Division of Intramural Research

NAEHS Council Update

February 2019

DIR RECRUITMENTS

Tenure-Track Investigator in Neurobiology
The National Institute of Environmental Health Sciences (NIEHS) is seeking an exceptional individual as a Tenure-Track Investigator in the Neurobiology Laboratory within the Division of Intramural Research. The successful candidate is expected to lead an innovative, independent research program and will have a strong record of accomplishments in the field of neuroscience. Preference will be given to candidates who utilize innovative methodological approaches to investigate basic mechanisms underlying neuroinflammation and neurodegeneration. Applicants should have a Ph.D., M.D. and/or equivalent doctoral degree with at least 3 years of postdoctoral research experience in their field and an outstanding publication record. Emphasis will be on identifying an exceptional scientist with an innovative and productive research program. Dr. Michael Fessler, Chief of the Immunity, Inflammation and Disease Laboratory serves as Chair of the Search Committee. The committee identified six outstanding candidates that were invited for interviews in December 2018 and January and one of these candidates will be invited to return for a second visit.

Recruitment of 2018-19 NIH Earl Stadtman Investigator Finalists
In addition to targeted recruitment, DIR is actively seeking outstanding scientists through the central NIH Stadtman recruitment mechanism. Ten 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 2019.

NEW APPOINTMENTS IN DIR

Chief of the Biostatistics and Computational Biology Branch
Dr. Alison Motsinger-Reif was appointed Chief of the Biostatistics and Computational Biology Branch (BCBB) in DIR and Senior Investigator. She was previously a Full Professor in the Department of Statistics at North Carolina State University and Director of the Bioinformatics Consulting and Service Core and the Statistical Consulting Core within the Bioinformatics Research Center. At NIEHS Dr. Motsinger-Reif will focus on development of statistical and bioinformatics methods and applying these to interesting environmental health problems with specific focus on developing methods for gene-gene interactions, dose response modeling, pharmacogenomics and toxicogenomics applications, and methods development for quantifying response to chemical mixtures.

Chief of the Immunity, Inflammation and Disease Laboratory
Dr. Michael Fessler was appointed Chief of the Immunity, Inflammation and Disease Laboratory and will continue his role as Senior Investigator leading the Clinical Investigation of Host Defense Group in the Immunity, Inflammation and Disease Laboratory.

New Tenure-Track Investigators

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

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

BSC REVIEW OF THE REPRODUCTIVE AND DEVELOPMENTAL BIOLOGY LABORATORY

The NIEHS DIR Board of Scientific Counselors reviewed the Reproductive and Developmental Biology Laboratory, October 28-30, 2018

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
- 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
- Roland A. Owens, Ph.D., Ex-Officio BSC Member, Assistant Director, Office of Intramural Research, NIH, Bethesda, MD

Ad Hoc Reviewers that Attended:

- Ying Qing Chen, Ph.D., Member of Vaccine and Infections Disease Division, Fred Hutchinson Cancer Research Center, Seattle, WA
- Sarah England, Ph.D., Alan A. and Edith L. Wolff Professor of Medicine and Associate Director, Center for Reproductive Health Sciences, Department of Obstetrics and Gynecology, Washington University School of Medicine, St. Louis, MO
- Asgi T. Fazleabas, Ph.D., University Distinguished Professor and Associate Chair of Research, Department of Obstetrics Gynecology and Reproductive Biology, College of Human Medicine, Michigan State University, East Lansing, MI
- Charles R. Gerfen, Ph.D., Senior Investigator, National Institute of Mental Health, National Institutes of Health, Bethesda, MD
- Mary Ann Handel, Ph.D., Professor, Reproductive Biology, Reproductive Disorders, Developmental Disorders, Genetics and Genomics, The Jackson Laboratory Cancer Center, Bar Harbor, ME

