Division of Intramural Research

NAEHS Council Update

September 2019

DIR RECRUITMENTS

Tenure-Track Investigator in the Clinical Research Branch
The National Institute of Environmental Health Sciences (NIEHS) is recruiting outstanding candidates for a Tenure-Track Investigator position in the Clinical Research Branch within the Division of Intramural Research at the NIEHS in Research Triangle Park, NC. The individual selected for this position will have a strong record of participation and publications in patient-oriented research defined as research that requires direct interactions with human subjects and may include the development of new technologies, understanding mechanisms of human disease, therapeutic interventions and/or clinical trials. The Clinical Research Branch is interested in candidates with expertise in areas such as endocrinology, neuroendocrinology, metabolism, exercise, sleep, immune-mediated diseases, pulmonology and human genetics, among others. Applicants should have an M.D. or equivalent doctoral degree with direct clinical research experience, with three or more years of research training in clinical research and publications and other evidence of the ability to design and carry out original, innovative patient-oriented research. Dr. Alison Motsinger-Reif, Chief of the Biostatistics and Computational Biology Branch serves as chair of the search committee which was launched on July 8, 2019.

Scientific Information Officer
The Division of Intramural Research is seeking an accomplished scientist in information technology to take on a leadership position as the NIEHS Scientific Information Officer (SIO). This individual will head the Office of Scientific Computing (OSC) and will lead a team that is directly focused on scientific information technology. The ideal candidate will have a record of accomplishment in information technology support to a scientific enterprise as well as application to basic and clinical research. Applicants should have a Ph.D., M.D., or equivalent advanced degree. Dr. Charles Schmitt, Director of the Office of Data Science serves as chair of the search committee which was launched on July 11, 2019.

Metabolomics Lead
The Division of Intramural Research of the National Institute of Environmental Health Sciences (NIEHS) is recruiting a Staff Scientist to function as the Metabolomics Lead within the Mass Spectrometry Research and Support Group. We are seeking an experienced scientist with a proven track record to increase the capabilities and capacity of metabolomic studies at NIEHS. The Metabolomics Lead will develop and implement innovative mass spectrometry-based metabolomic analytical methods to support the research needs of NIEHS investigators. The ideal candidate will also have extensive experience developing pipelines for analysis, visualization and interpretation of complex omics data and will work closely with members of the Integrative Bioinformatics Support Group. Dr. Xiaoling Li, Senior Investigator in the Signal Transduction Laboratory serves as chair of the search committee.

NEW HIRES

Deputy Chief of the Signal Transduction Laboratory
Dr. Anant Parekh has accepted an offer to become the Deputy Chief and Senior Investigator in the Signal Transduction Laboratory (STL) in DIR. He is arriving from the University of Oxford (UK) where he is a Professor in the Department of Physiology, Anatomy and Genetics and Director of the Centre for Integrative Physiology. At NIEHS, Dr. Parekh will continue his research program focused on defining molecular mechanisms that control intracellular calcium signaling through plasma membrane store-operated Ca2+ channels and how these calcium signals are altered in human disease. Dr. Parekh was awarded tenure by the NIH Central Tenure Committee on February 28, 2017 and is scheduled to start at NIEHS in October 2019.

New Tenure-Track Investigators
Dr. Marcos Morgan from the MRC Centre for Regenerative Medicine, University of Edinburgh, UK, and the European Bioinformatics Institute, accepted a position to join the Reproductive & Developmental Biology Laboratory as an Earl Stadtman Tenure Track Investigator. Dr. Morgan arrived at NIEHS on June 10, 2019 and will initiate a research program focused on the role of RNA modifications such as uridylation and cytidylation in regulating male fertility.

Dr. Benedict Anchang from the Department of Radiology at Stanford University accepted a position as an Earl Stadtman Tenure Track Investigator in the Biostatistics & Computational Biology Branch with a joint appointment in the NCI Center for Cancer Research. He was also selected as a member of the NIH Distinguished Scholars Program. Dr. Anchang arrived at NIEHS on August 5, 2019 and will initiate an independent research program focused on developing and applying novel and innovative computational models to better understand physiology, tumor progression and responses to environmental exposures using high-dimensional single-cell data.

Dr. Elizabeta Gjoneska from the Picower Institute for Learning and Memory at MIT has accepted an offer to join the Neurobiology Laboratory as a Tenure Track Investigator. Dr. Gjoneska will initiate an independent research program focused on dissecting mechanisms underlying microglial dysfunction during neurodegeneration. She is expected to start at NIEHS in October 2019.

Dr. Jason Watts from the Life Sciences Institute at the University of Michigan has accepted an offer to join the Epigenetics & Stem Cell Biology Laboratory as an Earl Stadtman Tenure Track Investigator. Dr. Watts will initiate an independent research program focused on understanding the mechanism of RNA polymerase pausing and its role in disease. He is expected to start at NIEHS in July 2020.

BSC REVIEW OF THE EPIGENETICS AND STEM CELL BIOLOGY LABORATORY

The NIEHS DIR Board of Scientific Counselors reviewed the Epigenetics and Stem Cell Biology Laboratory, July 28-30, 2019

Members of the Board of Scientific Counselors that Attended:

- Kathleen M. Caron, Ph.D., BSC Chair, Professor and Chair, Department of Cell Biology and Physiology, University of North Carolina at Chapel Hill, Chapel Hill, NC
- Christopher I. Amos, Ph.D., Director, Institute for Clinical and Translational Research, Baylor College of Medicine, Houston, TX
- Sylvie Doublie, Ph.D., Professor, Department of Microbiology and Molecular Genetics, University of Vermont, Burlington, VT
- Jeffrey J. Hayes, Ph.D., Professor and Chair, Department of Biochemistry and Biophysics, Shohei Koide Professor in Biochemistry and Biophysics, University of Rochester School of Medicine, Rochester, NY
- Deanna Kroetz, Ph.D., Professor, Department of Bioengineering and Therapeutic Sciences, University of California, San Francisco School of Pharmacy, San Francisco, CA
- Carol A. Lange, Ph.D., Professor, Departments of Medicine and Pharmacology, University of Minnesota, Minneapolis, MN
- Fernando J. Martinez, M.D., M.S., Chief of Pulmonary and Critical Care Medicine Division, Bruce Webster Professor of Medicine, Weill Cornell Medical Center, New York, NY
- Ivan Rusyn, M.D., Ph.D., Professor, Department of Veterinary Integrative Biosciences, Texas A&M University College of Veterinary Medicine & Biomedical Sciences, College Station, TX
- Daniel Stram, Ph.D., Professor, Department of Preventative Medicine and the Division of Biostatistics and Genetic Epidemiology, Keck School of Medicine, University of Southern California, Los Angeles, CA
- Roland A. Owens, Ph.D., Ex-Officio BSC Member, Assistant Director, Office of Intramural Research, NIH, Bethesda, MD

