investigator in the Epidemiology Branch in July 2018. Dr. Jukic was an Assistant Professor at the Yale School of Public Health for the since 2015. Her research focuses on early pregnancy – conception, implantation and early placentation with an interest in both the exposures that can influence these poorly understood biological events and how these events are related to pregnancy outcomes.

Dr. Alexandra White has accepted a position as an Earl Stadtman Tenure Track Investigator in the Epidemiology Branch. Dr. White is currently a postdoctoral intramural research training award (IRTA) fellow in the Epidemiology Branch. Dr. White's overall research objective aims to identify environment and lifestyle risk factors for cancer and to elucidate underlying biologic mechanisms. She is interested in achieving a better understanding of the health impact associated with complex exposure mixtures. Dr. White's current research is focused on toxic metals and air pollution exposure in relation to breast density and breast cancer risk. She is expected to start in Winter 2020.

Dr. Marcos Morgan from the MRC Centre for Regenerative Medicine, University of Edinburgh, UK, and the European Bioinformatics Institute, has accepted a position to join the Reproductive and Developmental Biology Laboratory as an Earl Stadtman Tenure Track Investigator. Dr. Morgan will initiate a research program at NIEHS focused on the role of RNA modifications such as uridylation and cytidylation in regulating male fertility. He is expected to start in Summer 2019.

SCIENTIFIC UPDATE BY A DIR PRINCIPAL INVESTIGATOR

EXPANDING THE TOOLSET OF STRUCTURAL BIOLOGY WITH MOLECULAR MICROSCOPY

MARIO JUAN BORGNIA, PH.D.
CRYO-ELECTRON MICROSCOPY CORE
GENOME INTEGRITY AND STRUCTURAL BIOLOGY LABORATORY
DIR, NIEHS

Cryo-electron microscopy (cryo-EM) is rapidly becoming a necessity in structural biology on par with x-ray diffraction methods (x-ray) and nuclear magnetic resonance (NMR). Several publications have unequivocally established the capabilities of this technique in determining the structure of macromolecules at atomic resolution. Cryo-EM requires smaller quantities of material than other structural methods and is especially suitable for the study of hard-to-crystallize large macromolecular complexes and membrane proteins. The success of this technique has spurred a wave of interest and many structural biology groups are incorporating it into their repertoire. In addition, there is emerging interest in the application of cryo-EM technologies to perform ultrastructural analysis of cellular compartments. This rapid increase in demand for a limited number of sites endowed with appropriate/expensive equipment and expertise is creating a significant constraint.

The Research Triangle Park area is home to a strong community of structural biologists who routinely use x-ray and NMR to solve the structures of macromolecules of biomedical interest. However, by 2016 only a dozen publications by local research groups used cryo-EM and the part of these studies involving microscopy was in all cases performed in collaboration non-regional groups. For these reasons Duke, NIEHS and UNC are collaborating in the formation of the Molecular Microscopy Consortium (MMC). The mission of the consortium is to enable the use of single particle cryo-EM and other tools in molecular microscopy by research groups at partner institutions. NIEHS led this effort by establishing the first of three facilities, managed by a single team to provide a collaborative environment for the training of structural biologists. The Cryo-EM Core at NIEHS was established in June 2017 and in the first year of operation the MMC has initiated more than two dozen projects and trained collaborators in the involved process of specimen optimization and data processing. To date, ten macromolecular complexes have been solved at the MMC at high resolution (3-5 Å). Three manuscripts based on these data are submitted or in preparation, while at least another three are expected to be submitted to high quality peer-reviewed journals before the end of 2018.

TRAINING AND MENTORING

The 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 received a $1500 travel award to attend a meeting in the United States at which they presented their abstract, either as a poster or a platform presentation. 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 success rate among all ICs and the total number of NIEHS awards was fourth behind much larger intramural research programs.

The NIEHS Division of Intramural Research had 18 FARE award winners:

FARE Awardee	Mentor	Laboratory/Branch
Jonathan T. Busada, Ph.D.	John Cidlowski, Ph.D.	Signal Transduction Laboratory
Helen B. Chin, Ph.D.	Donna Baird, Ph.D.	Biostatistics & Computational Biology Branch
Joanne C. Damborsky, Ph.D.	Jerrel Yakel, Ph.D.	Neurobiology Laboratory
Yi Fang, Ph.D.	Xiaoling Li, Ph.D.	Signal Transduction Laboratory
Chunfang Gu, Ph.D.	Stephen Shears, Ph.D.	Signal Transduction Laboratory
Hao Hu, Ph.D.	Masahiko Negishi, Ph.D.	Reproductive and Developmental Biology Laboratory
Kai Kang, Ph.D.	Leping Li, Ph.D.	Biostatistics and Computational Biology Branch
Lee F. Langer, Ph.D.	Trevor Archer, Ph.D.	Epigenetics and Stem Cell Biology Laboratory
Yu-Hua Lo, Ph.D.	Robin Stanley, Ph.D.	Signal Transduction Laboratory
Yong-Moon Park, MD, Ph.D.	Dale Sandler, Ph.D.	Epidemiology Branch
Maria G. Petrillo, Ph.D.	John Cidlowski, Ph.D.	Signal Transduction Laboratory
Yufeng Qin, Ph.D.	Paul Wade, Ph.D.	Epigenetics and Stem Cell Biology Laboratory

Prashant Rai, Ph.D.	Michael Fessler, MD	Immunity, Inflammation and Disease Laboratory
Cynthia J. Sakofsky, Ph.D.	Dmitry Gordenin, Ph.D.	Genome Integrity and Structural Biology Laboratory
Natale R. Sciolino, Ph.D.	Patricia Jensen, Ph.D.	Neurobiology Laboratory
Sheng Song, Ph.D.	Jau-Shyong Hong, Ph.D.	Neurobiology Laboratory
Heather L. Vellers, Ph.D.	Steven Kleeberger, Ph.D.	Immunity, Inflammation and Disease Laboratory
Sing-Wai Wong, Ph.D. candidate	Jennifer Martinez, Ph.D.	Immunity, Inflammation and Disease Laboratory

The NIH Pathway to Independence Award (K99/R00)

The Pathway to Independence (PI) Award Program is designed to facilitate receiving an R01 award earlier in an investigator's research career. The primary, long-term goal of the PI Award Program is to increase and maintain a strong cohort of new and talented, NIH-supported independent investigators. The PI Award will provide up to five years of support consisting of two phases. The initial phase will provide 1-2 years of mentored support for highly promising, postdoctoral research scientists. This phase will be followed by up to 3 years of independent 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.

Fei Zhao, Ph.D. received a K99/R00 award from the National Institute of Child Health and Human Development (NICHD). Dr. Zhao will train in the Reproductive and Developmental Biology Laboratory under the mentorship of Humphrey Yao, Ph.D.

Summer Internship Program Poster Awards

NIEHS takes a leadership role in science research and education. Scientists at NIEHS are committed to sharing with students the intensity, excitement, sense of discipline, and tremendous satisfaction that careers in science can impart to those who pursue them. To this end, the DIR established the Summer Internship Program for which internships are given to outstanding high school and college undergraduate and graduate students interested in pursuing careers in the biomedical/biological sciences. Participants are selected by intramural scientific mentors and spend between 8 to 12 weeks (during May through September) working on individual research projects that bring them exposure to the latest biochemical, molecular, and analytical techniques. This year there were 59 summer interns in the NIEHS program (57 in DIR and 2 in DNTP laboratories). There is a poster session at the end of the summer where participants display the results of their research efforts and respond to questions as though they were participating in a national scientific society meeting. This year the poster session was held on Thursday, July 26,

2018 and awards were presented in three categories, High School Interns, Undergraduate Interns and Graduate Interns. At the Awards Ceremony, the following awards were presented:

High School 1st Place:
Benjamin Sempowski
Durham School of the Arts
Dr. Anton Jetten (Principal Investigator)
Dr. David Scoville (Mentor)
Immunity, Inflammation & Disease Laboratory
"Identifying and Characterizing Novel lncRNAs Involved with Type-2 Diabetes"

Undergraduate 1st Place:
Samir Nacer
Nova Southeastern University
Dr. Jerry Yakel (Principal Investigator)
Dr. Simone Otto (Mentor)
Neurobiology Laboratory
"Examining Pilot Studies for α7nAChRs KO Sexual Dimorphisms amongst Neural Stem Cell Populations sing Spatial Operant Tasks and Flow Cytometry"

Undergraduate 2nd Place (tie):
Tasneem Essader
University of North Carolina- Chapel Hill
Dr. Shepherd Schurman (Principal Investigator & Mentor)
Clinical Research Branch
"Association of 177 C>T *RMRP* Polymorphism with Rheumatoid Arthritis in African-American Environmental Polymorphisms Registry Participants"

Kacey Fang
Yale University
Dr. Chandra Jackson (Principal Investigator)
Dr. Ketrell McWhorter (Mentor)
Epidemiology Branch
"Poor Sleep Characteristics and Type 2 Diabetes Risk: Does the Relationship Vary by Race/Ethnicity among Women in the Sister Study?"