- Chiung-Yu Huang, Ph.D., Professor, Department of Epidemiology and Biostatistics, School of Medicine, University of California San Francisco, San Francisco, CA
- Sara R. Jones, Ph.D., Associate Dean for Research and Professor, Department of Physiology and Pharmacology, Wake Forest School of Medicine, Winston-Salem, NC
- Anumantha Kanthasamy, M.S., M.Phil., Ph.D., Clarence Hartley Covault Distinguished Professor, Biomedical Sciences Chair, Iowa State University College of Veterinary Medicine, Ames, IA
- T. Rajendra Kumar, Ph.D., Edgar L. & Patricia M. Makowski Professor and Associate Vice Chair of Research, Department of Obstetrics and Gynecology, University of Colorado School of Medicine, Aurora, CO
- Mary Anne Lilly, Ph.D., Senior Investigator, Gamete Development
- Cell and Structural Biology, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD
- Carole Mendelson, Ph.D., Professor, Departments of Biochemistry, Obstetrics, and Gynecology, University of Texas Southwestern Medical Center, Dallas, TX
- Gary W. Miller, Ph.D., Vice Dean for Research Strategy and Innovation Professor, Department of Environmental Health Sciences, Columbia University, Mailman School of Public Health, New York, NY
- Edward Morgan, Ph.D., Professor, Department of Pharmacology, Emory University School of Medicine, Atlanta, GA
- Limin Peng, Ph.D., Professor, Department of Biostatistics and Bioinformatics, Rollins School of Public Health, Emory University, Atlanta, GA
- Lino Tessarollo, Ph.D., Program Director, Mouse Cancer Genetics Program and Senior Investigator, Center for Cancer Research, National Cancer Institute, Frederick, MD
- Judith R. Walters, Ph.D., Senior Investigator, Neurophysiological Pharmacology Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD
- Wen Xie, M.D., Ph.D., Chair of Pharmaceutical Sciences and The Joseph Koslow Endowed Chair, Professor, Pharmaceutical Sciences, University of Pittsburgh School of Pharmacy, Pittsburgh, PA
- Henry Yin, Ph.D., Associate Professor and Director of Graduate Studies, Department of Psychology and Neuroscience, Duke University, Durham, NC

Agenda

Sunday, October 28 – Hilton Garden Inn, Southpoint
Closed Evening Session

7:00 - 8:00 p.m.	Welcome and Discussion of Past Board Reviews, Drs. Darryl Zeldin, Francesco DeMayo, Jerrel Yakel and Clarice Weinberg
8:00 – end	BSC Discussion of Review, Dr. Kathleen Caron and panel

Monday, October 29 - NIEHS Rodbell Conference Rooms 101 ABC
Morning Session

8:30 - 8:45 a.m.	Welcome, Drs. Kathleen Caron and Linda Birnbaum

8:45 - 9:05	Overview, Reproductive and Developmental Biology Laboratory, Francesco DeMayo, Ph.D.
9:05 - 9:55	Pregnancy and Female Reproduction Group, Francesco DeMayo, Ph.D.
9:55 - 10:10	COFFEE BREAK
10:10 - 11:00	Reproductive Medicine Group, Carmen Williams, M.D., Ph.D.
11:00 - 11:50	Reproductive Developmental Biology Group, Humphrey Yao, Ph.D.
11:50 - 12:35	Closed 1:1 Sessions with Investigators, Drs. DeMayo, Williams, Yao
12:35 - 1:30	Closed Working Lunch, 101 ABC

Afternoon Session

1:30 - 2:45 p.m.	Poster Session, Rodbell Lobby
2:45 - 3:15	Closed Session with Fellows & Staff Scientists, 101 ABC
3:15 - 3:30	COFFEE BREAK
3:30 - 4:20	Pharmacogenetics Group, Masahiko Negishi, Ph.D.
4:20 - 5:10	Developmental Neurobiology Group, Patricia Jensen, Ph.D.
5:10 - 5:35	Closed 1:1 Sessions with Investigators, Drs. Negishi and Jensen
5:35	Return to Hilton Garden Inn, Southpoint
6:00 – end	Closed BSC Discussion of Review, All BSC reviewers at hotel