Ad Hoc Reviewers that Attended:

- Mark T. Bedford, Ph.D., Professor, Department of Epigenetics and Molecular Carcinogenesis, The University of Texas MD Anderson Cancer Center, Smithville, TX
- Hinrich Boeger, Ph.D., Professor of Molecular, Cell & Developmental Biology, University of California, Santa Cruz, Santa Cruz, CA
- Anita H. Corbett, Ph.D., Professor, Department of Biology, Emory University School of Medicine, Atlanta, GA
- John M. Denu, Ph.D., Professor, Department of Biomolecular Chemistry, University of Wisconsin School of Medicine and Public Health, Madison, WI

- Laura Elnitski, Ph.D., Senior Investigator, Translational and Functional Genomics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD
- Elena Ezhkova, Ph. D., Associate Professor, Department of Cell, Developmental & Regenerative Biology, Icahn School of Medicine at Mount Sinai, New York, NY
- P. Lee Ferguson, Ph.D., Associate Professor, Department of Civil & Environmental Engineering, Pratt School of Engineering, Duke University, Durham, NC
- Anthony N. Imbalzano, Ph.D., Professor, Department of Biochemistry and Molecular Pharmacology, University of Massachusetts Medical School, Worcester, MA
- Christina Leslie, Ph.D., Associate Member, Computational Biology Program, Memorial Sloan Kettering Cancer Center, New York, NY
- Joel Parker, Ph.D., Research Associate Professor, Department of Genetics, Lineberger Comprehensive Cancer Center, University of North Carolina School of Medicine, Chapel Hill, NC
- Pamela G. Robey, Ph.D., Senior Investigator, National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD
- William Stanford, Ph.D., Senior Scientist and Professor, Regenerative Medicine Program Ottawa Hospital Research Institute, University of Ottawa, Ottawa, Ontario, Canada
- Jamie Williamson, Ph.D., Professor, Departments of Integrative Structural & Computational and Chemistry, The Scripps Research Institute, La Jolla, CA

Agenda

Sunday, July 28 – Doubletree by Hilton, Durham
Closed Evening Session

7:00 - 8:00 p.m.	Welcome and Discussion of Past Board Reviews, Drs. Linda Birnbaum, Darryl Zeldin and Trevor Archer
8:00 – end	BSC Discussion of Review, Dr. Kathleen Caron and panel

Monday, July 29 - RTP Foundation of NC Headquarters Conference Center
Morning Session

8:30 - 8:45 a.m.	Welcome, Drs. Kathleen Caron and Linda Birnbaum
8:45 - 9:05	Overview, Epigenetics and Stem Cell Biology Laboratory, Trevor Archer, Ph.D.
9:05 - 9:55	Chromatin & Gene Expression Group, Trevor Archer, Ph.D.
9:55 - 10:10	Coffee Break
10:10 - 11:00	Single Cell Dynamics Group, Joseph Rodriguez, Ph.D.
11:00 - 11:50	Macromolecular Structure Group, Traci Hall, Ph.D.
11:50 - 12:35	Closed 1:1 Sessions with Investigators, Drs. Archer, Rodriguez and Hall
12:35 - 1:30	Closed Working Lunch

Afternoon Session

1:30 - 2:20 p.m.	Stem Cell Biology Group, Guang Hu, Ph.D.
2:20 - 3:10	Systems Biology Group, Raja Jothi, Ph.D.
3:10 - 3:30	Coffee Break
3:30 - 4:20	Eukaryotic Transcriptional Regulation Group, Paul Wade, Ph.D.

4:20 - 5:05	Closed 1:1 Sessions with Investigators, Drs. Hu, Jothi and Wade
5:05	Return to Doubletree Hotel, Durham
6:00 – end	Closed BSC Discussion of Review, All BSC reviewers at hotel

Tuesday July 30 - RTP Foundation of NC Headquarters Conference Center
Morning Session

8:30 - 9:30 a.m.	Closed Review of Epigenomics and DNA Sequencing Core Laboratory, Integrative Bioinformatics Support Group and the Mass Spectrometry Research Support Group, Guang Hu, Ph.D., Jian-Liang Li, Ph.D., Leesa J. Deterding, Ph.D. and Jason Williams, Ph.D.
9:30 - 9:45	Coffee Break
9:45 - 11:00	Poster Session with Trainees and Staff Scientists
11:00 - 11:30	Closed Sessions with Trainees and Staff Scientists
11:30 – 12:30 p.m.	Closed BSC Discussion
12:30 - 1:30	Closed Working Lunch
1:30 - 2:30	Closed Debriefing to NIEHS/DIR Leadership
2:30	Adjourn

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 21 FARE award winners:

FARE Awardee	Mentor	Laboratory/Branch
Qing Chen, Ph.D.	Guang Hu, Ph.D.	Epigenetics & Stem Cell Biology Laboratory
Alicia Chi, Ph.D.	Francesco DeMayo, Ph.D.	Reproductive & Developmental Biology Laboratory
Irina Evsyukova, Ph.D.	Patricia Jensen, Ph.D.	Neurobiology Laboratory
Wei Fan, Ph.D.	Xiaoling Li, Ph.D.	Signal Transduction Laboratory
Yi Fang, Ph.D.	Xiaoling Li, Ph.D.	Signal Transduction Laboratory
Symielle Gaston, Ph.D.	Chandra Jackson, Ph.D.	Epidemiology Branch
Chunfang Gu, Ph.D.	Stephen Shears, Ph.D.	Signal Transduction Laboratory
Dhirendra Kumar, Ph.D.	Raja Jothi, Ph.D.	Epigenetics & Stem Cell Biology Laboratory
Xingyao Li, Ph.D.	Stephen Shears, Ph.D.	Signal Transduction Laboratory
Wan-chi Lin, Ph.D.	Michael Fessler, M.D.	Immunity, Inflammation & Disease Laboratory
Yu-Hua Lo, Ph.D.	Robin Stanley, Ph.D.	Signal Transduction Laboratory
Kathleen McCann, Ph.D.	Traci Hall, Ph.D.	Epigenetics & Stem Cell Biology Laboratory

Angelico Mendy, Ph.D.	Darryl Zeldin, M.D.	Immunity, Inflammation & Disease Laboratory
Monica Pillon, Ph.D.	Robin Stanley, Ph.D.	Signal Transduction Laboratory
Prashant Rai, Ph.D.	Michael Fessler, MD	Immunity, Inflammation & Disease Laboratory
Yun-gil Roh, Ph.D.	Anton Jetten, Ph.D.	Immunity, Inflammation & Disease Laboratory
Chitrangda Srivastava, Ph.D.	Anton Jetten, Ph.D.	Immunity, Inflammation & Disease Laboratory
Zhenzhen Wang, Ph.D.	Stephen Shears, Ph.D.	Signal Transduction Laboratory
Hongyao Yu, Ph.D.	Guang Hu, Ph.D.	Epigenetics & Stem Cell Biology Laboratory
Fei Zhao, Ph.D.	Humphrey Yao, Ph.D.	Reproductive & Developmental Biology Laboratory
Jingheng Zhou, Ph.D.	Guohong Cui, Ph.D.	Neurobiology 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 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.

