Division of Intramural Research

NAEHS Council Update

February 2020

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 which was launched on February 12, 2019.

Recruitment of 2019-20 NIH Earl Stadtman Investigator Finalists
In addition to targeted recruitment, DIR is actively seeking outstanding scientists through the central NIH Stadtman recruitment mechanism. Seven outstanding candidates from a range of disciplines central to the NIEHS mission were identified from the Stadtman finalists for on-site interviews in January and February 2020.

NEW APPOINTMENTS IN DIR

Deputy Chief of the Signal Transduction Laboratory
Dr. Anant Parekh was appointed Deputy Chief and Senior Investigator in the Signal Transduction Laboratory (STL) in DIR on December 8, 2019. He was previously at the University of Oxford (UK) where he was 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 calcium channels and how these signals are altered in human disease.

New Tenure-Track Investigators
Dr. Elizabeta Gjoneska from the Picower Institute for Learning and Memory at MIT joined the Neurobiology Laboratory as a Tenure Track Investigator on October 27, 2019. At NIEHS, Dr. Gjoneska will initiate an independent research program focused on dissecting mechanisms underlying microglial dysfunction during neurodegeneration.

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 IMMUNITY, INFLAMMATION AND DISEASE LABORATORY

The NIEHS DIR Board of Scientific Counselors reviewed the Immunity, Inflammation and Disease Laboratory, November 17-19, 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
- Sarah K. England, Ph. D., Professor, Department of Obstetrics and Gynecology at the Washington University School of Medicine, St. Louis, MO
- 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:

- John B. Buse, M.D., Ph.D., Chief, Division of Endocrinology and Verne S. Caviness Distinguished Professor, Director, NC Translational and Clinical Sciences Institute at the University of North Carolina School of Medicine, Chapel Hill, NC
- Julie Magarian Blander, Ph.D., Professor of Microbiology and Immunology and the Jill Roberts Institute for Research in Inflammatory Bowel Disease at Weill Cornell School of Medicine, New York, NY
- Jia Chen, ScD, Professor in the Departments of Environmental Medicine and Public Health, Pediatrics & Oncological Sciences at the Icahn School of Medicine at Mount Sinai, New York, NY

- Gregory P. Downey, M.D., Professor and Executive Vice President for Academic Affairs, the Division of Pulmonary, Critical Care & Sleep Medicine at National Jewish Health and the University of Colorado, Denver, CO
- Rodney J. Folz, M.D., Ph.D., Chief, Division of Pulmonary, Critical Care and Sleep Medicine and Director, Respiratory Health Institute and Inkley Chair and Professor of Medicine at Case Western Reserve University School of Medicine, Cleveland, OH
- Maureen A. Gannon, Ph.D., Professor of Medicine and the Division of Diabetes, Endocrinology, & Metabolism at the Vanderbilt University Medical Center, Nashville, TN
- Diane R. Gold, D.T.M.&H., M.D., Professor of Environmental Health and the Harvard T.H. Chan, School of Public Health and Professor of Medicine, Harvard Medical School and Brigham & Women's Hospital, Boston, MA
- Cory Hogaboam, Ph.D., Professor of Medicine and the Women's Guild Lung Institute at Cedars Sinai Medical Center, Los Angeles, CA
- Adam Lacy-Hulbert, Ph.D., Associate Member at the Benaroya Research Institute at Virginia Mason and Affiliate Associate Professor in the Department of Immunology at the University of Washington, Seattle, WA
- Nancie Jo MacIver, M.D., Ph.D., Associate Professor of Pediatrics and Director, Duke Scholars in Molecular Medicine and the Departments of Pediatrics, Immunology, Pharmacology & Cancer Biology at the Duke University School of Medicine, Durham, NC
- Carmen J. Marsit, Ph.D., Professor in the Department of Environmental Health at the Rollins School of Public Health at Emory University, Atlanta, GA
- Barbara Methe, Ph.D., Visiting Professor of Medicine and Co-Director for Basic Sciences in the Division of Pulmonary, Allergy and Critical Care Medicine at the University of Pittsburgh School of Medicine, Pittsburgh, PA
- Rachel L. Miller, M.D., FAAAAI, the Merksamer Professor in Immunology and Chief, Division of Clinical Immunology in the Department of Medicine at the Icahn School of Medicine at Mount Sinai, New York, NY
- Kenneth M. Rice, Ph.D., Professor, Department of Biostatistics at the University of Washington, Seattle, WA
- Anne I. Sperling, Ph.D., Professor of Medicine and Associate Vice Chair for Research in the Department of Medicine at The University of Chicago School of Medicine, Chicago, IL
- Lori Sussel, Ph.D., Professor of Pediatrics and Director, Basic & Translational Research at the University of Colorado School of Medicine, Aurora, CO
- Suzanne J. Wingate, Ph.D., R.N., A.N.P-B.C., Clinical Director, Division of Intramural Research, National Institute of Nursing Research, National Institutes of Health, Bethesda, MD
- Steven F. Ziegler, Ph.D., Director, Academic Affairs and Immunology Research at the Benaroya Research Institute at Virginia Mason at the University of Washington, Seattle, WA