Graduate School 1st Place:
Jack Murphy
University of North Carolina- Chapel Hill
Dr. Katie O'Brien (Staff Scientist & Mentor)
Epidemiology Branch
"Severe Acne and Risk of Breast Cancer"

DIR RESEARCH ACCOMPLISHMENTS FOR FY 2017

ZATT protein licenses removal of DNA-protein crosslinks
We reported discovery of a novel DNA damage response protein ZATT (aka ZNF451) that is critical for resolution of Topoisomerase 2 DNA-protein crosslinks (TOP2-DPCs). TOP2-DPCs are a form of potent cell killing DNA damage induced by widely used anticancer drugs, environmental toxicants, chemical metabolites, tobacco exposures, or DNA damage caused by ultraviolet light. This paper reports the discovery of the ZATT-TDP2 complex, a novel sensor of TOP2-DPCs that facilitates the direct resolution of these highly genotoxic lesions, and underpins cellular resistance to TOP2 targeted cancer therapy.

Schellenberg MJ, Lieberman JA, Herrero-Ruiz A, Butler LR, Williams JG, Muñoz-Cabello AM, Mueller GA, London RE, Cortés-Ledesma F, Williams RS. ZATT (ZNF451)-mediated resolution of topoisomerase 2 DNA-protein cross-links. *Science*. 2017 Sep 29;357(6358):1412-1416. doi: 10.1126/science.aam6468. Epub 2017 Sep 14. PubMed PMID: 28912134; PubMed Central PMCID: PMC5623066.

Time-lapse crystallography reveals hidden features of a DNA polymerase
A NIEHS-NIH research team has made use of a new X-ray crystallography technique to reveal a hidden feature in the mechanism of double-strand break repair. The work has exciting implications for preventing adverse consequences of double-strand breaks in mammalian cells exposed to environmental stressors.

Jamsen JA, Beard WA, Pedersen LC, Shock DD, Moon AF, Krahn JM, Bebenek K, Kunkel TA, Wilson SH. Time-lapse crystallography snapshots of a double-strand break repair polymerase in action. *Nat Commun*. 2017 Aug 15;8(1):253. doi: 10.1038/s41467-017-00271-7. PubMed PMID: 28811466; PubMed Central PMCID: PMC5557891.

Insight on how DNA polymerase interrogates the genome searching for damage
NIEHS-NIH researchers discovered a search mechanism used by DNA repair DNA polymerases to locate places in the genome where their action is required. The enzymes have the surprising ability to cling to the genomic DNA while scanning tens of 1000s of base pairs in the search for DNA repair sites. The research team also found that lesions hidden deep within the nucleosome core particle can be located and repaired by the DNA repair polymerases.

Howard MJ and Wilson SH. DNA scanning by base excision repair enzymes and implications for pathway coordination. *DNA Repair* 2018, *In Press*.

Rodriguez Y, Howard MJ, Cuneo MJ, Prasad R, Wilson SH. Unencumbered Pol β lyase activity in nucleosome core particles. *Nucleic Acids Res*. 2017 Sep 6;45(15):8901-8915. doi: 10.1093/nar/gkx593. PubMed PMID: 28911106; PubMed Central PMCID: PMC5587807.

Howard MJ, Wilson SH. Processive searching ability varies among members of the gap-filling DNA polymerase X family. *J Biol Chem*. 2017 Oct 20;292(42):17473-17481. doi:

10.1074/jbc.M117.801860. Epub 2017 Sep 11. PubMed PMID: 28893909; PubMed Central PMCID: PMC5655522.

Recognition of a new mitochondrial DNA polymerase
A NIEHS-NIH research team discovered that DNA polymerase β is a component of mammalian mitochondria. A deficiency in this enzyme causes a disruption in mitochondrial metabolism, especially in response to oxidatively-induced stress.

Çaglayan M, Prasad R, Krasich R, Longley MJ, Kadoda K, Tsuda M, Sasanuma H, Takeda S, Tano K, Copeland WC, Wilson SH. Complementation of aprataxin deficiency by base excision repair enzymes in mitochondrial extracts. *Nucleic Acids Res*. 2017 Sep 29;45(17):10079-10088. doi: 10.1093/nar/gkx654. PubMed PMID: 28973450; PubMed Central PMCID: PMC5622373.

Prasad R, Çağlayan M, Dai DP, Nadalutti CA, Zhao ML, Gassman NR, Janoshazi AK, Stefanick DF, Horton JK, Krasich R, Longley MJ, Copeland WC, Griffith JD, Wilson SH. DNA polymerase β: A missing link of the base excision repair machinery in mammalian mitochondria. *DNA Repair* (Amst). 2017 Dec;60:77-88. doi: 10.1016/j.dnarep.2017.10.011. Epub 2017 Oct 28. PubMed PMID: 29100041; PubMed Central PMCID: PMC5919216.

Polymerase-ligase partnership prevents a fidelity checkpoint
NIEHS-NIH researchers discovered that the handoff from polymerase to ligase during the last step of base lesion repair can trigger promutagenic DNA repair. The handoff partnership between these two enzymes prevents a fidelity checkpoint that works in the absence of the partnership.

Çaglayan M, Wilson SH. Role of DNA polymerase β oxidized nucleotide insertion in DNA ligation failure. *J Radiat Res*. 2017 Sep 1;58(5):603-607. doi: 10.1093/jrr/rrx027. PubMed PMID: 28992331; PubMed Central PMCID: PMC5737452.

Çaglayan M, Wilson SH. Pol μ dGTP mismatch insertion opposite T coupled with ligation reveals promutagenic DNA repair intermediate. *Nat Commun*. 2018, *In Press*

New small molecule probes shine fresh new light on DNA synthesis
The mechanism of DNA synthesis by a model DNA polymerase, Pol β, was revealed by use of X-ray crystallography in combination with "chemical biology" which is the use of novel chemical reagents as probes. The approach enabled discovery of a robust reverse reaction by the DNA polymerase that has implications for drug design as well as understanding mutagenesis during the DNA repair process.

Shock DD, Freudenthal BD, Beard WA, Wilson SH. Modulating the DNA polymerase β reaction equilibrium to dissect the reverse reaction. *Nat Chem Biol*. 2017 Oct;13 (10):1074-1080. doi: 10.1038/nchembio.2450. Epub 2017 Jul 31. PubMed PMID: 28759020; PubMed Central PMCID: PMC5605435.

Batra VK, Oertell K, Beard WA, Kashemirov BA, McKenna CE, Goodman MF, Wilson SH. Mapping Functional Substrate-Enzyme Interactions in the pol β Active Site through Chemical Biology: Structural Responses to Acidity Modification of Incoming dNTPs. *Biochemistry*. 2018 Jul 3;57(26):3934-3944. doi: 10.1021/acs.biochem.8b00418. Epub 2018 Jun 21. PubMed PMID: 29874056.

Roles of accessory factors in base lesion repair

The roles of the base lesion DNA repair accessory factors PARP1 and XRCC1 were further revealed and reviewed. Studies of the response of cells to oxidatively-induced base lesions uncovered novel repair sub-pathways and the formation of toxic DNA-protein complexes involving PARP-1 and DNA repair intermediates.

Horton JK, Stefanick DF, Zhao ML, Janoshazi AK, Gassman NR, Seddon HJ, Wilson SH. XRCC1-mediated repair of strand breaks independent of PNKP binding. *DNA Repair* (Amst). 2017 Dec;60:52-63. doi: 10.1016/j.dnarep.2017.10.007. Epub 2017 Oct 19. PubMed PMID: 29100039; PubMed Central PMCID: PMC5696015.

Horton JK, Stefanick DF, Çağlayan M, Zhao ML, Janoshazi AK, Prasad R, Gassman NR, Wilson SH. XRCC1 phosphorylation affects aprataxin recruitment and DNA deadenylation activity. *DNA Repair* (Amst). 2018 Apr;64:26-33. doi: 10.1016/j.dnarep.2018.02.004. Epub 2018 Feb 15. PubMed PMID: 29477978.

Liu L, Kong M, Gassman NR, Freudenthal BD, Prasad R, Zhen S, Watkins SC, Wilson SH, Van Houten B. PARP1 changes from three-dimensional DNA damage searching to one-dimensional diffusion after auto-PARylation or in the presence of APE1. *Nucleic Acids Res*. 2017 Dec 15;45(22):12834-12847. doi: 10.1093/nar/gkx1047. PubMed PMID: 29121337; PubMed Central PMCID: PMC5728402.

Prasad, R., Horton, J.K., Dai, D.-P., and Wilson S.H. Repair pathway for PARP-1 DNA-protein crosslinks. *DNA Repair* 2018, *In Press*

Prasad, R., Horton, J.K., Liu, Y. and Wilson S. H. Central steps in mammalian BER and regulation by PARP1. In David M. Wilson III (ed.) The Base Excision Repair Pathway, World Scientific Publishing, 2017 pp. 253-280.

Publication of a new high-profile review of base lesion DNA repair

Recent research shining a light on how mammalian cells protect themselves against DNA base lesion-inducing environmental agents was reviewed. The molecular mechanisms of the two base lesion repair sub-pathways were discussed in this high-profile review article.

Beard, W.A., Horton, J.K., Prasad, R., and Wilson, S.H. Eukaryotic Base Excision Repair. *Annu Rev Biochem*. 2018, *In Press*.

Discovery of the robust cellular response to BPA

The effect of the industrial toxicant BPA on the mammalian cellular response to oxidative stress was further discussed and reviewed in this series of articles. BPA treatment of cells in culture

was found to elicit a surprisingly robust and broad alteration in gene expression. This included a suppression of gene expression for many DNA repair genes. These results point to a mechanism by which BPA exposure could alter cellular metabolism resulting in adverse consequences.