Natale Sciolino, Ph.D. received a K99/R00 award from the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK). Dr. Sciolino will train in the Neurobiology Laboratory under the mentorship of Patricia Jensen, Ph.D.

Joonas Jaemsen, Ph.D. was awarded a K99/R00 from NIEHS and will be mentored by Dr. Sam Wilson in the Genome Integrity and Structural Biology Laboratory.

Natalie Saini, Ph.D. was awarded a K99/R00 from NIEHS and will be mentored by Dr. Dmitry Gordenin in the Genome Integrity and Structural Biology Laboratory.

NIGMS PRAT Fellowship
The National Institute of General Medical Sciences (NIGMS) Postdoctoral Research Associate (PRAT) Program is a competitive postdoctoral fellowship program to pursue research in one of

the laboratories of the National Institutes of Health (NIH) or the Food and Drug Administration (FDA). PRAT is a 3-year program providing outstanding laboratory experiences, access to NIH's extensive resources, mentorship, career development activities and networking. The program places special emphasis on training fellows in all areas supported by NIGMS, including cell biology, biophysics, genetics, developmental biology, pharmacology, physiology, biological chemistry, computational biology, immunology, neuroscience, technology development and bioinformatics.

Elizabeth Martin, Ph.D., a fellow in the Eukaryotic Transcriptional Regulation Group, Epigenetics and Stem Cell Biology Laboratory, was awarded a 2019 PRAT Fellowship from NIGMS. Dr. Martin will be mentored by Dr. Paul Wade.

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 71 summer interns in the NIEHS program (61 in DIR and 10 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 25, 2019 and awards were presented in two categories Undergraduate Interns and Graduate Interns. At the Awards Ceremony, the following awards were presented:

Undergraduate 1st Place (tie):

Haya Jarad
University of Connecticut
Dr. Shepherd Schurman
Clinical Research Branch
"Isolating Zebrafish RMPR Protein"

Natalie Thomas
North Carolina State University
Dr. Tom Kunkel
Dr. Joseph Dahl
Genome Integrity and Structural Biology Laboratory
"Fidelity of DNA Polymerases with Mutations in the Catalytic Active Site"

Undergraduate 2nd Place:

Lily Huo
Massachusetts Institute of Technology
Dr. Guohong Cui
Dr. Chengbo Meng

Neurobiology Laboratory
“Silencing Dopamine Neurons During Sleep as a Novel Treatment for Parkinson’s Disease”

Undergraduate 3rd Place (tie):
Natalie Bell
East Carolina University
Dr. Alison Harrill
Biomolecular Screening Branch, National Toxicology Program
“Optimization of Tissue and RNA Preparation to Facilitate RNA-Seq Analysis of Metabolic Syndrome Biomarkers in a Diversity Outbred Mouse Population”

Nikitha Lanka
University of North Carolina- Charlotte
Dr. Samuel Wilson
Dr. Yesenia Rodriguez
Genome Integrity and Structural Biology Laboratory
“Regulation of AP Endonuclease 1 Incision Activity by PARP1 in Nucleosomal Substrates”

Graduate 1st Place:
Achal Patel
University of North Carolina- Chapel Hill
Dr. Suril Mehta
Office of Report on Carcinogens, National Toxicology Program
“Urinary Polycyclic Aromatic Hydrocarbon Metabolites and Mortality in the United States: National Health and Nutrition Examination Survey (NHANES) 2001-2015”

Graduate 2nd Place:
Joelle Atere-Roberts
University of North Carolina- Chapel Hill
Dr. Chandra Jackson
Dr. Symielle Gaston
Epidemiology Branch
“Racial/Ethnic Discrimination and Type 2 Diabetes Risk among White, Black, and Hispanic/Latina Women: Findings from the Sister Study”

Graduate 3rd Place:
Jennifer Woo
University of Wisconsin-Milwaukee
Dr. Dale Sandler
Epidemiology Branch
“Early Life Traumatic Experiences and Incident Breast Cancer Risk among Adult Women”

DIR RESEARCH ACCOMPLISHMENTS FOR FY 2019

Exposure to artificial light at night (ALAN) while sleeping is associated with weight gain in women

Studies in mice have shown that ALAN affects melatonin signaling and thereby disturbs the sleep-wake cycle, leading to weight gain. A study by NIEHS researchers is the first to describe this association in humans. A total of 43,722 women participating in the Sister Study, a national cohort of women with a sister who had breast cancer, did not have a prior cancer and provided information about different types of ALAN while sleeping when they enrolled in the cohort. Responses were categorized as no light, small nightlight in the room, light outside the room, and light or television on in the room. Women who slept at night in rooms with televisions or other lights on were more likely to have been overweight or obese at the start of the study and were more likely gain weight or become obese during an average 5.7 years of follow-up. Turning off the lights at night may be one more thing people can do for obesity prevention along with eating a healthy diet and maintaining a physically active lifestyle.

Park YM, White AJ, Jackson CL, Weinberg CR, Sandler DP. Association of Exposure to Artificial Light at Night While Sleeping with Risk of Obesity in Women. *JAMA Intern Med*. 2019 Jun 10. doi: 10.1001/jamainternmed.2019.0571. [Epub ahead of print] PubMed PMID: 31180469; PubMed Central PMCID: PMC6563591.

Architecture of a Ribosome Assembly Molecular Motor

The production of ribosomes, the protein making factories or the cell, requires the aid of numerous energy consuming enzymes, such as ATPases. Through a combination of biochemical and structural approaches the NIEHS research team determined how the ribosome assembly AAA-ATPase Rix7 drives ribosome production. The Cryo-EM structure of Rix7 revealed that the two ATP binding domains of Rix7 assemble into stacked hexameric rings. The hexameric rings form a central channel through which substrates are unraveled by successive rounds of ATP hydrolysis.

Lo YH, Sobhany M, Hsu AL, Ford BL, Krahn JM, Borgnia MJ, Stanley RE. Cryo-EM structure of the essential ribosome assembly AAA-ATPase Rix7. *Nat Commun*. 2019 Jan 31;10(1):513. doi: 10.1038/s41467-019-08373-0. PubMed PMID: 30705282; PubMed Central PMCID: PMC6355894.

Two are better than one: Protein domains collaborate to fine tune gene regulation

NIEHS researchers demonstrated a new mechanism of RNA recognition where cooperation between different modules within a single protein alters the specific genes that are controlled. These insights advance our understanding of RNA regulation and can also serve to propel forward greater depth of insight from genomic studies.