Tuesday October 30 - NIEHS Rodbell Conference Rooms 101 ABC

Morning Session

8:30 - 9:20 a.m.	Receptor Biology Group, Kenneth Korach, Ph.D.
9:20 - 10:10	In Vivo Neurobiology Group, Guohong Cui, M.D., Ph.D.
10:10 - 10:25	COFFEE BREAK
10:25 - 11:15	Applied Statistics Group, Shanshan Zhao, Ph.D.
11:15 - 12:05	Closed 1:1 Sessions with Investigators, Drs. Cui and Zhao
12:05 - 1:55	Closed Working Lunch, 101 ABC

Afternoon Session

1:55 - 2:30 p.m.	Closed Review of Knock Out Core Session with Core Leadership, Manas Ray, Ph.D.
2:30 - 3:30	BSC Discussion and Completion of Individual Review Assignments by each Member, 101 ABC
3:30 - 4:30	Closed Debriefing to NIEHS/DIR Leadership, 101 ABC
6:30	Adjourn, Transport to RDU

NIEHS SCIENCE DAYS

The Sixteenth Annual NIEHS Science Days were held on November 1-2, 2018 in the Rall Building on the NIEHS Campus to celebrate the achievements of NIEHS scientists. The event was open to the public with at least 250 attendees. The NIEHS Science Days program consisted of 13 oral presentations given by fellows, students, and technicians, 89 poster presentations, an awards ceremony and a grant writing workshop. Judging for the awards was done by extramural scientists from 10 universities and research organizations from across North Carolina, NIEHS Intramural Scientists and the NIEHS Trainees Assembly.

Mentor of the Year: Kelly Ferguson, M.P.H., Ph.D., Epidemiology Branch
Fellow of the Year: Monica Pillon, Ph.D., Signal Transduction Laboratory
Best Poster Presentation by a Fellow or Technician:

1. Gregory Whitehead, Ph.D., Immunity, Inflammation, and Disease Laboratory, "Airway neutrophils attenuate adaptive immune responses through a TGF-dependent-mechanism."
2. Ru Pin Chi, Ph.D., Reproductive and Developmental Biology Laboratory, "Wnk1 in the uterus: elucidating functions in morphology and pregnancy using a mouse model."
3. Fei Zhao, Ph.D., Reproductive and Developmental Biology Laboratory "Unexpected contribution of the male tract mesenchyme to the female reproductive tract."
4. Chitrangda Srivastava, Ph.D., Immunity, Inflammation, and Disease Laboratory,"GLIS3: An essential player in polycystic kidney disease."
5. Irina Evsyukova, Ph.D., Neurobiology Laboratory, "Sex-specific effects of locus coeruleus norepinephrine loss on hippocampus-dependent learning."
6. Melissa Wells, Ph.D., Signal Transduction Laboratory, "From yeast to human: The conservation of an RNA binding domain."
7. Alexander Foo, Ph.D., Genome Integrity and Structural Biology Laboratory, "Influence of hydrophobic cargo binding on the structure, stability, and allergenicity of the cockroach allergen Blag 1."
8. Payel Sil, Ph.D., Immunity, Inflammation and Disease Laboratory, "The role of LC3-associated phagocytosis in T cell-mediated contact dermatitis."
9. Barbara Nicol, Ph.D., Reproductive and Developmental Biology Laboratory, "RUNX1 and FOXL2 play complementary roles in maintaining fetal granulosa cell identity in the mouse ovary."

Best Poster Presentation by a Post-Baccalaureate Student: Brian Elgart, Molecular Genomics Core, "Purification of plasma circulating cell-free DNA and development of molecular assays for clinical and toxicology studies."
Best Oral Presentation: Monica Pillon, Ph.D., Signal Transduction Laboratory, "Structure of the essential multi-enzyme RNA processing complex Grc3/Las1 reveals the molecular basis for catalysis."

DIR PAPERS OF THE YEAR FOR 2018

Qin Y, Roberts JD, Grimm SA, Lih FB, Deterding LJ, Li R, Chrysovergis K, Wade PA. An obesity-associated gut microbiome reprograms the intestinal epigenome and leads to altered colonic gene expression. *Genome Biol*., 19(1):7, 2018.