Gassman NR, Coskun E, Jaruga P, Dizdaroglu M, Wilson SH. Combined Effects of High-Dose Bisphenol A and Oxidizing Agent (KBrO3) on Cellular Microenvironment, Gene Expression, and Chromatin Structure of Ku70-deficient Mouse Embryonic Fibroblasts. *Environ Health Perspect*. 2016 Aug;124(8):1241-52. doi: 10.1289/EHP237. Epub 2016 Apr 15. PubMed PMID: 27082013; PubMed Central PMCID: PMC4977032.

Gassman, N.R. and Wilson, S.H. Chapter 12. Bisphenol A and Nongenotoxic Drivers of Cancer. In Michael Waters and Claude Hughes, (eds.) Translational Toxicology and Therapeutics: Windows of Developmental Susceptibility in Reproduction and Cancer, John Wiley & Sons, Inc 2018 pp. 417-437.

Experimental methods used to study the effects of DNA damage caused by the Topoisomerase 1 enzyme

Researchers studying replication fidelity discovered that misincorporation of ribonucleotides occurs frequently and can cause genome instability. Mutations and other types of DNA damage can be generated upon removal of a ribonucleotide by the Topoisomerase 1 enzyme. This publication describes experimental methods that can be employed to identify different forms of DNA damage resulting from Topoisomerase 1 cleavage at ribonucleotides in DNA.

Williams JS, Kunkel TA. Studying Topoisomerase 1-Mediated Damage at Genomic Ribonucleotides. *Methods Mol Biol*. 2018;1703:241-257. doi: 10.1007/978-1-4939-7459-7_17. PubMed PMID: 29177746.

New technique for simultaneous imaging of multiple neural circuits during movement

A new tool developed by NIEHS researchers has determined, for the first time, how two distinct sets of neurons in the mouse brain work together to control movement. The method, which is called spectrally resolved fiber photometry (SRFP), can be used to simultaneously measure the activity of multiple neurons in healthy mice and in mice with brain disease. The scientists plan to use the technique to better understand what goes wrong in neurological disorders such as Parkinson's disease (PD). This technique will also have a profound impact on the study of other brain conditions, such as Alzheimer's disease, stroke, multiple sclerosis, and addiction.

Meng C, Zhou J, Papaneri A, Peddada T, Xu K, Cui G. Spectrally Resolved Fiber Photometry for Multi-component Analysis of Brain Circuits. *Neuron.* 2018 May16;98(4):707-717.e4. doi: 10.1016/j.neuron.2018.04.012. Epub 2018 May 3. PubMed PMID: 29731250; PubMed Central PMCID: PMC5957785.

Molecular crosstalk within an essential RNA processing complex

Ribonucleases are molecular scissors that catalyze the cleavage of RNA phosphodiester bonds and play essential roles in RNA processing and maturation. Precursor ribosomal RNA (rRNA) must be processed by several ribonucleases, including the endonuclease Las1, in a carefully orchestrated manner to generate the mature ribosomal subunits. Las1 is essential for cell viability

and mutations in the mammalian gene have been linked with human disease underscoring the importance of this enzyme. NIEHS researches have shown that on its own Las1 has weak nuclease activity, however when associated with its binding partner, the poly-nucleotide kinase Grc3, Las1 is programmed to specifically cleave pre-rRNA. Disruption of essential motifs within the Grc3 polynucleotide kinase active site impairs the activity of the Las1 nuclease *in vitro* and *in vivo*. The crosstalk between Grc3 and Las ensures the direct coupling of cleavage and phosphorylation during pre-rRNA processing.

Pillon MC, Sobhany M, Stanley RE. Characterization of the molecular crosstalk within the essential Grc3/Las1 pre-rRNA processing complex. *RNA*. 2018 May;24(5):721-738. doi: 10.1261/rna.065037.117. Epub 2018 Feb 9. PubMed PMID: 29440475; PubMed Central PMCID: PMC5900568.

DNA polymerase delta helps to initiate leading-strand DNA replication

Replication of DNA involves synthesis of a "leading strand" first, followed by synthesis of a lagging strand. For most of this replication, these tasks are accomplished by the concerted action of three DNA polymerases, with Pol epsilon primarily synthesizing the leading strand and Pols alpha and delta primarily synthesizing the lagging strand. However, this year we described strong evidence that when replication begins, Pol delta also has a brief but essential role in initiating leading strand replication. This discovery has important implications for evolution and for understanding the consequences of replication errors in initiating human diseases.

Garbacz MA, Lujan SA, Burkholder AB, Cox PB, Wu Q, Zhou ZX, Haber JE, Kunkel TA. Evidence that DNA polymerase δ contributes to initiating leading strand DNA replication in Saccharomyces cerevisiae. *Nat Commun*. 2018 Feb 27;9(1):858. doi: 10.1038/s41467-018-03270-4. PubMed PMID: 29487291; PubMed Central PMCID: PMC5829166.

How cells achieve high accuracy of chromosomal 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. But in addition, other DNA polymerases play a role (*E. coli* has five such accessory DNA polymerases) and they also affect the overall error rate. We have also demonstrated the important role of the 5'-deoxynucleoside-triphosphates (dNTPs), which are the building blocks used by the polymerases for synthesizing DNA.

Babu VMP, Itsko M, Baxter JC, Schaaper RM, Sutton MD. Insufficient levels of the nrdAB-encoded ribonucleotide reductase underlie the severe growth defect of the Δhda *E. coli* strain. *Mol Microbiol*. 2017 May;104(3):377-399. doi: 10.1111/mmi.13632. Epub 2017 Mar 13. PubMed PMID: 28130843; PubMed Central PMCID: PMC5397354.

Itsko M, Schaaper RM. Suppressors of dGTP Starvation in *Escherichia coli*. *J Bacteriol*. 2017 May 25;199(12). pii: e00142-17. doi: 10.1128/JB.00142-17. Print 2017 Jun 15. PubMed PMID: 28373271; PubMed Central PMCID: PMC5446616.

Maslowska KH, Makiela-Dzbenska K, Mo JY, Fijalkowska IJ, Schaaper RM. High-accuracy lagging-strand DNA replication mediated by DNA polymerase dissociation. *Proc Natl Acad Sci U S A*. 2018 Apr 17;115(16):4212-4217. doi: 10.1073/pnas.1720353115. Epub 2018 Apr 2. PubMed PMID: 29610333; PubMed Central PMCID: PMC5910852.

Researchers learn how DNA is ligated back together after damage

DNA ligase IV (LigIV) is the enzyme responsible for the ligation step of the nonhomologous end-joining (NHEJ) pathway that repairs highly toxic DNA double-strand breaks. Researchers have visualized the structures of LigIV in two distinct states of its catalytic cycle using X-ray crystallography. These structures reveal that the ligase encircles its DNA substrate, utilizing an extensive network of interactions that correctly position the broken phosphodiester backbone at the active site for repair. This work provides a means of understanding how mutations and deletions in LigIV can result in human disease.

Kaminski AM, Tumbale PP, Schellenberg MJ, Williams RS, Williams JG, Kunkel TA, Pedersen LC, Bebenek K. Structures of DNA-bound human ligase IV catalytic core reveal insights into substrate binding and catalysis. *Nat Commun*. 2018 Jul 6;9(1):2642. doi: 10.1038/s41467-018-05024-8. PubMed PMID: 29980672; PubMed Central PMCID: PMC6035275.

When DNA repair pathways collide

When cells sense that DNA damage has occurred, sets of enzymes and other repair proteins are recruited to the site that are dependent on the nature of the damage. These correspond to different repair pathways. In one example reported during the past year, two DNA repair scaffolds that facilitate either repair of single strand breaks (XRCC1) or re-attachment of non-homologous DNA termini (APLF) are found to interact with each other. This is a surprising response since this cross interaction competes with other interactions that support the repair activities of the two different pathways. The interaction was characterized structurally and found to be stronger than previously reported. It was proposed that this interaction facilitates competition to optimize the selection of the repair pathway with highest fidelity.

Kim K, Pedersen LC, Kirby TW, DeRose EF, London RE. Characterization of the APLF FHA-XRCC1 phosphopeptide interaction and its structural and functional implications. *Nucleic Acids Res*. 2017 Dec 1;45(21):12374-12387. doi: 10.1093/nar/gkx941. PubMed PMID: 29059378; PubMed Central PMCID: PMC5716189.

The dynamic response of a DNA repair polymerase.

In order to function effectively, DNA polymerases need to deal with flexible and compositionally variable substrates. During the past year, our group used NMR spectroscopy to explore how the dynamic characteristics of DNA pol β, an enzyme of central importance in the base excision repair pathway, facilitate enzyme function. Substrate recognition is accompanied by significant backbone and sidechain motion that may help to facilitate binding to the segments of the DNA upstream and downstream from the gap. Formation of an abortive ternary complex using a nonhydrolyzable dNTP results in sidechain motions that can be described by a single

exchange process within the catalytic subdomain, suggesting that this motion may play a role in catalysis.

DeRose EF, Kirby TW, Mueller GA, Beard WA, Wilson SH, London RE. Transitions in DNA polymerase β μs-ms dynamics related to substrate binding and catalysis. *Nucleic Acids Res*. 2018 Aug 21;46(14):7309-7322. doi: 10.1093/nar/gky503. PubMed PMID: 29917149.