Agenda

Sunday, November 17 – Hyatt Place, Durham
Closed Evening Session

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

Monday, November 18 - 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, Immunity, Inflammation and Disease Laboratory, Michael Fessler, M.D.
9:05 - 9:55	Clinical Investigation of Host Defense Group, Michael Fessler, M.D.
9:55 - 10:10	Coffee Break
10:10 - 11:00	Cell Biology Group, Anton Jetten, Ph.D.
11:00 - 11:50	Environmental Cardiopulmonary Disease Group, Darryl Zeldin, M.D.
11:50 - 12:35	Closed 1:1 Sessions with Investigators, Drs. Fessler, Jetten and Zeldin
12:35 - 1:30	Closed Working Lunch

Afternoon Session

1:30 - 3:00 p.m.	Poster Session - IIDL Fellows and Staff Scientists
3:00 - 3:30	Closed Sessions with Trainees and Staff Scientists
3:30 - 3:45	Coffee Break
3:45 - 4:35	Environmental Epigenomics & Disease Group, Douglas Bell, Ph.D.
4:35 - 4:55	Closed 1:1 Sessions with Investigator, Dr. Bell
4:55	Return to Hyatt Place Hotel, Durham
7:00 – end	Closed BSC Discussion and completion of individual review assignments by each member, All BSC reviewers at hotel

Tuesday November 19 - RTP Foundation of NC Headquarters Conference Center
Morning Session

8:30 - 9:20 a.m.	Immunogenetics Group, Donald Cook, Ph.D.
8:30 - 9:20	Inflammation & Autoimmunity Group, Jennifer Martinez, Ph.D.
10:10-10:40	Closed 1:1 Sessions with Investigators, Drs. Cook and Martinez
10:40 - 10:55	Coffee Break
10:55 - 11:45	Matrix Biology Group, Stavros Garantziotis, M.D.
11:45 - 12:35 p.m.	Environmental Genetics Group, Steven Kleeberger, Ph.D.
12:35 - 1:35	Closed Working Lunch
1:35 - 2:00	Closed 1:1 Session with Investigator, Dr. Stavros Garantziotis
2:00 - 2:30	Poster Session - Review of Clinical Research Unit and the Environmental Polymorphisms Registry

2:30 - 3:00	Closed 1:1 Session with Clinical Research Unit and Environmental Polymorphisms Registry Leadership, Dr. Janet Hall
3:00 - 4:00	Closed BSC Discussion and completion of individual review assignments by each member
4:00 - 5:30	Closed Session and Debriefing to NIEHS/DIR Leadership
5:30	Adjourn – Shuttle to RDU Airport

NIEHS SCIENCE DAYS

The Seventeenth Annual NIEHS Science Days were held on November 7-8, 2019 with the events of November 7th held in the EPA Auditorium and the events of November 8th held in the Rall Building on the NIEHS Campus. This "One NIEHS" event is held annually to celebrate the achievements of NIEHS scientists from all of our Divisions. The event was open to the public with at least 250 attendees. The NIEHS Science Days program consisted of 10 oral presentations given by fellows, students, and technicians, 87 poster presentations and a grant writing workshop. Judging for the awards was done by extramural scientists from several universities and research organizations located across North Carolina, NIEHS Intramural Scientists and the NIEHS Trainees Assembly.

Mentor of the Year: Robin E. Stanley, Ph.D., Signal Transduction Laboratory
Fellow of the Year: Fei Zhao, Ph.D., Reproductive and Developmental Biology Laboratory
Best Poster Presentation by a Fellow or Technician:

1. Jacob Gordon, Nucleolar Integrity Group, Signal Transduction Laboratory
2. Daisy Lo, Ph.D., Nucleolar Integrity Group, Signal Transduction Laboratory
3. Monica Pillon, Nucleolar Integrity Group, Signal Transduction Laboratory
4. Fei Zhao, Ph.D., Reproductive Developmental Biology Group, Reproductive & Developmental Biology Laboratory
5. Cassandra Hayne, Ph.D., Nucleolar Integrity Group, Signal Transduction Laboratory
6. Olivia Emery, Pregnancy & Female Reproduction Group, Reproductive & Developmental Biology Laboratory
7. Brad Klemm, Ph.D., Mechanisms of Mutation Group, Genome Integrity & Structural Biology Laboratory
8. Brad Lackford, Stem Cell Biology Group, Epigenetics & Stem Cell Biology Laboratory
9. Oswaldo Lozoya, Ph.D., Environmental Epigenomics & Disease Group, Immunity, Inflammation & Disease Laboratory

Best Poster Presentation by a Postbaccalaureate Student: Jacob Gordon, Nucleolar Integrity Group, Signal Transduction Laboratory
Best Oral Presentation: Jonathan Busada, Ph.D., Molecular Endocrinology Group, Signal Transduction Laboratory

DIR PAPERS OF THE YEAR FOR 2019

Busada JT, Ramamoorthy S, Cain DW, Xu X, Cook DN, Cidlowski JA. Endogenous glucocorticoids prevent gastric metaplasia by suppressing spontaneous inflammation. *J Clin Invest*. 2019 Mar 1;129(3):1345-1358. doi: 10.1172/JCI123233. Epub 2019 Feb 18. PubMed PMID: 30652972; PubMed Central PMCID: PMC6391099.