BACKGROUND: The gut microbiome, a key constituent of the colonic environment, has been implicated as an important modulator of human health. The eukaryotic epigenome is postulated to respond to environmental stimuli through alterations in chromatin features and, ultimately, gene expression. How the host mediates epigenomic responses to gut microbiota is an emerging area of interest. Here, we profile the gut microbiome and chromatin characteristics in colon epithelium from mice fed either an obesogenic or control diet, followed by an analysis of the resultant changes in gene expression.
RESULTS: The obesogenic diet shapes the microbiome prior to the development of obesity, leading to altered bacterial metabolite production which predisposes the host to obesity. This microbiota-diet interaction leads to changes in histone modification at active enhancers that are enriched for binding sites for signal responsive transcription factors. These alterations of histone methylation and acetylation are associated with signaling pathways integral to the development of colon cancer. The transplantation of obesogenic diet-conditioned microbiota into germ free mice, combined with an obesogenic diet, recapitulates the features of the long-term diet regimen. The diet/microbiome-dependent changes are reflected in both the composition of the recipient animals' microbiome as well as in the set of transcription factor motifs identified at diet-influenced enhancers.
CONCLUSIONS: These findings suggest that the gut microbiome, under specific dietary exposures, stimulates a reprogramming of the enhancer landscape in the colon, with downstream effects on transcription factors. These chromatin changes may be associated with those seen during colon cancer development.

Meng C, Zhou J, Papaneri A, Peddada T, Xu K, Cui G. Spectrally Resolved Fiber Photometry for Multi-component Analysis of Brain Circuits. *Neuron*, 98(4):707-717, 2018.

To achieve simultaneous measurement of multiple cellular events in molecularly defined groups of neurons in vivo, we designed a spectrometer-based fiber photometry system that allows for spectral unmixing of multiple fluorescence signals recorded from deep brain structures in behaving animals. Using green and red Ca2+ indicators differentially expressed in striatal direct- and indirect-pathway neurons, we were able to simultaneously monitor the neural activity in these two pathways in freely moving animals. We found that the activities were highly synchronized between the direct and indirect pathways within one hemisphere and were desynchronized between the two hemispheres. We further analyzed the relationship between the movement patterns and the magnitude of activation in direct- and indirect-pathway neurons and found that the striatal direct and indirect pathways coordinately control the dynamics and fate of movement.

Huang H, Tang S, Ji M, Tang Z, Shimada M, Liu X, Qi S, Locasale JW, Roeder RG, Zhao Y, Li X. EP300-Mediated Lysine 2-Hydroxyisobutyrylation Regulates Glycolysis. *Mol Cell*., 70(4):663-678, 2018.

Lysine 2-hydroxyisobutyrylation (Khib) is an evolutionarily conserved and widespread histone mark like lysine acetylation (Kac). Here we report that EP300 functions as a lysine 2-hyroxyisobutyryltransferase to regulate glycolysis in response to nutritional cues. We discovered that EP300 differentially regulates Khib and Kac on distinct lysine sites, with only 6 of the 149 EP300-targeted Khib sites overlapping with the 693 EP300-targeted Kac sites. We demonstrate that diverse cellular proteins, particularly glycolytic enzymes, are targeted by EP300 for Khib, but not for Kac. Specifically, deletion of EP300 significantly reduces Khib levels on several EP300-dependent, Khib-specific sites on key glycolytic enzymes including ENO1, decreasing their catalytic activities. Consequently, EP300-deficient cells have impaired glycolysis and are hypersensitive to glucose-depletion-induced cell death. Our study reveals an EP300-catalyzed, Khib-specific molecular mechanism that regulates cellular glucose metabolism and further indicate that EP300 has an intrinsic ability to select short-chain acyl-CoA-dependent protein substrates.

Salo PM, Wilkerson J, Rose KM, Cohn RD, Calatroni A, Mitchell HE, Sever ML, Gergen PJ, Thorne PS, Zeldin DC. Bedroom allergen exposures in US households. *J Allergy Clin Immunol*., 141(5):1870-1879, 2018.