Methionine metabolism is essential for SIRT1-regulated mouse embryonic stem cell maintenance and embryonic development

The developing embryos require a number of indispensable nutrients to support rapid cell division during the early stages of fetal development. In particular, embryonic stem cells (ESCs) derived from the inner cell mass of a blastocyst have a high dependence on methionine metabolism for epigenetic and redox homeostasis and maintenance of pluripotency compared to differentiated cells. However, remarkably, little is known about the regulation of cellular methionine metabolism. In this study, we discovered that SIRT1, the most conserved mammalian NAD+-dependent protein deacetylase, is critically involved in modulating methionine metabolism thereby impacting maintenance of mouse embryonic stem cells (mESCs) and subsequent embryogenesis. Through an amino-acid dropout screening, we discover that SIRT1 deficient mESCs are specifically sensitive to methionine restriction induced differentiation and apoptosis. Utilizing a large-scale metabolomic analysis and cellular rescue assays, we reveal that loss of SIRT1 primarily impairs conversion of methionine to S-adenosylmethionine (SAM) in mESCs, and this impairment is responsible for their hyper-sensitivity to methionine restriction. We further demonstrate that the reduced SAM production markedly decreases methylation levels of histones, resulting in dramatic alterations of gene expression profiles in SIRT1 deficient mESCs. Mechanistically, we discover that the enzyme converting methionine to S-adenosylmethionine in mESCs, methionine adenosyltransferase 2a (MAT2a), is under control of Myc and SIRT1. Consistently, SIRT1 KO embryos display reduced Mat2a expression and histone methylation, and are sensitive to maternal methionine restriction-induced lethality, whereas maternal methionine supplementation increases the survival of SIRT1 KO newborn mice. Our findings uncover a novel regulatory mechanism for methionine metabolism, and highlight the importance of methionine metabolism in SIRT1-mediated mESC maintenance and embryonic development.

Tang S, Fang Y, Huang G, Xu X, Padilla-Banks E, Fan W, Xu Q, Sanderson SM, Foley JF, Dowdy S, McBurney MW, Fargo DC, Williams CJ, Locasale JW, Guan Z, Li X. Methionine metabolism is essential for SIRT1-regulated mouse embryonic stem cell maintenance and embryonic development. *EMBO J*. 2017 Nov 2;36(21):3175-3193. doi: 10.15252/embj.201796708. Epub 2017 Oct 11. PubMed PMID: 29021282; PubMed Central PMCID: PMC5666621.

p300-mediated lysine 2-hydroxyisobutyrylation regulates glycolysis

Lysine acylations have emerged as a key regulatory mechanism in modulating cellular functions. Lysine 2-hydroxyisobutyrylation (Khib), a newly discovered lysine acylation, is a widespread histone mark like lysine acetylation (Kac). However, molecular machineries mediating 2-hydroxyisobutyrylation remain elusive, and its substrate landscape and biological consequences

are almost completely unknown. In the present study, through quantitative proteomics, global metabolomics, and functional metabolic analysis, we identified p300 as an acyltransferase for Khib, compared the p300-mediated Khib and Kac proteomics, and discovered a novel function of p300-mediated Khib in regulation of glycolysis. We discovered that p300 differentially regulates the Khib and Kac on distinct lysine sites, with only 6 out of the 149 p300-targeted Khib sites overlapping with the 693 p300-targeted Kac sites. We demonstrated that diverse cellular proteins, particularly glycolytic enzymes, are targeted by p300 for Khib but not for Kac. Specifically, deletion of p300 significantly reduces Khib levels on several p300-dependent, Khib-specific sites on key glycolytic enzymes including ENO1, decreasing their catalytic activities. Consequently, p300 deficient cells have impaired glycolysis and are hypersensitive to glucose depletion-induced cell death. Our study reveals a p300-catalyzed, Khib-specific molecular mechanism that regulates cellular glucose metabolism, and further indicate that p300 has an intrinsic ability to select short-chain acyl-CoA-dependent protein substrates.

Huang H, Tang S, Ji M, Tang Z, Shimada M, Liu X, Qi S, Locasale JW, Roeder RG, Zhao Y, Li X. p300-Mediated Lysine 2-Hydroxyisobutyrylation Regulates Glycolysis. *Mol Cell*. 2018 Jun 7;70(5):984. doi: 10.1016/j.molcel.2018.05.035. Epub 2018 Jun 7. PubMed PMID: 29883613; PubMed Central PMCID: PMC6037533.

Mitochondria have important functions that go beyond energy production

Mitochondria are organelles recognized primarily as the major energy producers in the cell. Within the mitochondria, the TCA cycle is responsible for cellular energy production and synthesis of biomass. Using genetic models to manipulate mitochondrial function, we found that mitochondrial nicotinamide adenine dinucleotide reduced (NADH) oxidation links the tricarboxylic acid (TCA) cycle with the metabolism of the amino acid methionine and the epigenetic regulation of nuclear gene expression. Our work offers insights into how mitochondrial dysfunction impacts health and disease through the regulation of genes expressed in the nucleus. From an environmental perspective, these findings also reveal a novel mechanism through which environmental toxicants that target the mitochondria can impact the biology of the organism.

Lozoya OA, Martinez-Reyes I, Wang T, Grenet D, Bushel P, Li J, Chandel N, Woychik RP, Santos JH. Mitochondrial nicotinamide adenine dinucleotide reduced (NADH) oxidation links the tricarboxylic acid (TCA) cycle with methionine metabolism and nuclear DNA methylation. *PLoS Biol*. 2018 Apr 18;16(4):e2005707. doi: 10.1371/journal.pbio.2005707. eCollection 2018 Apr. PubMed PMID: 29668680; PubMed Central PMCID: PMC5927466.

Altering neuronal activity patterns changes gene expression

Researchers from NIEHS, Harvard Medical School, and the University of California Merced determined that the history of neuronal activity patterns in the brain can be deduced by looking at gene expression profiles. The finding will help scientists better understand how the brain engages with the environment. Members of the research team used genome-scale technology to compare gene induction, or the turning on of genes, in response to brief and sustained neuronal activity patterns. They found that brief activity can induce a subset of activity-regulated genes (ARGs) that correlates with the first of three waves of ARGs induced by sustained activity. First-wave

ARGs are induced rapidly, require the calcium-dependent signaling pathway MAPK/ERK, and do not need the production of new proteins, known as de novo translation. In contrast, latter-wave ARGs are induced more slowly, do not need MAPK/ERK, but do need de novo translation. MAPK/ERK establishes multi-wave structure of gene induction and enables activity-duration-specific gene induction. In other words, the same mechanisms that establish rapid and slow gene responses also allow different genes to be induced by different durations of activity.

Tyssowski KM, DeStefino NR, Cho JH, Dunn CJ, Poston RG, Carty CE, Jones RD, Chang SM, Romeo P, Wurzelmann MK, Ward JM, Andermann ML, Saha RN, Dudek SM, Gray JM. Different Neuronal Activity Patterns Induce Different Gene Expression Programs. *Neuron*. 2018 May 2;98(3):530-546.e11. doi: 10.1016/j.neuron.2018.04.001. Epub 2018 Apr 19. PubMed PMID: 29681534; PubMed Central PMCID: PMC5934296.

Smoking activates AHRR enhancer

Using an innovative high-resolution reduced representation bisulfite sequencing (RRBS) technique, NIEHS researchers found novel modifications in DNA methylation patterns present in circulating immune cells from smokers in two independent human studies from the NIEHS Clinical Research Unit and the Multi-Ethnic Study of Atherosclerosis (MESA). DNA methylation plays an essential role in gene regulation in response to environmental and developmental stress. RRBS revealed novel smoking-associated differentially methylated regions (SM-DMRs) and a poised enhancer region of the aryl-hydrocarbon receptor repressor (*AHRR*) gene in the strongest of the SM-DMRs seen in CD15+ granulocytes and CD14+ monocytes. Surprisingly these were also easily detected in DNA from saliva cells, which are composed mostly of leukocytes similar to blood composition. Methylation of the *AHRR* CpG site, cg05575921, has been associated with smoking and subclinical atherosclerosis. In smokers, the *AHRR* SM-DMR activates the *AHRR* enhancer region, which increases enhancer non-coding RNA in monocytes and upregulates *AHRR* messenger RNA. This novel finding suggests that *AHRR* activation may be a risk factor in atherosclerosis and saliva DNA may be useful for detecting alterations in *AHRR* methylation.

Wan M, Bennett BD, Pittman GS, Campbell MR, Reynolds LM, Porter DK, Crowl CL, Wang X, Su D, Englert NA, Thompson IJ, Liu Y, Bell DA. Identification of Smoking-Associated Differentially Methylated Regions Using Reduced Representation Bisulfite Sequencing and Cell type-Specific Enhancer Activation and Gene Expression. *Environ Health Perspect*. 2018 Apr 27;126(4):047015. doi: 10.1289/EHP2395. PubMed PMID: 29706059; PubMed Central PMCID: PMC6071796.

Nucleic acid sensing mediates inflammation in Parkinson's disease

PINK1 and Parkin remove damaged mitochondria via a targeted form of autophagy, called mitophagy, and mutations in PINK1 and Parkin cause early-onset Parkinson's disease (PD). While serum from PD patients display increased levels of pro-inflammatory cytokines, whether inflammation contributes to or is a consequence of neuronal loss remains unknown. In this study, we demonstrate that both acute and chronic mitochondrial stress results in a strong inflammatory phenotype in both PINK1-/- and Parkin-/- mice, which is fully rescued by concurrent loss of STING, a sensor of cytosolic DNA. Strikingly, the Parkinsonian motor defects observed in aged Parkin-/-; Mutator mice is also rescued by loss of STING, suggesting

that inflammation facilitates this phenotype. Moreover, human Parkin heterozygotes also display elevated pro-inflammatory cytokines in serum. These results support an unanticipated function for mitophagy and a novel link to PD.