Qiu C, Dutcher RC, Porter DF, Arava Y, Wickens M, Hall TMT. Distinct RNA-binding modules in a single PUF protein cooperate to determine RNA specificity. *Nucleic Acids Res.* 2019 Jul 11. pii: gkz583. Doi:10.1093/nar/gkz583. [Epub ahead of print] PubMed PMID: 31294800.

Mutagenesis during the process of double-strand break repair
We were surprised to observe that a double-stranded DNA break repair polymerase (pol), termed pol mu, conducts error-prone gap filling DNA synthesis during double-strand break repair. The article describes important features of the active site of this human DNA repair polymerase that allows it to accommodate the T:G mispair about as well as the normal C:G base pair. These results have implications for understanding mutagenesis during the process of double-strand break repair.

Çağlayan M, Wilson SH. Pol μ dGTP mismatch insertion opposite T coupled with ligation reveals promutagenic DNA repair intermediate. *Nat Commun*. 2018 Oct 11;9(1):4213. doi: 10.1038/s41467-018-06700-5. PubMed PMID: 30310068; PubMed Central PMCID: PMC6181931.

Breast cancer risk is increased in young women after childbirth
Childbirth is widely recognized as protective for breast cancer, but breast cancer risk may be increased shortly after childbirth. NIEHS researchers and collaborators used data from 15 prospective cohort studies in the international Premenopausal Breast Cancer Collaborative Group to evaluate breast cancer risk after childbirth in women under age 55 and determine whether this risk varies with breastfeeding, family history of breast cancer, or specific tumor subtype. During 9.6 million person-years of follow-up, 18,826 incident cases of breast cancer were diagnosed. Compared with women who never had a child, women who had a full-term birth had an increased risk of breast cancer that peaked at 80% greater risk about 5 years after their most recent birth. Childbirth did not become protective for breast cancer until more than 20 years after a birth. This pattern was mostly seen for estrogen receptor positive breast cancer. The increased risk after childbirth was more pronounced among women with a family history of breast cancer and among women who were older at first birth or who have more than one birth. Health care providers should consider recent childbirth a risk factor for breast cancer in young women.

Nichols HB, Schoemaker MJ, Cai J, Xu J, Wright LB, Brook MN, Jones ME, Adami HO, Baglietto L, Bertrand KA, Blot WJ, Boutron-Ruault MC, Dorronsoro M, Dossus L, Eliassen AH, Giles GG, Gram IT, Hankinson SE, Hoffman-Bolton J, Kaaks R, Key TJ, Kitahara CM, Larsson SC, Linet M, Merritt MA, Milne RL, Pala V, Palmer JR, Peeters PH, Riboli E, Sund M, Tamimi RM, Tjønneland A, Trichopoulou A, Ursin G, Vatten L, Visvanathan K, Weiderpass E, Wolk A, Zheng W, Weinberg CR, Swerdlow AJ, Sandler DP. Breast Cancer Risk After Recent Childbirth: A Pooled Analysis of 15 Prospective Studies. *Ann Intern Med.* 2018 Dec 11. doi: 10.7326/M18-1323. [Epub ahead of print] PubMed PMID: 30534999.

Active Site Coordination within a Multienyzme Complex
Precursor ribosomal RNA (rRNA) must be processed by many trans-acting enzymes including the endonuclease Las1 and the kinase Grc3, in a highly coordinated 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. Through a series of atomic resolution cryo-EM structures NIEHS researchers revealed that the Las1

nuclease and Grc3 kinase assemble into butterfly-like structure harboring a composite nuclease active site flanked by discrete RNA kinase sites. Las1 and Grc3 harbor molecular switches that coordinate the enzymatic functions of the complex and promote ribosome production.

Pillon MC,Hsu AL, Krahn JM, Williams JG, Goslen KH, Sobhany M, Borgnia MJ, and Stanley RE. Cryo-EM Reveals Active Site Coordination within a Multienyzme pre-rRNA Processing Complex. 2019, *Nat Struct Mol Biol*, in press

SOX17 regulates the ability of the uterus to support embryo implantation by regulating uterine epithelial gene expression.
The transcription factor Sox17 was ablated in the mouse uterus and the resulting mice were sterile due to failure of embryo implantation. Utilizing whole genome RNA sequencing and protein binding to chromatin identified the regulatory units govern uterine epithelial gene expression. Sox17 regulation is conserved in the human and is altered in uterine diseases such as endometriosis.

Wang X, Li X, Wang T, Wu SP, Jeong JW, Kim TH, et al. SOX17 regulates uterine epithelial-stromal cross-talk acting via a distal enhancer upstream of Ihh. *Nat Commun*. 2018;9(1):4421. Epub 2018/10/26. doi: 10.1038/s41467-018-06652-w. PubMed PMID: 30356064; PubMed Central PMCID: PMCPMC6200785.

FOXO1 regulates embryo implantation in the mouse uterus and is a marker of uterine receptivity.
Foxo1 was ablated in the mouse uterus and the female mice were sterile due to a failure of the uterine epithelium to undergo changes that would allow embryo attachment and penetration of the uterus. Further analysis revealed that in the normal mouse and human uterus FOXO1 protein localizes to the nucleus of the uterine epithelial cells . This nuclear localization is a sign that the uterus is ready for embryo implantation.

Vasquez YM, Wang X, Wetendorf M, Franco HL, Mo Q, Wang T, Lanz RB, Young SL, Lessey BA, Spencer TE, Lydon JP, DeMayo FJ. FOXO1 regulates uterine epithelial integrity and progesterone receptor expression critical for embryo implantation. *PLoS Genet*. 2018 Nov 19;14(11):e1007787. doi: 10.1371/journal.pgen.1007787. eCollection 2018 Nov. PubMed PMID: 30452456; PubMed Central PMCID: PMC6277115.

Imaging reveals DNA wrapping around mitochondrial protein
A collaboration between scientists at NIEHS and North Carolina State University demonstrated that mitochondrial single-stranded DNA binding proteins (mtSSBs) may not always protect single-stranded replication intermediates, which results in improper maintenance of mitochondrial DNA (mtDNA) and metabolic diseases. During DNA replication, DNA strands are separated and become more vulnerable to nuclease attack, chemical modifications, and the binding of inappropriate proteins. Single-stranded DNA binding proteins (SSBs) are believed to safeguard the integrity of mtDNA, protecting it from degradation. The researchers used a recently developed atomic force microscopy (AFM) imaging technique, called Dual-Resonance-frequency-Enhanced Electrostatic force Microscopy (DREEM), to measure surface electric potential differences across mtSSB-DNA complexes. Their results showed that the non-

cooperative wrapping of ssDNA around SSBs during replication could leave the mitochondrial genome vulnerable.