> In the stomach, chronic inflammation causes metaplasia and creates a favorable environment for the evolution of gastric cancer. Glucocorticoids are steroid hormones that repress proinflammatory stimuli, but their role in the stomach is unknown. In this study, we show that endogenous glucocorticoids are required to maintain gastric homeostasis. Removal of circulating glucocorticoids in mice by adrenalectomy resulted in the rapid onset of spontaneous gastric inflammation, oxyntic atrophy, and spasmolytic polypeptide-expressing metaplasia (SPEM), a putative precursor of gastric cancer. SPEM and oxyntic atrophy occurred independently of lymphocytes. However, depletion of monocytes and macrophages by clodronate treatment or inhibition of gastric monocyte infiltration using the Cx3cr1 knockout mouse model prevented SPEM development. Our results highlight the requirement for endogenous glucocorticoid signaling within the stomach to prevent spontaneous gastric inflammation and metaplasia, and suggest that glucocorticoid deficiency may lead to gastric cancer development.

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.

> Rix7 is an essential type II AAA-ATPase required for the formation of the large ribosomal subunit. Rix7 has been proposed to utilize the power of ATP hydrolysis to drive the removal of assembly factors from pre-60S particles, but the mechanism of release is unknown. Rix7's mammalian homolog, NVL2 has been linked to cancer and mental illness disorders, highlighting the need to understand the molecular mechanisms of this essential machine. Here we report the cryo-EM reconstruction of the tandem AAA domains of Rix7 which form an asymmetric stacked homohexameric ring. We trapped Rix7 with a polypeptide in the central channel, revealing Rix7's role as a molecular unfoldase. The structure establishes that type II AAA-ATPases lacking the aromatic-hydrophobic motif within the first AAA domain can engage a substrate throughout the entire central channel. The structure also reveals that Rix7 contains unique post-α7 insertions within both AAA domains important for Rix7 function.

Grimm SA, Shimbo T, Takaku M, Thomas JW, Auerbach S, Bennett BD, Bucher JR, Burkholder AB, Day F, Du Y, Duncan CG, French JE, Foley JF, Li J, Merrick BA, Tice RR, Wang T, Xu X; NISC Comparative Sequencing Program, Bushel PR, Fargo DC, Mullikin JC, Wade PA. DNA methylation in mice is influenced by genetics as well as sex and life experience. *Nat Commun*. 2019 Jan 18;10(1):305. doi: 10.1038/s41467-018-08067-z. PubMed PMID: 30659182; PubMed Central PMCID: PMC6338756.

DNA methylation is an essential epigenetic process in mammals, intimately involved in gene regulation. Here we address the extent to which genetics, sex, and pregnancy influence genomic DNA methylation by intercrossing 2 inbred mouse strains, C57BL/6N and C3H/HeN, and analyzing DNA methylation in parents and offspring using whole-genome bisulfite sequencing. Differential methylation across genotype is detected at thousands of loci and is preserved on parental alleles in offspring. In comparison of autosomal DNA methylation patterns across sex, hundreds of differentially methylated regions are detected. Comparison of animals with different histories of pregnancy within our study reveals a CpG methylation pattern that is restricted to female animals that had borne offspring. Collectively, our results demonstrate the stability of CpG methylation across generations, clarify the interplay of epigenetics with genetics and sex, and suggest that CpG methylation may serve as an epigenetic record of life events in somatic tissues at loci whose expression is linked to the relevant biology.

Xu Z, Sandler DP, Taylor JA. Blood DNA Methylation and Breast Cancer: A Prospective Case-Cohort Analysis in the Sister Study. *J Natl Cancer Inst*. 2020 Jan 1;112(1):87-94. doi: 10.1093/jnci/djz065. PubMed PMID: 30989176.

BACKGROUND: Peripheral blood DNA methylation may be associated with breast cancer, but studies of candidate genes and global and genome-wide DNA methylation have been inconsistent.
METHODS: We performed an epigenome-wide study using Infinium HumanMethylation450 BeadChips with prospectively collected blood DNA samples from the Sister Study (1552 cases, 1224 subcohort). Differentially methylated cytosine-phosphate-guanine sites (dmCpGs) were identified using case-cohort proportional hazard models and replicated using deposited data from European Prospective Investigation into Cancer and Nutrition in Italy (EPIC-Italy) (n = 329). The correlation between methylation and time to diagnosis was examined using robust linear regression. Causal or consequential relationships of methylation to breast cancer were examined by Mendelian randomization using OncoArray 500 K single-nucleotide polymorphism data. All statistical tests were two-sided.
RESULTS: We identified 9601 CpG markers associated with invasive breast cancer (false discovery rate = $q < 0.01$), with 510 meeting a strict Bonferroni correction threshold (10-7). A total of 2095 of these CpGs replicated in the independent EPIC-Italy dataset, including 144 meeting the Bonferroni threshold. Sister Study women who developed ductal carcinoma in situ had methylation similar to noncases. Most (1501, 71.6%) dmCpGs showed lower methylation in invasive cases. In case-only analysis, methylation was statistically significantly associated (false discovery rate = $q < 0.05$) with time to diagnosis for 892 (42.6%) of the dmCpGs. Analyses based on genetic association suggest that methylation differences are likely a consequence rather than a cause of breast cancer. Pathway analysis shows enrichment of breast cancer-related gene pathways, and dmCpGs are overrepresented in known breast cancer susceptibility genes.
CONCLUSIONS: Our findings suggest that the DNA methylation profile of blood starts to change in response to invasive breast cancer years before the tumor is clinically detected.