Sliter DA, Martinez J, Hao L, Chen X, Sun N, Fischer TD, Burman JL, Li Y, Zhang Z, Narendra DP, Cai H, Borsche M, Klein C, Youle RJ. Parkin and PINK1 mitigate STING-induced inflammation. *Nature*. 2018 Aug 22. doi: 10.1038/s41586-018-0448-9. [Epub ahead of print] PubMed PMID: 30135585.

Acetylcholine suppresses the hippocampal output to the cortex, the gateway to memory consolidation

Impairment of the cholinergic system and resulting insufficient acetylcholine (ACh) are hallmarks of alzheimer's disease (AD). Therefore, medicines that boost ACh levels have been shown to increase memory encoding and are prevalently used to treat AD. However, how ACh modulates memory consolidation is yet unknown. In this study, we show that ACh suppresses the hippocampal output, the first step to memory consolidation, and prevents the consolidation process from interfering with memory encoding.

Haam J, Zhou J, Cui G, Yakel JL. Septal cholinergic neurons gate hippocampal output to entorhinal cortex via oriens lacunosum moleculare interneurons. *Proc Natl Acad Sci U S A*. 2018 Feb 20;115(8):E1886-E1895. doi: 10.1073/pnas.1712538115. Epub 2018 Feb 7. PubMed PMID: 29437952; PubMed Central PMCID: PMC5828580.

Sulfite promotes formation of damaging protein radicals in the lung

Exposure to bisulfite and sulfite causes a wide range of adverse reactions in sensitive individuals, but the underlying mechanisms are poorly understood. A team of NIEHS scientists has found that sulfite exposure promotes the formation of protein radicals in the lungs of mice co-exposed to inhaled endotoxin. It was found that oxidants in the endotoxin-inflamed lung catalyze oxidation of the neutrophil protein myeloperoxidase into a protein radical in the presence of sulfite. These findings suggest that one mechanism by which sulfite may cause respiratory and other reactions in humans is via promoting oxidative damage to proteins inside immune cells. Moreover, the findings also raise the possibility that protein radicals (oxidized proteins) may contribute to the pathogenesis of human lung diseases, such as asthma.

Kumar A, Triquigneaux M, Madenspacher J, Ranguelova K, Bang JJ, Fessler MB, Mason RP. Sulfite-induced protein radical formation in LPS aerosol-challenged mice: Implications for sulfite sensitivity in human lung disease. *Redox Biol*. 2018 May;15:327-334. doi: 10.1016/j.redox.2017.12.014. Epub 2017 Dec 29. PubMed PMID: 29306790; PubMed Central PMCID: PMC5756054.

Intragenic enhancers attenuate gene expression

Enhancers are thought to activate or enhance transcription of their target genes. Jothi and colleagues challenge this conventional view by demonstrating that intragenic enhancers, besides activating genes, also suppress host gene transcription through transcription interference. Through genetic deletions, they show that enhancer-mediated attenuation determines cell fate decisions.

Cinghu S, Yang P, Kosak JP, Conway AE, Kumar D, Oldfield AJ, Adelman K, Jothi R. Intragenic Enhancers Attenuate Host Gene Expression. *Mol Cell*. 2017 Oct 5;68(1):104-117.e6. doi: 10.1016/j.molcel.2017.09.010. PubMed PMID: 28985501; PubMed Central PMCID: PMC5683415.

Chromatin remodeling protein governs steroid receptor function across the genome
Steroid hormones play a number of roles in the body, including controlling the immune system and the body's response to stress. The hormones affect the behavior of cells by binding to and activating hormone receptor proteins that bind to genomic DNA and modulate the activity of nearby genes. Gaining access to particular sites on a strand of DNA is not always easy. Cells pack DNA into a structure called chromatin. In some regions the DNA is so tightly wrapped in the chromatin that the receptors cannot access it. The structure of the chromatin therefore affects how a cell responds to steroid hormones. Inaccessible regions of chromatin can be 'opened up' by two groups of proteins, known as remodeling proteins and pioneer factors. Hormone receptors can work with these proteins to access particular DNA regions, but exactly how all these proteins work together was not fully understood. This study used DNA and RNA sequencing technologies to examine the roles of a hormone receptor called the glucocorticoid receptor, a remodeling protein called BRG1, and various pioneer factors in human breast cancer cells. This revealed three ways in which the glucocorticoid receptors worked with the other proteins when binding to chromatin. Future research into how these proteins work together could ultimately help us to improve how we use steroid hormones to treat diseases.

Hoffman JA, Trotter KW, Ward JM, Archer TK. BRG1 governs glucocorticoid receptor interactions with chromatin and pioneer factors across the genome. *Elife*. 2018 May 24;7. pii: e35073. doi: 10.7554/eLife.35073. PubMed PMID: 29792595; PubMed Central PMCID: PMC5967868.

Repressive chromatin state protects against endogenous retrovirus activation
Endogenous retroviruses (ERVs) comprise ~10% of the mammalian genome and play critical roles in genome evolution as sources of genetic novelty and diversity. However, aberrant ERV activation leads to genome instability and erroneous transcription, and host mechanisms have evolved to restrict ERV activities. In this study, we reported the identification of novel epigenetic factors in ERV repression via an RNAi screen. We further studied the function of one factor Rif1, and showed that Rif1 silences ERVs by promoting a repressive chromatin state at ERV regions in the genome.

Li P, Wang L, Bennett BD, Wang J, Li J, Qin Y, Takaku M, Wade PA, Wong J, Hu G. Rif1 promotes a repressive chromatin state to safeguard against endogenous retrovirus activation. *Nucleic Acids Res*. 2017 Dec 15;45(22):12723-12738. doi: 10.1093/nar/gkx884. PubMed PMID: 29040764; PubMed Central PMCID: PMC5727408.

GATA3 zinc finger 2 mutations reprogram the breast cancer transcriptional network
NIEHS scientists identified GATA3-specific genetic mutations in breast cancer cells that are associated with poor survival of patients. They demonstrated that the loss of two nucleotides in

one allele of GATA3 drastically changed the transcriptional program and biology of tumor cells. These findings demonstrate that GATA3 mutations in zinc-finger 2 reprogram breast cancer cell properties and might contribute to poor health outcomes in certain breast cancer patients.

Takaku M, Grimm SA, Roberts JD, Chrysovergis K, Bennett BD, Myers P, Perera L, Tucker CJ, Perou CM, Wade PA. GATA3 zinc finger 2 mutations reprogram the breast cancer transcriptional network. *Nat Commun*. 2018 Mar 13;9(1):1059. doi: 10.1038/s41467-018-03478-4. PubMed PMID: 29535312; PubMed Central PMCID: PMC5849768.

Diet-associated microbiome reprograms gene expression in the colon.
The gut microbiome, a key constituent of the colonic environment, has been implicated as an important modulator of human health. Our results highlight potential interactions between host diet and microbiome and their effects on the host epigenome, which prime enhancers in the host colon epithelium for obesity and obesity-related conditions. These findings provide new insights into host–microbiota interactions with potential relevance to obesity and obesity-related diseases.

Qin Y, Roberts JD, Grimm SA, Lih FB, Deterding LJ, Li R, Chrysovergis K, Wade PA. An obesity-associated gut microbiome reprograms the intestinal epigenome and leads to altered colonic gene expression. *Genome Biol*. 2018 Jan 23;19(1):7. doi: 10.1186/s13059-018-1389-1. PubMed PMID: 29361968; PubMed Central PMCID: PMC5782396.

DES reprograms chromatin during uterus development
The synthetic estrogen diethylstilbestrol (DES), once prescribed clinically to treat pregnancy complications, induces abnormal uterine structure and function and increases cancer risk in women who were exposed to DES while fetuses. Using a mouse model, we found that DES can cause widespread epigenetic changes and alter gene expression in the developing uterus. The findings provide a crucial mechanism for the detrimental effects of estrogenic endocrine disruptors on development of the female reproductive system.

Jefferson WN, Kinyamu HK, Wang T, Miranda AX, Padilla-Banks E, Suen AA, Williams CJ. Widespread enhancer activation via ERα mediates estrogen response *in vivo* during uterine development. *Nucleic Acids Res*. 2018 Jun 20;46(11):5487-5503.doi: 10.1093/nar/gky260. PubMed PMID: 29648668; PubMed Central PMCID: PMC6009594.

Novel target identified for improving recovery from heart attacks
An NIEHS study identification of an enzyme that impairs recovery from cardiac arrest. The enzyme, known as microsomal epoxide hydrolase (mEH), degrades a set of molecules called epoxyeicosatrienoic acids (EETs) that are typically beneficial in situations such as oxygen deprivation (ischemia) which occurs during a heart attack. The authors showed that genetic knockout of mEH decreased degradation of EETs and subsequently improved heart recovery after ischemia. These data suggest that mEH inhibitors might offer a novel approach for improving recovery of patients who suffer a heart attack.

Edin ML, Hamedani BG, Gruzdev A, Graves JP, Lih FB, Arbes SJ 3rd, Singh R, Orjuela Leon AC, Bradbury JA, DeGraff LM, Hoopes SL, Arand M, Zeldin DC. Epoxide hydrolase 1 (EPHX1) hydrolyzes epoxyeicosanoids and impairs cardiac recovery after

ischemia. *J Biol Chem*. 2018 Mar 2;293(9):3281-3292. doi: 10.1074/jbc.RA117.000298. Epub 2018 Jan 3. PubMed PMID: 29298899; PubMed Central PMCID: PMC5836130.