BACKGROUND: Bedroom allergen exposures contribute to allergic disease morbidity because people spend considerable time in bedrooms, where they come into close contact with allergen reservoirs.
OBJECTIVE: We investigated participant and housing characteristics, including sociodemographic, regional, and climatic factors, associated with bedroom allergen exposures in a nationally representative sample of the US population.
METHODS: Data were obtained from National Health and Nutrition Examination Survey 2005-2006. Information on participant and housing characteristics was collected by using questionnaires and environmental assessments. Concentrations of 8 indoor allergens (Alt a 1, Bla g 1, Can f 1, Fel d 1, Der f 1, Der p 1, Mus m 1, and Rat n 1) in dust vacuumed from nearly 7000 bedrooms were measured by using immunoassays. Exposure levels were classified as increased based on percentile (75th/90th) cutoffs. We estimated the burden of exposure to multiple allergens and used multivariable logistic regression to identify independent predictors for each allergen and household allergen burden.
RESULTS: Almost all participants (>99%) had at least 1 and 74.2% had 3 to 6 allergens detected. More than two thirds of participants (72.9%) had at least 1 allergen and 18.2% had 3 or more allergens exceeding increased levels. Although exposure variability showed significant racial/ethnic and regional differences, high exposure burden to multiple allergens was most consistently associated with the presence of pets and pests, living in mobile homes/trailers and older and rental homes, and living in nonmetropolitan areas.
CONCLUSIONS: Exposure to multiple allergens is common. Despite highly variable exposures, bedroom allergen burden is strongly associated with the presence of pets and pests.

Pillon MC, Sobhany M, Stanley RE. Characterization of the molecular crosstalk within the essential Grc3/Las1 pre-rRNA processing complex. *RNA*, 24(5):721-738, 2018.

> Grc3 is an essential well-conserved eukaryotic polynucleotide kinase (PNK) that cooperates with the endoribonuclease Las1 to process the preribosomal RNA (rRNA). Aside from being dependent upon Las1 for coordinated kinase and nuclease function, little is known about Grc3 substrate specificity and the molecular mechanisms governing kinase activity. Here we characterize the kinase activity of Grc3 and identify key similarities and differences between Grc3 and other polynucleotide kinase family members. In contrast to other PNK family members, Grc3 has distinct substrate preference for RNA substrates in vitro. By disrupting conserved residues found at the Grc3 kinase active site, we identified specific residues required to support Grc3-directed Las1-mediated pre-rRNA cleavage in vitro and in vivo. The crosstalk between Grc3 and Las1 ensures the direct coupling of cleavage and phosphorylation during pre-rRNA processing. Taken together, our studies provide key insight into the polynucleotide kinase activity of the essential enzyme Grc3 and its molecular crosstalk with the endoribonuclease Las1.

Jefferson WN, Kinyamu HK, Wang T, Miranda AX, Padilla-Banks E, Suen AA, Williams CJ. Widespread enhancer activation via ERα mediates estrogen response *in vivo* during uterine development. *Nucleic Acids Res*.,46(11):5487-5503, 2018.

> Little is known regarding how steroid hormone exposures impact the epigenetic landscape in a living organism. Here, we took a global approach to understanding how exposure to the estrogenic chemical, diethylstilbestrol (DES), affects the neonatal mouse uterine epigenome. Integration of RNA- and ChIP-sequencing data demonstrated that ~80% of DES-altered genes had higher H3K4me1/H3K27ac signal in close proximity. Active enhancers, of which ~3% were super-enhancers, had a high density of estrogen receptor alpha (ERα) binding sites and were correlated with alterations in nearby gene expression. Conditional uterine deletion of ERα, but not the pioneer transcription factors FOXA2 or FOXO1, prevented the majority of DES-mediated changes in gene expression and H3K27ac signal at target enhancers. An ERα dependent super-enhancer was located at the Padi gene locus and a topological connection to the Padi1 TSS was documented using 3C-PCR. Chromosome looping at this site was independent of ERα and DES exposure, indicating that the interaction is established prior to ligand signaling. However, enrichment of H3K27ac and transcriptional activation at this locus was both DES and ERα-dependent. These data suggest that DES alters uterine development and consequently adult reproductive function by modifying the enhancer landscape at ERα binding sites near estrogen-regulated genes.