Kaur P, Longley MJ, Pan H, Wang H, Copeland WC. Single-molecule DREEM imaging reveals DNA wrapping around human mitochondrial single-stranded DNA binding protein. *Nucleic Acids Res*. 2018 Nov 30;46(21):11287-11302. doi: 10.1093/nar/gky875. PubMed PMID: 30256971; PubMed Central PMCID: PMC6265486.

JNK1/2 are stress proteins that protect the lung from the development of Squamous Cell Carcinoma.

Utilizing genetically engineered mice we demonstrated that LKB1 ablation resulted in a mouse model for Squamous Cell Carcinoma. Further analysis identified that loss of LKB1 inhibits the activity of the stress kinases Jnk1/2. Inhibition of JNK1/2 promoted cancer development while activation of Jnk1/2 was able to slow down the development of cancer. This shows that JNK1/2 proteins may be a therapeutic target for the treatment of lung cancer.

Liu J, Wang T, Creighton CJ, Wu SP, Ray M, Janardhan KS, Willson CJ, Cho SN, Castro PD, Ittmann MM, Li JL, Davis RJ, DeMayo FJ. JNK(1/2) represses Lkb(1)-deficiency-induced lung squamous cell carcinoma progression. *Nat Commun*. 2019 May 14;10(1):2148. doi: 10.1038/s41467-019-09843-1. PubMed PMID: 31089135; PubMed Central PMCID: PMC6517592.

Identification of a new blood test for patients with severe lung injury

Pneumonia and other severe infections can lead to a life-threatening condition of severe lung damage called acute respiratory distress syndrome (ARDS). Unfortunately, currently, there are no clinically validated blood tests for grading the severity of ARDS and, with it, the prognosis of ARDS patients. In a recent report, NIEHS scientists identified that bloodstream levels of cholestenoic acid, a fat that is thought to be made in the lung, predict survival of ARDS patients as well as the degree of active inflammation in the lung. While further study is needed to validate this finding, this preliminary study suggests that measurement of cholestenoic acid may be a useful guide in the treatment of ARDS patients.

Madenspacher JH, Stapleton RD, Suratt BT, Dixon AE, Lih FB, Lowe JM, Mould KJ, Janssen WJ, Morrell ED, Wurfel MM, Garantziotis S, Tomer KB, Fessler MB. Cholestenoic acid is a prognostic biomarker in acute respiratory distress syndrome. *J Allergy Clin Immunol*. 2019 Jan;143(1):440-442.e8. doi:10.1016/j.jaci.2018.09.017. Epub 2018 Oct 5. PubMed PMID: 30296525; PubMed Central PMCID: PMC6322978.

The brain's stress chemical has surprising effects

Norepinephrine, which is secreted by noradrenergic neurons in the brain, has long been regarded as a stress chemical that triggers anxiety. However, our understanding of the role of norepinephrine in stress-related behaviors is derived from research that focuses primarily on noradrenergic neurons of the locus coeruleus. IRP researchers, led by Patricia Jensen, Ph.D., identified a population of noradrenergic neurons that when activated, mimic the effects of antidepressants by promoting a better coping response to stress and decreasing anxiety-like behavior. These results are in contrast with the general belief that noradrenergic signaling

promotes the stress response. The finding from this study argue that greater caution is needed when interpreting clinical effects of pharmacological compounds that affect noradrenergic signaling and phenotypes resulting from experimental manipulation of the entire noradrenergic system.

Chen YW, Das M, Oyarzabal EA, Cheng Q, Plummer NW, Smith KG, Jones GK, Malawsky D, Yakel JL, Shih YI, Jensen P. Genetic identification of a population of noradrenergic neurons implicated in attenuation of stress-related responses. *Mol Psychiatry*. 2019 May;24(5):710-725. doi: 10.1038/s41380-018-0245-8. Epub 2018 Sep 13. PubMed PMID: 30214043; PubMed Central PMCID: PMC6416086.

Age-related DNA modifications linked to breast cancer risk

A DNA-based measure of biologic age is associated with future development of breast cancer, according to scientists at the National Institutes of Health. For every 5 years that a woman's biologic age was older than her chronological age, she experienced a 15% increase in her chance of developing breast cancer. Researchers determined a woman's biologic age by measuring DNA methylation, a chemical modification to DNA that is part of the normal aging process that can be used as a biologic clock. The study used DNA from blood samples provided by women when they enrolled in the NIEHS-led Sister Study, a prospective cohort of more than 50,000 women in the U.S. and Puerto Rico. Biologic age may be tied to environmental exposures and be a useful index of risk for cancer and other diseases.

Kresovich JK, Xu Z, O'Brien KM, Weinberg CR, Sandler DP, Taylor JA. Methylation-based biological age and breast cancer risk. *J Natl Cancer Inst*. 2019 Feb 22. pii: djz020. doi: 10.1093/jnci/djz020. [Epub ahead of print] PubMed PMID: 30794318.

Corticosteroid receptor balance regulates life and death in cardiomyocytes

Mineralocorticoid receptor (MR) antagonists are effective at treating heart failure. Studies conducted at NIEHS provide new insight into their cardioprotective actions and highlight the importance of the opposing relationship between the MR and the related glucocorticoid receptor (GR) in the response to cardiomyocyte injury. Answering these questions could help address the wider clinical benefits of MR antagonists in heart failure.

Oakley RH, Cruz-Topete D, He B, Foley JF, Myers PH, Xu X, Gomez-Sanchez CE, Chambon P, Willis MS, Cidlowski JA. Cardiomyocyte glucocorticoid and mineralocorticoid receptors directly and antagonistically regulate heart disease in mice. *Sci Signal*. 2019 Apr 16;12(577). pii: eaau9685. doi: 10.1126/scisignal.aau9685. PubMed PMID: 30992401.

Sinus Surgery and Aspirin Sensitivity in AERD Patients

Nasal polyps influence the burden of aspirin exacerbated respiratory disease (AERD) by contributing to eicosanoid production. AERD is diagnosed through graded aspirin challenges. It is not known how sinus surgery affects aspirin challenge outcomes. Our objective was to investigate the effects of endoscopic sinus surgery (ESS) on aspirin-induced reaction severity

and on the levels of eicosanoids associated with these reactions. 28 AERD patients were challenged with aspirin before and 3-4 weeks after ESS. Respiratory parameters and plasma and urine levels of eicosanoids were compared before and after challenges. Before ESS, AERD diagnosis was confirmed in all study patients by aspirin challenges that resulted in hypersensitivity reactions. After ESS, reactions to aspirin were less severe in all patients and twelve out of twenty-eight patients had no obvious reaction. Lack of clinical reaction to aspirin was associated with lower peripheral blood eosinophilia, lower urinary leukotriene E4 levels after aspirin challenge and lower plasma prostaglandin D2 to prostaglandin E2 ratio. We conclude that sinus surgery results in decreased aspirin sensitivity and a decrease in several plasma and urine eicosanoid levels in AERD patients. Diagnostic aspirin challenges should be offered to patients with suspected AERD prior to ESS to increase diagnostic accuracy. Patients with established AERD should undergo aspirin desensitization after ESS as the severity of their aspirin-induced hypersensitivity reactions lessens.