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.

Mechanisms of lung squamous cell carcinoma (LSCC) development are poorly understood. Here, we report that JNK1/2 activities attenuate Lkb1-deficiency-driven LSCC initiation and progression through repressing ΔNp63 signaling. In vivo Lkb1 ablation alone is sufficient to induce LSCC development by reducing MKK7 levels and JNK1/2 activities, independent of the AMPKα and mTOR pathways. JNK1/2 activities are positively regulated by MKK7 during LSCC development. Pharmaceutically elevated JNK1/2 activities abates Lkb1 dependent LSCC formation while compound mutations of Jnk1/2 and Lkb1 further accelerate LSCC progression. JNK1/2 is inactivated in a substantial proportion of human LSCC and JNK1/2 activities positively correlates with survival rates of lung, cervical and head and neck squamous cell carcinoma patients. These findings not only determine a suppressive role of the stress response regulators JNK1/2 on LSCC development by acting downstream of the key LSCC suppresser Lkb1, but also demonstrate activating JNK1/2 activities as a therapeutic approach against LSCC.

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.

IMPORTANCE: Short sleep has been associated with obesity, but to date the association between exposure to artificial light at night (ALAN) while sleeping and obesity is unknown.
OBJECTIVE: To determine whether ALAN exposure while sleeping is associated with the prevalence and risk of obesity.
DESIGN, SETTING, AND PARTICIPANTS: This baseline and prospective analysis included women aged 35 to 74 years enrolled in the Sister Study in all 50 US states and Puerto Rico from July 2003 through March 2009. Follow-up was completed on August 14, 2015. A total of 43 722 women with no history of cancer or cardiovascular disease who were not shift workers, daytime sleepers, or pregnant at baseline were included in the analysis. Data were analyzed from September 1, 2017, through December 31, 2018.
EXPOSURES: Artificial light at night while sleeping reported at enrollment, categorized as no light, small nightlight in the room, light outside the room, and light or television in the room.
MAIN OUTCOMES AND MEASURES: Prevalent obesity at baseline was based on measured general obesity (body mass index [BMI] ≥30.0) and central obesity (waist circumference [WC] ≥88 cm, waist-to-hip ratio [WHR] ≥0.85, or waist-to-height ratio [WHtR]≥0.5). To evaluate incident overweight and obesity, self-reported BMI at enrollment was compared with self-reported BMI at follow-up (mean [SD] follow-up, 5.7 [1.0] years). Generalized log-linear models with robust error variance were used to estimate multivariable-adjusted prevalence ratios (PRs) and relative risks (RRs) with 95% CIs for prevalent and incident obesity.

RESULTS: Among the population of 43 722 women (mean [SD] age, 55.4 [8.9] years), having any ALAN exposure while sleeping was positively associated with a higher prevalence of obesity at baseline, as measured using BMI (PR, 1.03; 95% CI, 1.02-1.03), WC (PR, 1.12; 95% CI, 1.09-1.16), WHR (PR, 1.04; 95% CI, 1.00-1.08), and WHtR (PR, 1.07; 95% CI, 1.04-1.09), after adjusting for confounding factors, with $P < .001$ for trend for each measure. Having any ALAN exposure while sleeping was also associated with incident obesity (RR, 1.19; 95% CI, 1.06-1.34). Compared with no ALAN, sleeping with a television or a light on in the room was associated with gaining 5 kg or more (RR, 1.17; 95% CI, 1.08-1.27; $P < .001$ for trend), a BMI increase of 10% or more (RR, 1.13; 95% CI, 1.02-1.26; $P = .04$ for trend), incident overweight (RR, 1.22; 95% CI,1.06-1.40; $P = .03$ for trend), and incident obesity (RR, 1.33; 95% CI, 1.13-1.57; $P < .001$ for trend). Results were supported by sensitivity analyses and additional multivariable analyses including potential mediators such as sleep duration and quality, diet, and physical activity.
CONCLUSIONS AND RELEVANCE: These results suggest that exposure to ALAN while sleeping may be a risk factor for weight gain and development of overweight or obesity. Further prospective and interventional studies could help elucidate this association and clarify whether lowering exposure to ALAN while sleeping can promote obesity prevention.

Reese SE, Xu CJ, den Dekker HT, Lee MK, Sikdar S, Ruiz-Arenas C, Merid SK, Rezwan FI, Page CM, Ullemar V, Melton PE, Oh SS, Yang IV, Burrows K, Söderhäll C, Jima DD, Gao L, Arathimos R, Küpers LK, Wielscher M, Rzehak P, Lahti J, Laprise C, Madore AM, Ward J, Bennett BD, Wang T, Bell DA; BIOS consortium, Vonk JM, Håberg SE, Zhao S, Karlsson R, Hollams E, Hu D, Richards AJ, Bergström A, Sharp GC, Felix JF, Bustamante M, Gruzieva O, Maguire RL, Gilliland F, Baïz N, Nohr EA, Corpeleijn E, Sebert S, Karmaus W, Grote V, Kajantie E, Magnus MC, Örtqvist AK, Eng C, Liu AH, Kull I, Jaddoe VWV, Sunyer J, Kere J, Hoyo C, Annesi-Maesano I, Arshad SH, Koletzko B, Brunekreef B, Binder EB, Räikkönen K, Reischl E, Holloway JW, Jarvelin MR, Snieder H, Kazmi N, Breton CV, Murphy SK, Pershagen G, Anto JM, Relton CL, Schwartz DA, Burchard EG, Huang RC, Nystad W, Almqvist C, Henderson AJ, Melén E, Duijts L, Koppelman GH, London SJ. Epigenome-wide meta-analysis of DNA methylation and childhood asthma. *J Allergy Clin Immunol*. 2019 Jun;143(6):2062-2074. doi: 10.1016/j.jaci.2018.11.043. Epub 2018 Dec 21. PubMed PMID: 30579849; PubMed Central PMCID: PMC6556405.