Responses to allergens are coordinated by two distinct cell types in the lung.
Allergic sensitization to inhaled allergens is one of the earliest events in the development of allergic asthma, and likely determines the nature and severity of the disease. A gene known as Myd88 has been previously shown to be essential for allergic sensitization, although its precise role has remained elusive. By deleting this gene in two distinct cell types, known as dendritic cells and epithelial cells, the authors show that each of these cell types has a distinct role during allergic sensitization. When Myd88 was deleted from dendritic cells, the mice had reduced neutrophils in the airway following allergic sensitization and re-exposure to that same allergen. By contrast, deleting Myd88 from epithelial cells led to decreases in a different cell type, known as eosinophils. The authors further showed that deleting Myd88 from epithelial cells led to marked differences in the gene expression and chromatin accessibility of dendritic cells. Thus, both cell-intrinsic and cell-extrinsic Myd88 controls gene expression in dendritic cells, thereby orchestrating distinct types of immune responses to inhaled allergens.

Thomas SY, Whitehead GS, Takaku M, Ward JM, Xu X, Nakano K, Lyons-Cohen MR, Nakano H, Gowdy KM, Wade PA, Cook DN. MyD88-dependent dendritic and epithelial cell crosstalk orchestrates immune responses to allergens. *Mucosal Immunol*. 2018 May;11(3):796-810. doi: 10.1038/mi.2017.84. Epub 2017 Oct 25. PubMed PMID:29067999; PubMed Central PMCID: PMC5918466.

Obese women have lower risk of breast cancer before menopause
It is well known that weight gain and obesity after menopause is a risk factor for postmenopausal breast cancer, but this may not be true for premenopausal breast cancer. We developed the Premenopausal Breast Cancer Collaborative Group, an international consortium of more than 20 prospective cohorts, to study risk factors for premenopausal breast cancer that cannot be well studied in a single cohort. In the first report using pooled data from 19 of the cohorts (including 758,592 women, 13,082 with breast cancer), we found that premenopausal breast cancer risk decreases with increasing levels of body mass index (BMI). Results were strongest for BMI at ages 18-24; women who were very obese at ages 18-24 (BMI of >35 kg/m2) were 4.2 times less likely to develop premenopausal breast cancer compared to women classified as having a very low BMI (<17 kg/m2) at the same age. Results point to the possibility that the mechanisms leading to breast cancer differ before and after menopause.

Premenopausal Breast Cancer Collaborative Group, Schoemaker MJ, Nichols HB, Wright LB, Brook MN, Jones ME, O'Brien KM, Adami HO, Baglietto L, Bernstein L, Bertrand KA, Boutron-Ruault MC, Braaten T, Chen Y, Connor AE, Dorronsoro M, Dossus L, Eliassen AH, Giles GG, Hankinson SE, Kaaks R, Key TJ, Kirsh VA, Kitahara CM, Koh WP, Larsson SC, Linet MS, Ma H, Masala G, Merritt MA, Milne RL, Overvad K, Ozasa K, Palmer JR, Peeters PH, Riboli E, Rohan TE, Sadakane A, Sund M, Tamimi RM, Trichopoulou A, Ursin G, Vatten L, Visvanathan K, Weiderpass E, Willett WC, Wolk A, Yuan JM, Zeleniuch-Jacquotte A, Sandler DP, Swerdlow AJ. Association of Body Mass Index and Age with Subsequent Breast Cancer Risk in Premenopausal Women. *JAMA*

Oncol. 2018 Jun 21:e181771. doi: 10.1001/jamaoncol.2018.1771. [Epub ahead of print] PubMed PMID: 29931120.

Nichols HB, Schoemaker MJ, Wright LB, McGowan C, Brook MN, McClain KM, Jones ME, Adami HO, Agnoli C, Baglietto L, Bernstein L, Bertrand KA, Blot WJ, Boutron-Ruault MC, Butler L, Chen Y, Doody MM, Dossus L, Eliassen AH, Giles GG, Gram IT, Hankinson SE, Hoffman-Bolton J, Kaaks R, Key TJ, Kirsh VA, Kitahara CM, Koh WP, Larsson SC, Lund E, Ma H, Merritt MA, Milne RL, Navarro C, Overvad K, Ozasa K, Palmer JR, Peeters PH, Riboli E, Rohan TE, Sadakane A, Sund M, Tamimi RM, Trichopoulou A, Vatten L, Visvanathan K, Weiderpass E, Willett WC, Wolk A, Zeleniuch-Jacquotte A, Zheng W, Sandler DP, Swerdlow AJ. The Premenopausal Breast Cancer Collaboration: A Pooling Project of Studies Participating in the National Cancer Institute Cohort Consortium. *Cancer Epidemiol Biomarkers Prev*. 2017 Sep;26(9):1360-1369. doi: 10.1158/1055-9965.EPI-17-0246. Epub 2017 Jun 9. Review. PubMed PMID: 28600297; PubMed Central PMCID: PMC5581673.

Reduced lung function found in oil spill clean-up workers exposed to burning oil

We studied lung function in 7,775 adults living in the Gulf states who either participated in oil spill response and clean-up efforts (workers) or received safety training but were not hired (nonworkers), 1-3 years after the 2010 Deepwater Horizon disaster in the Gulf of Mexico. We administered spirometry tests to evaluate clinical measures of lung function including forced expiratory volume in 1 second (FEV1; mL), forced vital capacity (FVC; mL), and the ratio (FEV1/FVC%) in relation to oil work, broad classes of clean-up jobs, and exposure to dispersants or burning oil/gas. While we found no differences between workers and nonworkers, overall, among workers, we observed a small decrement in FEV1 (Beta, -71 mL; 95% confidence interval [CI], -127 to -14) in decontamination workers compared with support workers. Workers with high potential exposure to burning oil/gas had significantly reduced lung function compared with unexposed workers: FEV1 (Beta, -183 mL; 95% CI, -316 to -49) and FEV1/FVC (Beta, -1.93%; 95% CI, -3.50 to -0.36). The reduced lung function in workers exposed to burning was equivalent to effects seen with 10 years of smoking.

Gam KB, Kwok RK, Engel LS, Curry MD, Stewart PA, Stenzel MR, McGrath JA, Jackson WB 2nd, Jensen RL, Keil AP, Lichtveld MY, Miller AK, Sandler DP. Lung Function in Oil Spill Response Workers 1-3 Years After the Deepwater Horizon Disaster. *Epidemiology*. 2018 May;29(3):315-322. doi: 10.1097/EDE.0000000000000808. PubMed PMID: 29381492; PubMed Central PMCID: PMC5882518.

Pesticides are associated with hypothyroid disease in women living on farms

Several pesticides have been implicated in thyroid function disruption, but clinical implications are not clear. Using data from the Agricultural Health Study, a prospective study of pesticide applicators and their spouses followed since 1993, we found that compared to women who did not use these pesticides, the risk of developing hypothyroid disease was 50 to 250 percent higher in spouses who used the fungicides benomyl, maneb/mancozeb, and metalaxyl, the herbicide pendimethalin, and among those over 60 years of age the insecticides parathion and permethrin. Some other pesticides were associated with decreased risk, as was long-term farm residence. This is the largest study to date of thyroid disease in women using pesticides. Results are

consistent with mechanistic studies and results from prior research on prevalent thyroid disease in the same cohort.

Shrestha S, Parks CG, Goldner WS, Kamel F, Umbach DM, Ward MH, Lerro CC, Koutros S, Hofmann JN, Beane Freeman LE, Sandler DP. Incident thyroid disease in female spouses of private pesticide applicators. *Environ Int*. 2018 Sep;118:282-292. doi: 10.1016/j.envint.2018.05.041. Epub 2018 Jun 13. PubMed PMID: 29908479.

NIEHS Scientists lead international team to identify the genetic basis of lung traits in diverse populations

Genome wide association studies (GWAS) of pulmonary function, done at NIEHS and elsewhere, have identified many genes underlying these clinically important lung parameters that form the basis for diagnosing chronic obstructive pulmonary disease. However, GWAS of lung function have been limited to European populations. We combined data from multiple ethnic groups to perform the largest GWAS of lung function to date thus increasing the number of loci by 50%. These results extend our understanding of the genetic basis of lung function and increase the generalizability of this work to the diverse population of the US.

Wyss AB, Sofer T, Lee MK, Terzikhan N, Nguyen JN, Lahousse L, Latourelle JC, Smith AV, Bartz TM, Feitosa MF, Gao W, Ahluwalia TS, Tang W, Oldmeadow C, Duan Q, de Jong K, Wojczynski MK, Wang XQ, Noordam R, Hartwig FP, Jackson VE, Wang T, Obeidat M, Hobbs BD, Huan T, Gui H, Parker MM, Hu D, Mogil LS, Kichaev G, Jin J, Graff M, Harris TB, Kalhan R, Heckbert SR, Paternoster L, Burkart KM, Liu Y, Holliday EG, Wilson JG, Vonk JM, Sanders JL, Barr RG, de Mutsert R, Menezes AMB, Adams HHH, van den Berge M, Joehanes R, Levin AM, Liberto J, Launer LJ, Morrison AC, Sitlani CM, Celedón JC, Kritchevsky SB, Scott RJ, Christensen K, Rotter JI, Bonten TN, Wehrmeister FC, Bossé Y, Xiao S, Oh S, Franceschini N, Brody JA, Kaplan RC, Lohman K, McEvoy M, Province MA, Rosendaal FR, Taylor KD, Nickle DC, Williams LK, Burchard EG, Wheeler HE, Sin DD, Gudnason V, North KE, Fornage M, Psaty BM, Myers RH, O'Connor G, Hansen T, Laurie CC, Cassano PA, Sung J, Kim WJ, Attia JR, Lange L, Boezen HM, Thyagarajan B, Rich SS, Mook-Kanamori DO, Horta BL, Uitterlinden AG, Im HK, Cho MH, Brusselle GG, Gharib SA, Dupuis J, Manichaikul A, London SJ. Multiethnic meta-analysis identifies ancestry-specific and cross-ancestry loci for pulmonary function. *Nat Commun*. 2018 Jul 30;9(1):2976. doi: 10.1038/s41467-018-05369-0. PubMed PMID: 30061609; PubMed Central PMCID: PMC6065313.