Wyss AB, Sofer T, Lee MK, Terzikhan N, Nguyen JN, Lahousse L, Latourelle JC, Smith AV, Bartz TM, Feitosa MF, Gao W, Ahluwalia TS, Tang W, Oldmeadow C, Duan Q, de Jong K, Wojczynski MK, Wang XQ, Noordam R, Hartwig FP, Jackson VE, Wang T, Obeidat M, Hobbs BD, Huan T, Gui H, Parker MM, Hu D, Mogil LS, Kichaev G, Jin J, Graff M, Harris TB, Kalhan R, Heckbert SR, Paternoster L, Burkart KM, Liu Y, Holliday EG, Wilson JG, Vonk JM, Sanders JL, Barr RG, de Mutsert R, Menezes AMB, Adams HHH, van den Berge M, Joehanes R, Levin AM, Liberto J, Launer LJ, Morrison AC, Sitlani CM, Celedón JC, Kritchevsky SB, Scott RJ, Christensen K, Rotter JI, Bonten TN, Wehrmeister FC, Bossé Y, Xiao S, Oh S, Franceschini N,

Brody JA, Kaplan RC, Lohman K, McEvoy M, Province MA, Rosendaal FR, Taylor KD, Nickle DC, Williams LK, Burchard EG, Wheeler HE, Sin DD, Gudnason V, North KE, Fornage M, Psaty BM, Myers RH, O'Connor G, Hansen T, Laurie CC, Cassano PA, Sung J, Kim WJ, Attia JR, Lange L, Boezen HM, Thyagarajan B, Rich SS, Mook-Kanamori DO, Horta BL, Uitterlinden AG, Im HK, Cho MH, Brusselle GG, Gharib SA, Dupuis J, Manichaikul A, London SJ. Multiethnic meta-analysis identifies ancestry-specific and cross-ancestry loci for pulmonary function. *Nat Commun*., 9(1):2976, 2018.

Nearly 100 loci have been identified for pulmonary function, almost exclusively in studies of European ancestry populations. We extend previous research by meta-analyzing genome-wide association studies of 1000 Genomes imputed variants in relation to pulmonary function in a multiethnic population of 90,715 individuals of European (N = 60,552), African (N = 8429), Asian (N = 9959), and Hispanic/Latino (N = 11,775) ethnicities. We identify over 50 additional loci at genome-wide significance in ancestry-specific or multiethnic meta-analyses. Using recent fine-mapping methods incorporating functional annotation, gene expression, and differences in linkage disequilibrium between ethnicities, we further shed light on potential causal variants and genes at known and newly identified loci. Several of the novel genes encode proteins with predicted or established drug targets, including KCNK2 and CDK12. Our study highlights the utility of multiethnic and integrative genomics approaches to extend existing knowledge of the genetics of lung function and clinical relevance of implicated loci.

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*., ePub ahead of print, Sep 13, 2018.

Noradrenergic signaling plays a well-established role in promoting the stress response. Here we identify a subpopulation of noradrenergic neurons, defined by developmental expression of Hoxb1, that has a unique role in modulating stress-related behavior. Using an intersectional chemogenetic strategy, in combination with behavioral and physiological analyses, we show that activation of Hoxb1-noradrenergic (Hoxb1-NE) neurons decreases anxiety-like behavior and promotes an active coping strategy in response to acute stressors. In addition, we use cerebral blood volume-weighted functional magnetic resonance imaging to show that chemoactivation of Hoxb1-NE neurons results in reduced activity in stress-related brain regions, including the bed nucleus of the stria terminalis, amygdala, and locus coeruleus. Thus, the actions of Hoxb1-NE neurons are distinct from the well-documented functions of the locus coeruleus in promoting the stress response, demonstrating that the noradrenergic system contains multiple functionally distinct subpopulations.

Nguyen TT, Grimm SA, Bushel PR, Li J, Li Y, Bennett BD, Lavender CA, Ward JM, Fargo DC, Anderson CW, Li L, Resnick MA, Menendez D. Revealing a human p53 universe. *Nucleic Acids Res*., 46(16):8153-8167, 2018.