BACKGROUND: Epigenetic mechanisms, including methylation, can contribute to childhood asthma. Identifying DNA methylation profiles in asthmatic patients can inform disease pathogenesis.
OBJECTIVE: We sought to identify differential DNA methylation in newborns and children related to childhood asthma.
METHODS: Within the Pregnancy And Childhood Epigenetics consortium, we performed epigenome-wide meta-analyses of school-age asthma in relation to CpG methylation (Illumina450K) in blood measured either in newborns, in prospective analyses, or cross-sectionally in school-aged children. We also identified differentially methylated regions.
RESULTS: In newborns (8 cohorts, 668 cases), 9 CpGs (and 35 regions) were differentially methylated (epigenome-wide significance, false discovery rate < 0.05) in relation to asthma development. In a cross-sectional meta-analysis of asthma and methylation in children (9 cohorts, 631 cases), we identified 179 CpGs (false discovery rate < 0.05) and 36

differentially methylated regions. In replication studies of methylation in other tissues, most of the 179 CpGs discovered in blood replicated, despite smaller sample sizes, in studies of nasal respiratory epithelium or eosinophils. Pathway analyses highlighted enrichment for asthma-relevant immune processes and overlap in pathways enriched both in newborns and children. Gene expression correlated with methylation at most loci. Functional annotation supports a regulatory effect on gene expression at many asthma-associated CpGs. Several implicated genes are targets for approved or experimental drugs, including IL5RA and KCNH2.
CONCLUSION: Novel loci differentially methylated in newborns represent potential biomarkers of risk of asthma by school age. Cross-sectional associations in children can reflect both risk for and effects of disease. Asthma-related differential methylation in blood in children was substantially replicated in eosinophils and respiratory epithelium.

Oldfield AJ, Henriques T, Kumar D, Burkholder AB, Cinghu S, Paulet D, Bennett BD, Yang P, Scruggs BS, Lavender CA, Rivals E, Adelman K, Jothi R. NF-Y controls fidelity of transcription initiation at gene promoters through maintenance of the nucleosome-depleted region. *Nat Commun.* 2019 Jul 11;10(1):3072. doi: 10.1038/s41467-019-10905-7. PubMed PMID: 31296853; PubMed Central PMCID: PMC6624317.

Faithful transcription initiation is critical for accurate gene expression, yet the mechanisms underlying specific transcription start site (TSS) selection in mammals remain unclear. Here, we show that the histone-fold domain protein NF-Y, a ubiquitously expressed transcription factor, controls the fidelity of transcription initiation at gene promoters in mouse embryonic stem cells. We report that NF-Y maintains the region upstream of TSSs in a nucleosome-depleted state while simultaneously protecting this accessible region against aberrant and/or ectopic transcription initiation. We find that loss of NF-Y binding in mammalian cells disrupts the promoter chromatin landscape, leading to nucleosomal encroachment over the canonical TSS. Importantly, this chromatin rearrangement is accompanied by upstream relocation of the transcription pre-initiation complex and ectopic transcription initiation. Further, this phenomenon generates aberrant extended transcripts that undergo translation, disrupting gene expression profiles. These results suggest NF-Y is a central player in TSS selection in metazoans and highlight the deleterious consequences of inaccurate transcription initiation.

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 Sep 19;47(16):8770-8784. doi: 10.1093/nar/gkz583. PubMed PMID: 31294800.

> PUF proteins, named for Drosophila Pumilio (PUM) and Caenorhabditis elegans fem-3-binding factor (FBF), recognize specific sequences in the mRNAs they bind and control. RNA binding by classical PUF proteins is mediated by a characteristic PUM homology domain (PUM-HD). The Puf1 and Puf2 proteins possess a distinct architecture and comprise a highly conserved subfamily among fungal species. Puf1/Puf2 proteins contain two types of RNA-binding domain: a divergent PUM-HD and an RNA recognition motif (RRM). They recognize RNAs containing UAAU motifs, often in clusters. Here, we report a crystal structure of the PUM-HD of a fungal Puf1 in complex with a dual UAAU motif RNA. Each of the two UAAU tetranucleotides are bound by a Puf1 PUM-HD forming a 2:1 protein-to-RNA complex. We also determined crystal structures of the Puf1 RRM domain that identified a dimerization interface. The PUM-HD and RRM domains act in concert to determine RNA-binding specificity: the PUM-HD dictates binding to UAAU, and dimerization of the RRM domain favors binding to dual UAAU motifs rather than a single UAAU. Cooperative action of the RRM and PUM-HD identifies a new mechanism by which multiple RNA-binding modules in a single protein collaborate to create a unique RNA-binding specificity.