Jerschow E, Edin ML, Chi Y, Hurst B, Abuzeid WM, Akbar NA, Gibber M, Fried MP, Han W, Pelletier T, Ren Z, Keskin T, Roizen G, Lih FB, Gruzdev A, Bradbury JA, Schuster V, Spivack S, Rosenstreich D, Zeldin DC. Sinus Surgery Is Associated with a Decrease in Aspirin-Induced Reaction Severity in Patients with Aspirin Exacerbated Respiratory Disease. *J Allergy Clin Immunol Pract*. 2019 May - Jun;7(5):1580-1588. doi: 10.1016/j.jaip.2018.12.014. Epub 2018 Dec 21. PubMed PMID: 30580047; PubMed Central PMCID: PMC6511299.

NIEHS Sister Study finds possible association between talc and uterine cancer

Using data from 33,609 women enrolled in the Sister Study, scientists at the National Institute of Environmental Health Sciences (NIEHS) saw a positive association between genital talc use and the risk of uterine cancer. The association was stronger among women who reported frequent talc use, compared to those who never used talc or only applied it sometimes. While the findings do not mean that talc use causes uterine cancer, the result is consistent with other studies. Furthermore, the results add support to studies linking talc and ovarian cancer since the powder would need to pass through other reproductive organs including the uterus before reaching the ovaries.

O'Brien KM, D'Aloisio AA, Shi M, Murphy JD, Sandler DP, Weinberg CR. Perineal talc use, douching, and the risk of uterine cancer. *Epidemiology* 2019; doi:10.1097/EDE.0000000000001078. E-pub 29 July 2019.

Eating poultry instead of red meat may help reduce breast cancer incidence

In a study of 42,000 women ages 35-74 from across the US who are enrolled in the Sister Study cohort, researchers found that increasing consumption of red meat was associated with increased risk of invasive breast cancer: women who consumed the highest amount of red meat had a 23% higher risk compared with women who consumed the lowest amount. Conversely, increasing consumption of poultry was associated with a 15% lower risk. Importantly statistical analysis suggested that breast cancer risk could be reduced for women who currently eat red meat and poultry if they replace red meat with poultry in their diets. Substituting poultry for red meat may be a simple change that can help reduce the incidence of breast cancer.

Lo JJ, Park YM, Sinha R, Sandler DP. Association between meat consumption and risk of breast cancer: Findings from the Sister Study. *Int J Cancer*. 2019 Aug 6. doi: 10.1002/ijc.32547. [Epub ahead of print] PubMed PMID: 31389007.

Spatial Regulation of a Human Pre-rRNA Processing Complex

The nucleolus is a sub nucleolar compartment that is the hub of ribosome production. Proteins that participate in the early stages of ribosome production must transit into the nucleolus. Through super-resolution microscopy the NIEHS researchers uncovered the spatial regulation of the Nol9 kinase – Las1 nuclease pre-rRNA processing complex. The polynucleotide kinase Nol9 encodes for a sequence that is responsible for targeting both Nol9 and Las1 for nucleolar localization.

Gordon J, Pillon MC, Stanley RE. Nol9 Is a Spatial Regulator for the Human ITS2 Pre-rRNA Endonuclease-Kinase Complex. *J Mol Biol*. 2019 Jul 6. pii: S0022-2836(19)30430-9. doi: 10.1016/j.jmb.2019.07.007. PubMed PMID: 31288032.

High preconception vitamin D (25-hydroxyvitamin D, 25(OH)D) may increase the probability of pregnancy

In a paper published this year, we found that, compared to women with sufficient vitamin D (25(OH)D of 30-40 ng/ml), women with low vitamin D (<20 ng/ml) had an estimated 45% lower chance of conceiving a pregnancy (CI: -77%, 32%), and women with high vitamin D (at least 50 ng/ml) had an estimated 35% higher probability of conception (CI: -5%, 91%). Across these three categories of vitamin D (25(OH)D of <20ng/ml, 30-40ng/ml, and >50ng/ml), the probability of taking longer than six months to conceive a pregnancy was, respectively, 51% (17%, 74%), 28% (17%, 39%), and 15% (10%, 37%). Our findings are consistent with prior reports of reduced fertility in women with 25(OH)D concentrations below the clinically-defined deficiency level (20 ng/ml). Further studies are needed to evaluate the possible reproductive benefits of considerably higher 25(OH)D concentration (>50 ng/ml).

Jukic AMZ, Baird DD, Weinberg CR, Wilcox AJ, McConnaughey DR, Steiner AZ. Pre-conception 25-hydroxyvitamin D (25(OH)D) and fecundability. *Human Reproduction*, in press.

Association of Ultraviolet Radiation Exposure with Dermatomyositis in a National Myositis Patient Registry

Dermatomyositis has been associated with geospatial differences in ultraviolet (UV) radiation, but further research has been needed on the role of individual determinants of UV exposure prior to diagnosis. We analyzed questionnaire data from 1350 adults in a U.S. national myositis registry (638 with dermatomyositis, 422 with polymyositis, and 290 with inclusion body myositis), examining the likelihood of dermatomyositis compared with polymyositis and inclusion body myositis, in relation to self-reported sunburn history and job- and hobby-related sun exposures in the year prior to diagnosis. We also evaluated the proportion of dermatomyositis by maximum daily ambient UV exposure, based on UV-B erythemal irradiances for participant residence the year prior to diagnosis. We found dermatomyositis, as opposed to polymyositis and inclusion body myositis, was associated with sunburn in the year before diagnosis and with having elevated job- or hobby-related sun exposure. Ambient UV

intensity at the residential location was associated with dermatomyositis in females, but not overall, confirming our prior published findings that suggest a differential effect of UV by gender. These findings suggest that high or moderate personal exposure to intense sunlight is associated with developing dermatomyositis compared with other types of myositis. Taken together, this evidence suggests that personal exposure to environmental ultraviolet radiation may be a modifiable risk factor for dermatomyositis.

Parks CG, Wilkerson J, Rose KM, Faiq A, Noroozi Farhadi P, Long CS, Bayat N, Brunner HI, Goldberg B, McGrath JA, Miller FW, and Rider LG. Association of Ultraviolet Radiation Exposure with Dermatomyositis in a National Myositis Patient Registry. 2019, *Arthritis Care and Research*, in press.

Epidermal Growth Factor signaling regulates MED24, a key regulator of gene transcription in the progression of lung cancer.