> p53 transcriptional networks are well-characterized in many organisms. However, a global understanding of requirements for in vivo p53 interactions with DNA and relationships with transcription across human biological systems in response to various p53 activating situations remains limited. Using a common analysis pipeline, we analyzed 41 data sets from genome-wide ChIP-seq studies of which 16 have associated gene expression data, including our recent primary data with normal human lymphocytes. The resulting extensive analysis, accessible at p53 BAER hub via the UCSC browser, provides a robust platform to characterize p53 binding throughout the human genome including direct influence on gene expression and underlying mechanisms. We establish the impact of spacers and mismatches from consensus on p53 binding in vivo and propose that once bound, neither significantly influences the likelihood of expression. Our rigorous approach revealed a large p53 genome-wide cistrome composed of >900 genes directly targeted by p53. Importantly, we identify a core cistrome signature composed of genes appearing in over half the data sets, and we identify signatures that are treatment- or cell-specific, demonstrating new functions for p53 in cell biology. Our analysis reveals a broad homeostatic role for human p53 that is relevant to both basic and translational studies.

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*., 143(1):440-442, 2019.

> Despite improvements in supportive care, mortality from acute respiratory distress syndrome (ARDS) remains high (approximately 30% to 40%). In recent years, several biomarkers of inflammation, epithelial damage, endothelial damage, and coagulation have been identified that show promise for identifying ARDS endotypes with different prognosis and therapeutic responsiveness. Unfortunately, few lung-specific biomarkers have been validated, and none have been adopted into routine clinical practice. We identify cholestenoic acid (CA) as a novel ARDS biomarker. We speculate that plasma CA might represent a valuable new peripheral blood indicator of mitochondrial function and propose that it should now be measured in patients with a wider range of lung diseases and potentially in emerging studies of cell-based mitochondrial rescue in the lung.

Wang X, Li X, Wang T, Wu SP, Jeong JW, Kim TH, Young SL, Lessey BA, Lanz RB, Lydon JP, DeMayo FJ. SOX17 regulates uterine epithelial-stromal cross-talk acting via a distal enhancer upstream of Ihh. *Nat Commun.*, 9(1):4421, 2018.

> Mammalian pregnancy depends on the ability of the uterus to support embryo implantation. Previous studies reveal the Sox17 gene as a downstream target of the Pgr-Gata2-dependent transcription network that directs genomic actions in the uterine endometrium receptive for embryo implantation. Here, we report that ablating Sox17 in the uterine epithelium impairs leukemia inhibitory factor (LIF) and Indian hedgehog homolog (IHH) signaling, leading to

failure of embryo implantation. In vivo deletion of the SOX17-binding region 19 kb upstream of the Ihh locus by CRISPR-Cas technology reduces Ihh expression specifically in the uterus and alters proper endometrial epithelial-stromal interactions, thereby impairing pregnancy. This SOX17-binding interval is also bound by GATA2, FOXA2, and PGR. This cluster of transcription factor binding is common in 737 uterine genes and may represent a key regulatory element essential for uterine epithelial gene expression.

Schoemaker MJ, Nichols HB, Wright LB, Brook MN, Jones ME, O'Brien KM, Adami HO, Baglietto L, Bernstein L, Bertrand KA, Boutron-Ruault MC, Braaten T, Chen Y, Connor AE, Dorronsoro M, Dossus L, Eliassen AH, Giles GG, Hankinson SE, Kaaks R, Key TJ, Kirsh VA, Kitahara CM, Koh WP, Larsson SC, Linet MS, Ma H, Masala G, Merritt MA, Milne RL, Overvad K, Ozasa K, Palmer JR, Peeters PH, Riboli E, Rohan TE, Sadakane A, Sund M, Tamimi RM, Trichopoulou A, Ursin G, Vatten L, Visvanathan K, Weiderpass E, Willett WC, Wolk A, Yuan JM, Zeleniuch-Jacquotte A, Sandler DP, Swerdlow AJ. Association of Body Mass Index and Age With Subsequent Breast Cancer Risk in Premenopausal Women. *JAMA Oncol*., 4(11):e181771, 2018.