Zhou ZX, Lujan SA, Burkholder AB, Garbacz MA, Kunkel TA. Roles for DNA polymerase δ in initiating and terminating leading strand DNA replication. *Nat Commun*. 2019 Sep 5;10(1):3992. doi: 10.1038/s41467-019-11995-z. PubMed PMID: 31488849; PubMed Central PMCID: PMC6728351.

> Most current evidence indicates that DNA polymerases ε and δ, respectively, perform the bulk of leading and lagging strand replication of the eukaryotic nuclear genome. Given that ribonucleotide and mismatch incorporation rates by these replicases influence somatic and germline patterns of variation, it is important to understand the details and exceptions to this overall division of labor. Using an improved method to map where these replicases incorporate ribonucleotides during replication, here we present evidence that DNA polymerase δ universally participates in initiating leading strand synthesis and that nascent leading strand synthesis switches from Pol ε to Pol δ during replication termination. Ribonucleotide maps from both the budding and fission yeast reveal conservation of these processes. These observations of replisome dynamics provide important insight into the mechanisms of eukaryotic replication and genome maintenance.

Nicol B, Grimm SA, Chalmel F, Lecluze E, Pannetier M, Pailhoux E, Dupin-De-Beyssat E, Guiguen Y, Capel B, Yao HH. RUNX1 maintains the identity of the fetal ovary through an interplay with FOXL2. *Nat Commun*. 2019 Nov 11;10(1):5116. doi: 10.1038/s41467-019-13060-1. PubMed PMID: 31712577; PubMed Central PMCID: PMC6848188.

> Sex determination of the gonads begins with fate specification of gonadal supporting cells into either ovarian pre-granulosa cells or testicular Sertoli cells. This fate specification hinges on a balance of transcriptional control. Here we report that expression of the transcription

factor RUNX1 is enriched in the fetal ovary in rainbow trout, turtle, mouse, goat, and human. In the mouse, RUNX1 marks the supporting cell lineage and becomes pre-granulosa cell-specific as the gonads differentiate. RUNX1 plays complementary/redundant roles with FOXL2 to maintain fetal granulosa cell identity and combined loss of RUNX1 and FOXL2 results in masculinization of fetal ovaries. At the chromatin level, RUNX1 occupancy overlaps partially with FOXL2 occupancy in the fetal ovary, suggesting that RUNX1 and FOXL2 target common sets of genes. These findings identify RUNX1, with an ovary-biased expression pattern conserved across species, as a regulator in securing the identity of ovarian-supporting cells and the ovary.

Sil P, Suwanpradid J, Muse G, Gruzdev A, Liu L, Corcoran DL, Willson CJ, Janardhan K, Grimm S, Myers P, Degraff LM, MacLeod AS, Martinez J. Non-canonical autophagy in dermal dendritic cells mediates immunosuppressive effects of UV exposure. *J Allergy Clin Immunol*. 2019 Dec 11. pii: S0091-6749(19)31637-9. doi: 10.1016/j.jaci.2019.11.041. [Epub ahead of print] PubMed PMID: 31837371.

BACKGROUND: Control of the inflammatory response is critical to maintaining homeostasis, and failure to do so contributes to the burden of chronic inflammation associated with several disease states. The mechanisms that underlie immunosuppression, however, remain largely unknown. While defects in autophagy machinery have been associated with inflammatory pathologies, we now appreciate that autophagic components participate in non-canonical pathways distinct from classical autophagy. We have previously demonstrated that LC3-associated phagocytosis (LAP), a non-canonical autophagic process dependent on Rubicon (RUBCN), contributes to immunosuppression.
OBJECTIVE: We used Rubcn-/- mice to examine the role of in mediating the UV-induced immunotolerant program in a model of contact hypersensitivity (CHS).
METHODS: Flow cytometry and transcriptional analysis was used to measure immune cell infiltration and activation in the skin of Rubcn+/+ and Rubcn-/- mice during the CHS response.
RESULTS: Here, we demonstrate that LAP is required for UV-induced immunosuppression, and UV exposure induces a broadly anti-inflammatory transcriptional program dependent on Rubicon. Rubcn-/- mice are resistant to UV-induced immunosuppression and instead display exaggerated inflammation in a model of contact hypersensitivity (CHS). Specifically, RUBCN deficiency in CD301b+ dermal dendritic cells (dDC2s) results in their increased antigen presentation capacity and subsequent hyperactivation of the CD8+ T cell response.
CONCLUSIONS: LAP functions to limit the immune response and is critical in maintaining the balance between homeostasis and inflammation.

AWARDS AND HONORS

Scientific Awards

Dr. Trevor Archer (Chief, Epigenetics and Stem Cell Biology Laboratory) was selected as an NIH Distinguished Investigator. This honorific title is awarded to the top 2-3% of scientists in the NIH Intramural Research Program.

Dr. Chandra Jackson (Epidemiology Branch) and Dr. Jennifer Martinez (Immunity, Inflammation and Disease Laboratory) were selected as recipients of the Presidential Early Career Award for Scientists and Engineers (PECASE). PECASE is the highest honor bestowed by the U.S. government on outstanding scientists and engineers at the beginning of their independent research careers.