Genetically engineered mice were used to investigate the pathways regulating the progression of Non-Small Cell Lung Cancer (NSLC) in mice. Ablation of the tumor suppressor genes Pten and Smad4 in the mouse lung resulted in the development of NSLC in mice in part by activating the Epithermal Growth Factor Signaling (EGF) pathway. Ablation of the EGF receptor ERBB2 attenuated the development of cancer in these mice. Analysis genes regulated by ERBB2 identified the transcriptional regulator MED24 in the regulation of lung cancer. MED24 is a key regulator of gene transcription and may present a therapeutic target for the treatment of lung cancer.

Liu J, Wang T, Willson CJ, Janardhan KS, Wu SP, Li JL, DeMayo FJ. ERBB2 Regulates MED24 during Cancer Progression in Mice with Pten and Smad4 Deletion in the Pulmonary Epithelium. *Cells*. 2019 Jun 19;8(6). pii: E615. doi: 10.3390/cells8060615. PubMed PMID: 31248101; PubMed Central PMCID: PMC6627404.

NIH team discovers crystal structure of the protein SMCHD1.

Mutations in the gene SMCHD1 are associated with two distinct human conditions, congenital arhinia (absent external nose) and a rare form of muscular dystrophy (FSHD type 2). To begin to understand how changes in the SMCHD1 protein may lead to disease, Pedersen and Inoue et al. solved the crystal structure of the end of the protein where most mutations lie. They discovered that this region normally binds to the same region on another copy of the protein (so-called dimerization) and that some disease mutations prevent dimerization.

Pedersen LC, Inoue K, Kim S, Perera L, Shaw ND. A ubiquitin-like domain is required for stabilizing the N-terminal ATPase module of human SMCHD1. *Commun Biol*. 2019 Jul 10;2:255. doi: 10.1038/s42003-019-0499-y. eCollection 2019. PubMed PMID: 31312724; PubMed Central PMCID: PMC6620310.

Unexpected regional differences in mitochondrial function identified from dendritic transcriptomes

RNA localization is one mechanism that neurons use to spatially and temporally regulate gene expression at sites of connections (synapses) but how the dendritic mRNAs in different areas of the brain differ by region is unknown. Here we tested the hypothesis that neurons having distinct

forms of synaptic plasticity will have differences in dendritically localized RNAs. We discovered that each major subregion of the mouse hippocampus expresses a unique complement of dendritic RNAs. Unexpectedly, we uncovered a surprising number of cell type and compartment specific differences related to mitochondrial function. Our results support accumulating evidence that thousands of RNAs are present in neuronal dendrites and extend those findings by identifying over one thousand differentially expressed dendritic RNAs.

Farris S, Ward JM, Carstens KE, Samadi M, Wang Y and Dudek SM. Hippocampal subregions express distinct dendritic transcriptomes that reveal unexpected differences in mitochondrial function in CA2. 2019, *Cell Reports*, in press.

p53-responsive TLR8 SNP enhances human innate immune response to respiratory syncytial virus

We have established that the tumor suppressor p53 plays important physiologic roles in the immune system. p53 upregulates most members of the pathogen sensor Toll-Like Receptor (TLR) family in human cells to consequently enhance TLR-dependent production of proinflammatory cytokines in response to cognate ligands. We reported previously that TLR8 expression was increased directly by the tumor suppressor and transcription factor p53 via a single nucleotide polymorphism (SNP: rs3761624) in the TLR8 promoter, thereby placing TLR8 in the p53/immune axis. TLR8 has an important role in innate immune responses to RNA viral infections including respiratory syncytial virus (RSV). As part of the NIEHS Environmental Polymorphism Registry project, using human primary lymphocytes, p53 induction by chemotherapeutic agents such as ionizing radiation caused TLR8 RNA and protein expression along with p53 binding at the TLR-p53 SNP site in a SNP dependent manner. This differential regulation was associated with SNP-dependent synergistic increases in IL-6 following incubation with an TLR8 ssRNA ligand. In addition, we found a corresponding association of the p53-responsive allele with RSV disease severity in infants hospitalized with RSV infection.
We conclude that p53 can strongly influence TLR8 mediated immune responses and that knowledge of the p53 responsive SNP can inform diagnosis and prognosis of RSV disease and other diseases that might have a TLR8 component, including cancer.

Menéndez D, Snipe J, Marzec J, Innes CL, Polack FP, Caballero M, Schurman SH, Kleeberger SR, Resnick MA. p53-responsive TLR8 SNP enhances human innate immune response to respiratory syncytial virus. 2019, *Journal of Clinical Investigation*, in press.

Quality Control of Quantitative High Throughput Screening Data

Quantitative high throughput screening (qHTS) data from large-scale cell culture experiments contains concentration-response profiles for thousands of compounds tested for a biological activity. Compound potencies derived from qHTS data are used for numerous applications, including toxicological assessment and drug discovery. However, the estimated potency for a single compound can vary considerably in qHTS experiments that produce multiple profiles per compound. We introduce an automated and statistically supported quality control procedure for qHTS data to identify and filter out compounds with “inconsistent” response patterns across multiple runs. By filtering out noisy responses, our approach produces trustworthy potency estimates.

Shockley KR, Gupta S, Harris SF, Lahiri SN, Peddada SD. Quality Control of Quantitative High Throughput Screening Data. *Front Genet*. 2019 May 9;10:387. doi:10.3389/fgene.2019.00387. eCollection 2019. PubMed PMID: 31143201; PubMed Central PMCID: PMC6520559.

Metallic air pollutant exposure is associated with a higher risk of breast cancer
Toxic metals are suspected to act as carcinogens and endocrine disruptors, however their relationship with breast cancer is not well established. In the large prospective Sister Study cohort, we obtained estimated residential airborne metal concentrations from the Environmental Protection Agency's National Air Toxics Database and evaluated the association between airborne metal levels, individually and combined, in relation to breast cancer risk. We observed that women who lived in areas of higher overall airborne exposure to toxic metals were at a higher risk of developing postmenopausal breast cancer and that this association was driven by lead, cadmium and mercury.

White AJ, O'Brien KM, Niehoff NM, Carroll R, Sandler DP. Metallic Air Pollutants and Breast Cancer Risk in a Nationwide Cohort Study. *Epidemiology*. 2019 Jan;30(1):20-28. doi: 10.1097/EDE.0000000000000917. PubMed PMID: 30198937; PubMed Central PMCID: PMC6269205.

Risk of miscarriage begins to increase as women reach their late twenties
It is well known that miscarriage risk increases with women's age. Recent national data from Norway show that this increase begins even as women reach their late twenties, usually regarded as their prime reproductive years. Miscarriage risk is also higher among women whose previous pregnancy ended in a stillbirth, neonatal death, or preterm delivery, suggesting there are shared underlying causes for these reproductive problems.