Genetic variability and pollution exposure together dictate severity of asthma symptoms

We have shown that asthma patients that have a specific genetic profile are particularly susceptible to pollution in terms of having increased asthma symptoms. Asthma patients who lack this genetic profile do not have the same sensitivity to pollution, and people who are not exposed to pollution do well regardless of genetic profile. This is a step towards establishing a precision medicine approach in environmental medicine; e.g. we can specifically approach patients who have this genetic profile and are exposed to pollution for air purification interventions like HEPA filters at home.

Schurman SH, Bravo MA, Innes CL, Jackson WB 2nd, McGrath JA, Miranda ML, Garantziotis S. Toll-like Receptor 4 Pathway Polymorphisms Interact with Pollution to Influence Asthma Diagnosis and Severity. *Sci Rep*. 2018 Aug 23;8(1):12713. doi: 10.1038/s41598-018-30865-0. PubMed PMID: 30140039.

Identification of a new regulator of thyroid hormone biosynthesis and the development of hypothyroidism and goiter

Thyroid hormone plays a critical role in the regulation of many developmental and metabolic processes. Abnormalities in thyroid development or thyroid hormone biosynthesis are involved in many pathologies, including neonatal hypothyroidism, enlargement of thyroid (goiter), and thyroid cancer. In this study, the investigators identify the transcription regulator, GLI-similar 3 (GLIS3), as a new and key regulator of thyroid hormone biosynthesis and proliferation of thyroid follicular cells, and uncover a mechanism by which GLIS3-deficiency causes neonatal hypothyroidism and prevents goiter development.

Kang HS, Kumar D, Liao G, Lichti-Kaiser K, Gerrish K, Liao XH, Refetoff S, Jothi R, Jetten AM. GLIS3 is indispensable for TSH/TSHR-dependent thyroid hormone biosynthesis and follicular cell proliferation. *J Clin Invest*. 2017 Dec 1;127(12):4326-4337. doi: 10.1172/JCI94417. Epub 2017 Oct 30. PubMed PMID: 29083325; PubMed Central PMCID: PMC5707155.

More evidence that vitamin D can reduce the risk of breast cancer

O'Brien and colleagues at NIEHS continued to explore the role of vitamin D in breast cancer. Work last year by the same investigators had shown that women with serum vitamin D levels in the upper quartile had their risk of breast cancer reduced by about 20%, based on the NIEHS Sister Study. There was also reduced risk in those who reported at baseline that they took vitamin D supplements. The possibility that these associations are causal gained important support this year through a further paper that explored the effects of vitamin D related genetic variants and found that the estimated effect of serum levels of D was modified by polymorphisms in the vitamin D receptor gene. Further work suggested a possible mediating or interacting role for methylation at vitamin D related genes.

O'Brien KM, Sandler DP, Kinyamu HK, Taylor JA, Weinberg CR. Single-Nucleotide Polymorphisms in Vitamin D-Related Genes May Modify Vitamin D-Breast Cancer Associations. *Cancer Epidemiol Biomarkers Prev*. 2017 Dec;26(12):1761-1771. doi: 10.1158/1055-9965.EPI-17-0250. Epub 2017 Oct 25. PubMed PMID: 28830874; PubMed Central PMCID: PMC5906103

O'Brien KM, Sandler DP, Xu Z, Kinyamu HK, Taylor JA, Weinberg CR. Vitamin D, DNA methylation, and breast cancer. *Breast Cancer Res*. 2018 Jul 11;20(1):70. doi: 10.1186/s13058-018-0994-y. PubMed PMID: 29996894; PubMed Central PMCID: PMC6042268.

Pet Allergen Exposure and Asthma

While pets are found in more than 50% of U.S. homes, the effect of pet allergen exposure on asthma morbidity in the United States population is not well documented. We examined the

effect of dog and cat allergen exposures on asthma morbidity in the U.S. population in the National Health and Nutrition Examination Survey (NHANES). The prevalence of allergic sensitization in the NHANES population was similar for dog and cat with both being approximately 12%. Among those who were sensitized, elevated exposure to pet allergens was associated with an increased prevalence of asthma and asthma attacks. Indeed, 44% of the asthma attacks were attributable to exposure to high levels of dog allergen in the bedroom among asthmatics sensitive to dog and 30% attributable to cat allergen exposure among the comparable cat sensitive-exposed group. Projecting these results to the U.S. population, indicates more than 1 million increased asthma attacks each year for the dog sensitive-exposed group and more than 500,000 increased asthma attacks for the cat sensitive-exposed population of asthmatics. Elevated exposure to dog and cat allergens among those sensitized individuals with asthma is associated with excess asthma attacks. Reducing pet allergen exposures has the potential for a significant decrease in asthma morbidity.

Gergen PJ, Mitchell HE, Calatroni A, Sever ML, Cohn RD, Salo PM, Thorne PS, Zeldin DC. Sensitization and Exposure to Pets: The Effect on Asthma Morbidity in the US Population. *J Allergy Clin Immunol Pract*. 2018 Jan - Feb;6(1):101-107.e2. doi: 10.1016/j.jaip.2017.05.019. Epub 2017 Jul 8. PubMed PMID: 28694047; PubMed Central PMCID: PMC5756688

Bedroom Allergen Exposure in the U.S.

Bedroom allergen exposures contribute to allergic disease morbidity because people spend considerable time in bedrooms, having close contact with allergen reservoirs. We investigated participant and housing characteristics, including sociodemographic, regional and climatic factors, associated with bedroom allergen exposures in a nationally representative sample of the US population enrolled in the National Health and Nutrition Examination Survey (NHANES). Almost all participants (>99%) had at least one and 74% had 3-6 allergens detected. Over 2/3 of participants (73%) had at least one allergen and 18% had ≥3 allergens exceeding elevated levels. Although exposure variability showed significant racial/ethnic and regional differences, high exposure burden to multiple allergens was most consistently associated with the presence of pets and pests, living in mobile homes/trailers, older and rental homes, and in non-metropolitan areas. Exposure to multiple allergens is common. Despite highly variable exposures, bedroom allergen burden is strongly associated with the presence of pets and pests.

Salo PM, Wilkerson J, Rose KM, Cohn RD, Calatroni A, Mitchell HE, Sever ML, Gergen PJ, Thorne PS, Zeldin DC. Bedroom allergen exposures in US households. *J Allergy Clin Immunol*. 2018 May;141(5):1870-1879.e14. doi: 10.1016/j.jaci.2017.08.033. Epub 2017 Nov 30. PubMed PMID: 29198587; PubMed Central PMCID: PMC5938098

Adherence to NAEPP Guidelines for the Diagnosis and Management of Asthma

The 2007 Guidelines for the Diagnosis and Management of Asthma provide evidence-based recommendations to improve asthma care. Limited national-level data are available about clinician agreement and adherence to these guidelines. To assess clinician-reported adherence with specific guideline recommendations, as well as agreement with and self-efficacy to implement guidelines, we analyzed the 2012 National Asthma Survey of Physicians data for 1412 primary care clinicians and 233 asthma specialists about 4 cornerstone guideline domains:

asthma control, patient education, environmental control, and pharmacologic treatment. Asthma specialists expressed stronger agreement, higher self-efficacy, and greater adherence with guideline recommendations than did primary care clinicians. Adherence was low among both groups for specific core recommendations, including written asthma action plan, home peak flow monitoring, spirometry testing, and repeated assessment of inhaler technique. Among primary care clinicians, greater self-efficacy was associated with greater adherence. For specialists, self-efficacy was associated only with increased odds of spirometry testing. Guideline agreement was generally not associated with adherence. We conclude that agreement with and adherence to asthma guidelines was higher for specialists than for primary care clinicians, but was low in both groups for several key recommendations. Self-efficacy was a good predictor of guideline adherence among primary care clinicians but not among specialists.

Cloutier MM, Salo PM, Akinbami LJ, Cohn RD, Wilkerson JC, Diette GB, Williams S, Elward KS, Mazurek JM, Spinner JR, Mitchell TA, Zeldin DC. Clinician Agreement, Self-Efficacy, and Adherence with the Guidelines for the Diagnosis and Management of Asthma. *J Allergy Clin Immunol Pract*. 2018 May -Jun;6(3):886-894.e4. doi: 10.1016/j.jaip.2018.01.018. Epub 2018 Feb 3. PubMed PMID: 29408439; PubMed Central PMCID: PMC5948143.

Genome Sequencing of the House Dust Mite

Researchers at NIEHS and NISC have completed the whole genome sequencing of the common house dust mite, *Dermatophagoides pteronyssinsus*. The project identified and completed the DNA sequence of all the known house dust mite allergens. Of particular interest, the highly quality of the current data allowed the researchers to identify naturally occurring isoforms of common allergens, which will aid in improving environmental detection assays and allow doctors to correctly diagnose the source species of patient allergies.