Dr. Frederick Miller and Dr. Lisa Rider (Clinical Research Branch) received the Global Genes RARE Champion of Hope Award for their leadership of the International Myositis Assessment and Clinical Studies Group (IMACS) of the International Myositis Foundation.

Dr. Dale Sandler (Chief, Epidemiology Branch) received NIH Director's Award for her leadership of the Agricultural Health (AgHealth) Study and was awarded the NIH Graduate Partnerships Program Outstanding Mentor Award.

Dr. Alexandra White (Epidemiology Branch) received an award from the NIH Office of Women's Health Research.

Dr. Humphrey Yao (Reproductive and Developmental Biology Laboratory) received the 2019 Research Award from the Society for the Study of Reproduction.

Named Professorships/Lectures

Dr. Donald Cook (Immunity, Inflammation and Disease Laboratory) present the Keynote Lecture at the Visiting Pulmonary Scholars Symposium at the University of North Carolina School of Medicine, Chapel Hill, NC.

Dr. William Copeland (Chief, Genome Integrity and Structural Biology Laboratory) presented the Keynote address at the Children's Hospital of Philadelphia (CHoP), Mitochondrial Research Affinity Group Retreat.

Dr. Traci Hall (Epigenetics and Stem Cell Biology Laboratory) was invited to present the Keynote Lecture at the RNA Society Salon Symposium at Emory University School of Medicine.

Dr. Thomas Kunkel (Genome Integrity and Structural Biology Laboratory) was invited to present Keynote addresses for the Genetic Toxicology Association Annual Meeting at the University of Delaware, Newark Delaware and at the 6th DNA Polymerase Meeting in Stockholm, Sweden.

Dr. Lisa Rider (Clinical Research Branch) presented the Mary Jane Keller Memorial Lecture at the Yale University School of Medicine.

Dr. Clarice Weinberg (Biostatistics and Computational Biology Branch) presented the Sholom Wacholder Distinguished Lecture in Quantitative Health Sciences at the National Cancer Institute in Bethesda, MD.

Dr. Carmen Williams (Reproductive and Developmental Biology Laboratory) presented the 3rd Annual Dr. Yves Clermont Lecture in Reproduction at the McGill Centre for

Research in Reproduction and Development in Montreal, Canada. She also presented the Kathleen Osborn Lecture at the Department of Molecular and Integrative Physiology at the University of Kansas Medical Center in Kansas City, KS.

Dr. Samuel Wilson (Genome Integrity and Structural Biology Laboratory) presented the Keynote Lecture at the Smerdon-Reeves Symposium, Washington State University.

Dr. Humphrey Yao (Reproductive and Developmental Biology Laboratory) presented the Keynote address at the inaugural Janice Bahr Lectureship on Reproductive Biology Series at the University of Illinois.

Dr. Darryl Zeldin (Scientific Director and Immunity, Inflammation and Disease Laboratory) gave the Keynote Lecture at the 12th Tongji Cardiovascular Disease Forum held in Wuhan, China and at the 20th Frontier Scientists Workshop of the Korean Academy of Science and Technology in Honolulu, HI.

Advisory/Editorial Boards

Dr. William Copeland (Chief, Genome Integrity and Structural Biology Laboratory) served on the Mitochondrial Disease Gene Curation Expert Panel and the POLG Expert Panel organized by the Children's Hospital of Philadelphia, to curate mitochondrial disease genes that cause Leigh syndrome spectrum and POLG disease mutations for the ClinGen Scientific Planning committee of the United Mitochondria Disease Foundation

Dr. Francesco DeMayo (Chief, Reproductive and Developmental Biology Laboratory) served as Vice President of the Society for the Study of Reproduction

Dr. Paul Doetsch (Deputy Scientific Director and Genome Integrity and Structural Biology Laboratory) served on the Department of Defense Programmatic Panel (Grants Council) for Cancer Research Program. He also served as an Academic Editor for *BioMed Research International* and on the editorial boards *Nucleic Acids Research* and *DNA Repair*.

Dr. Serena Dudek (Neurobiology Laboratory) served as treasurer of the Society for Neuroscience.

Dr. Michael Fessler (Chief, Immunity, Inflammation and Disease Laboratory) served as a member of the External Advisory Committee for the Lung Biology and Disease Center of Biomedical Research Excellence (COBRE) at Louisiana State University. He also served as an Associate Editor for the *American Journal of Respiratory Cell and Molecular Biology*

Dr. Stavros Garantziotis (Immunity, Inflammation and Disease Laboratory) was appointed to the Editorial Board and also served as a Guest Editor of a special issue on Hyaluronan Biology for *Matrix Biology*. He was also appointed as an Associate Editor for *Lung.*

Dr. Dmitry Gordenin (Genome Integrity and Structural Biology Laboratory) served as Associate Editor for *PLoS Genetics* and on the Editorial Board of *Mutation Research, Fundamental and Molecular Mechanisms of Mutagenesis*.

Dr. Traci Hall (Epigenetics and Stem Cell Biology Laboratory) served as a faculty member of *F1000 Prime* in the *Structure: RNA & DNA section*.

Dr. Chandra Jackson (Epidemiology Branch) was selected to participate in the National Academy of Medicine (NAM) Emerging Leaders in Health and Medicine Forum held in Washington, DC. She was also selected as a Nutrition Obesity Research Center at Harvard (NORCH) Diversity Scholar and will participate in the 20th Annual Harvard

Medical School Nutrition Symposium, Longevity & Aging: Nutritional and Metabolic Mechanisms in Boston, MA.