Magnus MC, Wilcox AJ, Morken NH, Weinberg CR, Håberg SE. Role of maternal age and pregnancy history in risk of miscarriage: prospective register-based study. *BMJ*. 2019 Mar 20;364:l869. doi: 10.1136/bmj.l869. PubMed PMID: 30894356; PubMed Central PMCID: PMC6425455.

Dissecting the roles of DNA polymerases in eukaryotic replication
Studies conducted at NIEHS provide substantial evidence indicating that DNA replication in eukaryotic cells is performed by three of 17 known DNA polymerases, DNA polymerases alpha, delta and epsilon. Among these three polymerases, DNA polymerase delta is the most versatile, being involved in initiating, extending and terminating replication. This basic research has implications for the origin of human diseases, including cancer.

Zhou Z, Lujan SA, Burkholder AB, Garbacz MA and Kunkel TA. Roles for DNA polymerase d in initiating and terminating leading strand replication. 2019, *Nat Commun.*, in press.

Calcium channels that regulate fertilization are identified

At fertilization, calcium enters the egg through calcium channels and this calcium entry is essential for the success of embryo development. Using a mouse model, we identified the two required egg calcium channels. One of these, TRPM7, is blocked by magnesium present in the culture medium. These findings provide guidance on the design of optimal culture media for successful fertilization and embryo development during human assisted reproduction procedures.

Bernhardt ML, Stein P, Carvacho I, Krapp C, Ardestani G, Mehregan A, Umbach DM, Bartolomei MS, Fissore RA, Williams CJ. TRPM7 and $Ca_V3.2$ channels mediate Ca^{2+} influx required for egg activation at fertilization. *Proc Natl Acad Sci U S A*. 2018 Oct 30;115(44):E10370-E10378. doi: 10.1073/pnas.1810422115. Epub 2018 Oct 15. PubMed PMID: 30322909; PubMed Central PMCID: PMC6217414.

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. 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 demonstrated the important role of the 5'-deoxynucleoside-triphosphates (dNTPs), which are the building blocks used by the polymerases for synthesizing DNA.

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.

Makiela-Dzbenska K, Maslowska KH, Kuban W, Gawel D, Jonczyk P, Schaaper RM, Fijalkowska IJ. Replication fidelity in *E. coli*: Differential leading and lagging strand effects for dnaE antimutator alleles. *DNA Repair* (Amst). 2019 Jul 4:102643. doi: 10.1016/j.dnarep.2019.102643. [Epub ahead of print] PubMed PMID: 31324532.

Kozmin SG, Rogozin IB, Moore EA, Abbney M, Schaaper RM and Pavlov YI. 6-N-hydroxylaminopurine nucleotide is responsible for the toxic and mutagenic effects of the antineoplastic Staphylococcus epidermidis strain MO34. 2019, *Sci Adv.*, in press.

The sunshine vitamin may protect you from breast cancer

Using data from the Sister Study, investigators at NIEHS studied breast cancer risk in women who each had a sister formerly diagnosed with breast cancer. Women with higher serum levels of vitamin D at enrollment had lower rates of breast cancer, based on the first 5 years of follow up. There was also an apparently protective effect of taking vitamin D supplements.

O'Brien KM, Sandler DP, House M, Taylor JA, Weinberg CR. The Association of a Breast Cancer Diagnosis with Serum 25-Hydroxyvitamin D Concentration Over Time. *Am J*

Epidemiol. 2019 Apr 1;188(4):637-645. doi: 10.1093/aje/kwy285. PubMed PMID:30608512; PubMed Central PMCID: PMC6454838.

Adherence to NAEPP Guidelines Among Primary Care Providers

Although primary care clinicians provide >60% of U.S. asthma care, no nationally representative study has examined variation in adherence among primary care groups to four cornerstone domains of the Expert Panel Report-3 asthma guidelines: assessment/monitoring, patient education, environmental assessment, and medications. We used the 2012 National Asthma Survey of Physicians: National Ambulatory Medical Care Survey to compare adherence by family/general medicine practitioners (FM/GM), internists, pediatricians and Community Health Center mid-level clinicians (CHC). Adherence was self-reported. Adjusted odds of almost always adhering to each recommendation (≥75% of the time) were estimated controlling for clinician/practice characteristics, and agreement and self-efficacy with guideline recommendations. A higher percentage of pediatricians adhered to most assessment/monitoring recommendations compared to FM/GM and other groups but low percentages from all groups almost always performed spirometry. Pediatricians were more likely to provide asthma action/treatment plans than FM/GM and internists. Internists were more likely to assess school/work triggers than pediatricians and CHC. All groups prescribed inhaled corticosteroids for daily control. In adjusted analyses, pediatric specialty, high self-efficacy and frequent specialist referral were associated with high adherence. In conclusion, pediatricians were more likely to report high adherence than other clinicians. Self-efficacy and frequent referral were also associated with adherence. Adherence was higher for history-taking recommendations and lower for recommendations involving patient education, equipment and expertise.

Akinbami LJ, Salo PM, Cloutier MM, Wilkerson JC, Elward KS, Mazurek JM, Williams S, Zeldin DC. Primary care clinician adherence with asthma guidelines: the National Asthma Survey of Physicians. *J Asthma*. 2019 Mar 1:1-13. doi: 10.1080/02770903.2019.1579831. [Epub ahead of print] PubMed PMID: 30821526.

Influence of Exposure to Endotoxin and Ambient Air Pollution in Asthma Morbidity

Endotoxin is a lipopolysaccharide on the cell wall of gram-negative bacteria known to cause bronchial asthma and asthma-like symptoms. Ambient air pollutants exacerbate existing asthma and may contribute to causing the disease. In-vitro and animal studies suggest that co-exposure to residential endotoxin and ambient air pollutants may have effects on the respiratory system worse than the sum of the individual exposures' effects. We examined the synergistic association of co-exposure to house dust endotoxin and ambient air pollution with asthma outcomes in a nationwide study including both children and adults. We demonstrated that co-exposure to elevated levels of endotoxin and particulate matter ≤2.5 μm (PM2.5) was synergistically associated with more ER visits for asthma in the past 12 months in all participants, especially children, and individuals sensitized to inhalant allergens. In children, co-exposure to higher concentrations of endotoxin and nitrogen dioxide (NO2) was also synergistically associated with the outcome. Therefore, comprehensive measures to decrease both residential endotoxin and ambient air pollution exposures might be more effective than interventions targeting a single exposure at reducing asthma morbidity.

Mendy A, Wilkerson J, Salo PM, Weir CH, Feinstein L, Zeldin DC, Thorne PS. Synergistic Association of House Endotoxin Exposure and Ambient Air Pollution with Asthma Outcomes. *Am J Respir Crit Care Med*. 2019 Apr 9. doi: 10.1164/rccm.201809-1733OC. [Epub ahead of print] PubMed PMID: 30965018.