Randall TA, Mullikin JC, Mueller GA. The Draft Genome Assembly of *Dermatophagoides pteronyssinus* Supports Identification of Novel Allergen Isoforms in *Dermatophagoides* Species. *Int Arch Allergy Immunol*. 2018;175(3):136-146. doi: 10.1159/000481989. Epub 2018 Jan 11. PubMed PMID: 29320781; PubMed Central PMCID: PMC5847439.

Biomarkers of ovarian reserve are not reliable indicators of fertility for Older Women.

Anti-Müllerian hormone (AMH) and follicle stimulating hormone (FSH) are used by infertility clinics as biomarkers of ovarian reserve to predict egg yield. The value of these biomarkers for predicting fertility in a general population had not been adequately evaluated. The Time to Conceive study was designed to address this gap. We follow 750 women, aged 30-44 through their pregnancy attempts to assess their fertility with prospective time-to-pregnancy data. These markers of ovarian reserve were no better predictors of fertility than age, even in the oldest subgroup of participants. Findings suggest that commercial products that use urinary FSH to assess fertility potential are unlikely to be useful for women in this age group.

Steiner AZ, Pritchard D, Stanczyk FZ, Kesner JS, Meadows JW, Herring AH, Baird DD. Association Between Biomarkers of Ovarian Reserve and Infertility Among Older Women of Reproductive Age. *JAMA*. 2017 Oct 10;318(14):1367-1376. doi:

10.1001/jama.2017.14588. PubMed PMID: 29049585; PubMed Central PMCID: PMC5744252.

Individuals with the same mutation in the gene SMCHD1 are born without an external nose or develop muscular dystrophy as adults – but not both.
Congenital arrhinia (absent nose), which is often associated with eye and reproductive defects, and facioscapulohumeral muscular dystrophy type 2 (FSHD2) are two seemingly unrelated disorders which are both caused by mutations in the SMCHD1 gene. We investigated whether patients with FSHD2 have subtle craniofacial abnormalities suggestive of a mild form of arhinia, which if present, would indicate that these two conditions represent the opposite extremes of one disease spectrum. Patients with FSHD2, however, had no defects in the structure of the nose, sense of smell, vision, or reproductive function, suggesting that arhinia and FSHD2 are both caused by an abnormal SMCHD1 protein but also by critical genetic and/or environmental factors unique to each condition.

Mul K, Lemmers RJLF, Kriek M, van der Vliet PJ, van den Boogaard ML, Badrising UA, Graham JM Jr, Lin AE, Brand H, Moore SA, Johnson K, Evangelista T, Töpf A, Straub V, Kapetanovic García S, Sacconi S, Tawil R, Tapscott SJ, Voermans NC, van Engelen BGM, Horlings CGC, Shaw ND, van der Maarel SM. FSHD type 2 and Bosma arhinia microphthalmia syndrome: Two faces of the same mutation. *Neurology*. 2018 Aug 7;91(6):e562-e570. doi: 10.1212/WNL.0000000000005958. Epub 2018 Jul 6. PubMed PMID: 29980640; PubMed Central PMCID: PMC6105048.

New Classification Criteria Developed for Adult and Juvenile Myositis
The growing differences among specialties in terms of how the idiopathic inflammatory myopathies (IIM) and their major subgroups are defined is leading to difficulties in conducting multispecialty international clinical trials and in comparing new findings from multiple basic and clinical research studies. To address this, candidate variables were assembled from published criteria and expert opinion using consensus methodology. Data were collected from 47 rheumatology, dermatology, neurology, and pediatric clinics worldwide based on data from 976 IIM patients (74% adults; 26% children) and 624 non-IIM patients with mimicking conditions. New classification criteria for IIM with readily assessable measurements and symptoms have been developed that generally show superior performance compared with existing criteria. These criteria use a model system with differential weights for the clinical and laboratory variables, and then a classification tree approach to the sub-classification of clinical subgroups of myositis. These criteria have been accepted by the American College of Rheumatology- European League Against Rheumatism and have been endorsed by international rheumatology, dermatology, neurology, and pediatric groups. They employ easily accessible and operationally defined elements, and enable classification of "definite," "probable," and "possible" IIM, in addition to the major subgroups of IIM. These new classification criteria had excellent performance characteristics and should be sensitive criteria that will provide a uniform approach for assessing in future clinical studies of IIM patients.

Lundberg IE, Tjärnlund A, Bottai M, Werth VP, Pilkington C, Visser M, Alfredsson L, Amato AA, Barohn RJ, Liang MH, Singh JA, Aggarwal R, Arnardottir S, Chinoy H, Cooper RG, Dankó K, Dimachkie MM, Feldman BM, Torre IG, Gordon P, Hayashi T,

Katz JD, Kohsaka H, Lachenbruch PA, Lang BA, Li Y, Oddis CV, Olesinska M, Reed AM, Rutkowska-Sak L, Sanner H, Selva-O'Callaghan A, Song YW, Vencovsky J, Ytterberg SR, Miller FW, Rider LG; International Myositis Classification Criteria Project consortium, The Euromyositis register and The Juvenile Dermatomyositis Cohort Biomarker Study and Repository (JDRG) (UK and Ireland). 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. *Ann Rheum Dis*. 2017 Dec;76(12):1955-1964. doi: 10.1136/annrheumdis-2017-211468. Epub 2017 Oct 27. Erratum in: Ann Rheum Dis. 2018 Sep;77(9):e64. PubMed PMID: 29079590; PubMed Central PMCID: PMC5736307.

Lundberg IE, Tjärnlund A, Bottai M, Werth VP, Pilkington C, de Visser M, Alfredsson L, Amato AA, Barohn RJ, Liang MH, Singh JA, Aggarwal R, Arnardottir S, Chinoy H, Cooper RG, Dankó K, Dimachkie MM, Feldman BM, Garcia-De La Torre I, Gordon P, Hayashi T, Katz JD, Kohsaka H, Lachenbruch PA, Lang BA, Li Y, Oddis CV, Olesinska M, Reed AM, Rutkowska-Sak L, Sanner H, Selva-O'Callaghan A, Song YW, Vencovsky J, Ytterberg SR, Miller FW, Rider LG; International Myositis Classification Criteria Project Consortium, the Euromyositis Register, and the Juvenile Dermatomyositis Cohort Biomarker Study and Repository (UK and Ireland). 2017 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Adult and Juvenile Idiopathic Inflammatory Myopathies and Their Major Subgroups. *Arthritis Rheumatol*. 2017 Dec;69(12):2271-2282. doi: 10.1002/art.40320. Epub 2017 Oct 27. PubMed PMID: 29106061; PubMed Central PMCID: PMC5846474.

Bottai M, Tjärnlund A, Santoni G, Werth VP, Pilkington C, de Visser M, Alfredsson L, Amato AA, Barohn RJ, Liang MH, Singh JA, Aggarwal R, Arnardottir S, Chinoy H, Cooper RG, Danko K, Dimachkie MM, Feldman BM, García-De La Torre I, Gordon P, Hayashi T, Katz JD, Kohsaka H, Lachenbruch PA, Lang BA, Li Y, Oddis CV, Olesinka M, Reed AM, Rutkowska-Sak L, Sanner H, Selva-O'Callaghan A, Wook Song Y, Vencovsky J, Ytterberg SR, Miller FW, Rider LG, Lundberg IE; International Myositis Classification Criteria Project consortium, the Euromyositis register and the Juvenile Dermatomyositis Cohort Biomarker Study and Repository (JDRG) (UK and Ireland) . EULAR/ACR classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups: a methodology report. *RMD Open*. 2017 Nov 14;3(2):e000507. doi: 10.1136/rmdopen-2017-000507. eCollection 2017. PubMed PMID: 29177080; PubMed Central PMCID: PMC5687535.

Assessment of study to study variation in statistical significance in the current replicability crisis.

Increased availability of data and accessibility of computational tools in recent years have created an unprecedented upsurge of scientific studies driven by statistical analysis. Limitations inherent to statistics impose constraints on the reliability of conclusions drawn from data, so misuse of statistical methods is a growing concern. We propose Bayesian intervals for prediction of P-value variability in replication studies which are resistant to selection bias and have endpoints that are directly interpretable as probabilistic bounds for replication P-values. Our

intervals equip researchers with quantitative assessment of what they may expect if they would have repeated their statistical analysis using an independent confirmatory sample.

Vsevolozhskaya O, Ruiz G, Zaykin D. Bayesian prediction intervals for assessing P-value variability in prospective replication studies. *Transl Psychiatry*. 2017 Dec 8;7(12):1271. doi: 10.1038/s41398-017-0024-3. PubMed PMID: 29217835; PubMed Central PMCID: PMC5802740.

A new statistical method to extract biological information from noisy 'omics' data sets
The next-generation DNA sequencing tools are being used to estimate changes in gene expression levels with an unprecedented resolution. However, its high cost limits experimental replicates, which often results in statistically underpowered analysis and poor reproducibility. We developed a new statistical method that combines differential measurements with resolving power that can detect differences in gene expression with high accuracy and reproducibility even when there are only a limited number of replicates.

Lozoya OA, Santos JH, Woychik RP. A Leveraged Signal-to-Noise Ratio (LSTNR) Method to Extract Differentially Expressed Genes and Multivariate Patterns of Expression from Noisy and Low-Replication RNAseq Data. *Front Genet*. 2018 May 16;9:176. doi: 10.3389/fgene.2018.00176. eCollection 2018. PubMed PMID: 29868123; PubMed Central PMCID: PMC5964166.