Dr. Anton Jetten (Immunity, Inflammation and Disease Laboratory) served on the Editorial Boards for *Nuclear Receptor Research*, *Stem Cell Investigation* and *Cells*

Dr. Anne Marie Jukic (Epidemiology Branch) served on the Editorial Board of *Environmental Health Perspectives* and received a Star Reviewer award from the Editor of *Fertility and Sterility.*

Dr. Stephanie London served as Chair of the Environmental and Occupational Population Health Assembly of the American Thoracic Society and also served on the American Thoracic Society Board of Directors.

Dr. Negin Martin (Neurobiology Laboratory) served on the Editorial Board of *PLoS One.*

Dr. Jennifer Martinez (Immunity, Inflammation and Disease Laboratory) served on the Editorial Board of *Frontiers in Cellular and Infection Microbiology*

Dr. Fredrick Miller (Clinical Research Branch) served on the Editorial Board of *Annals of the Rheumatic Diseases*.

Dr. Geoffrey Mueller (Genome Integrity and Structural Biology Laboratory) served as a member of the World Health Organization and International Union of Immunologicial Societies Allergen Nomenclature Subcommittee.

Dr. James Putney (Signal Transduction Laboratory) served as a member of Exchange Visitor Review Board for the U.S. Department of Health and Human Services (DHHS).

Dr. Lalith Perera (Genome Integrity and Structural Biology Laboratory) served on the Editorial Board of *International Journal of Molecular Sciences.*

Dr. Lisa Rider (Clinical Research Branch) served as an Associate Editor for *Autoimmune and Autoinflammatory Disorders, Frontiers in Immunology*, and served on the Editorial Board of *Journal of Neuromuscular Diseases*. She also served as an advisory member of the Cure JM Foundation.

Dr. Natalie Shaw (Clinical Research Branch) was selected to participate in the National Academy of Medicine (NAM) Emerging Leaders in Health and Medicine Forum held in Washington, DC.

Dr. Robin Stanley (Signal Transduction Laboratory) served on the Editorial Board of the *Journal of Visualized Experiments.*

Dr. Carmen Williams (Reproductive and Developmental Biology Laboratory) served as an Academic Editor for *PLoS Biology*.

Dr. R. Scott Williams (Genome Integrity and Structural Biology Laboratory) served on the Editorial Board of the *Journal of Biological Chemistry.*

Dr. Samuel Wilson (Genome Integrity and Structural Biology Laboratory) served as the Editor-in-Chief for *DNA Repair.* He also served on the Scientific Advisory Board for the DNA Repair and Genome Integrity Joint Program of Brandeis University and Tufts University.

Dr. Humphrey Yao (Reproductive and Developmental Biology Laboratory) served on the Editorial Board for *Sexual Development* and on the Board of Reviewing Editors for *Biology of Reproduction.* He also served as a member of the Advisory Boards for the Campion Fund of the Leppert Foundation and for the State Key Laboratory of Reproductive Biology in Beijing, China.

Dr. Darryl Zeldin (Scientific Director and Immunity, Inflammation and Disease Laboratory) served as an Associate Editor for *Pharmacology and Therapeutics* and on the Editorial

Boards of *Journal of Biological Chemistry*, the *American Journal of Physiology: Lung Cellular and Molecular Biology*, *American Journal of Respiratory Cell and Molecular Biology*, *Prostaglandins and Other Lipid Mediators*, *Open Environmental Research Journal, Molecular and Cellular Pharmacology* and the *Journal of Lipid Research.* He also served on the National Asthma Education and Prevention Program Advisory Committee.

Dr. Shanshan Zhao (Biostatistics and Computational Biology Branch) served as an Associate Editor of *Biometrics* and as an academic advisor for *PLoS One*.

Training and Mentoring

NIEHS Trainee Alumni

A total of 72 trainees departed NIEHS between January 1, 2019 and December 31, 2019. These include 24 postbaccalaureate and 7 predoctoral trainees. Below is a summary of where the 41 postdoctoral trainees have gone upon completing their training at NIEHS, what they are doing and the type of the positions they took.

What are they doing?

Additional postdoctoral training	2
Internship	0
Additional advanced degree	0
Primarily teaching	1
Primarily basic research	15
Primarily clinical research	1
Primarily clinical practice	0
Primarily applied research	12
Primarily patient care	1
Regulatory affairs	0
Science administration/project management	0
Intellectual property/ licensing and patenting	0
Consulting	0
Public policy	0
Science writing or communications	2
Grants management	1
Business development or Operations	0
Computation/informatics	2
Sales/marketing	0
Technical/customer support	1
Unknown or Undecided	1
Other	1
Unemployed	1
TOTAL	41

Where did they go?

Academic institution	16
Government agency	5
For-profit company	17
Non-profit organization	1
Private medical practice	0
Independent/self-employed	0
Unknown or Undecided	1
Unemployed	1
TOTAL	41

What is the level of their position?

Tenure track faculty	7
Non-tenure track faculty	2
Professional staff	25
Support staff	1
Management	1
Trainee	3
Unknown or Undecided	1
Unemployed	1
TOTAL	41