IMPORTANCE: The association between increasing body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) and risk of breast cancer is unique in cancer epidemiology in that a crossover effect exists, with risk reduction before and risk increase after menopause. The inverse association with premenopausal breast cancer risk is poorly characterized but might be important in the understanding of breast cancer causation.
OBJECTIVE: To investigate the association of BMI with premenopausal breast cancer risk, in particular by age at BMI, attained age, risk factors for breast cancer, and tumor characteristics.
DESIGN, SETTING, AND PARTICIPANTS: This multicenter analysis used pooled individual-level data from 758 592 premenopausal women from 19 prospective cohorts to estimate hazard ratios (HRs) of premenopausal breast cancer in association with BMI from ages 18 through 54 years using Cox proportional hazards regression analysis. Median follow-up was 9.3 years (interquartile range, 4.9-13.5 years) per participant, with 13 082 incident cases of breast cancer. Participants were recruited from January 1, 1963, through December 31, 2013, and data were analyzed from September 1, 2013, through December 31, 2017.
EXPOSURES: Body mass index at ages 18 to 24, 25 to 34, 35 to 44, and 45 to 54 years.
MAIN OUTCOMES AND MEASURES: Invasive or in situ premenopausal breast cancer.
RESULTS: Among the 758 592 premenopausal women (median age, 40.6 years; interquartile range, 35.2-45.5 years) included in the analysis, inverse linear associations of BMI with breast cancer risk were found that were stronger for BMI at ages 18 to 24 years (HR per 5 kg/m2 [5.0-U] difference, 0.77; 95% CI, 0.73-0.80) than for BMI at ages 45 to 54 years (HR per 5.0-U difference, 0.88; 95% CI, 0.86-0.91). The inverse associations were observed even among nonoverweight women. There was a 4.2-fold risk gradient between the highest and lowest BMI categories (BMI≥35.0 vs <17.0) at ages 18 to 24 years (HR, 0.24; 95% CI, 0.14-0.40). Hazard ratios did not appreciably vary by attained age or between strata of other breast cancer risk factors. Associations were stronger for estrogen receptor-positive and/or progesterone receptor-positive than for hormone receptor-negative breast cancer for BMI at every age group (eg, for BMI at age 18 to 24 years: HR per 5.0-U difference for estrogen receptor-positive and progesterone receptor-positive tumors, 0.76 [95% CI, 0.70-0.81] vs

hormone receptor-negative tumors, 0.85 [95% CI: 0.76-0.95]); BMI at ages 25 to 54 years was not consistently associated with triple-negative or hormone receptor-negative breast cancer overall.
CONCLUSIONS AND RELEVANCE: The results of this study suggest that increased adiposity is associated with a reduced risk of premenopausal breast cancer at a greater magnitude than previously shown and across the entire distribution of BMI. The strongest associations of risk were observed for BMI in early adulthood. Understanding the biological mechanisms underlying these associations could have important preventive potential.

AWARDS AND HONORS

Scientific Awards

Dr. Chandra Jackson (Epidemiology Branch) was selected as a JPB Environmental Health Fellow by the Harvard T.H. Chan School of Public Health.
Dr. Kathy Laber received the Joseph J. Garvey Management Award from the American Association of Laboratory Animal Science.
Dr. Stephanie London was elected Chair of the Environmental and Occupational Population Health Assembly of the American Thoracic Society and will also serve on the American Thoracic Society Board of Directors.
Dr. Lisa Rider (Clinical Research Branch) received the "10 Year Center of Excellence Award" from the Cure JM Foundation and the 25th Anniversary Research Award: For Outstanding Contributions to Myositis Research over the past 15 years from the Myositis Association.
Dr. Allen Wilcox received the 2018 Rothman Career Achievement Award from the Society for Epidemiologic Research.
Dr. Dale Sandler (Chief, Epidemiology Branch) received the Visiting Scholar Award from the Division of Cancer Epidemiology and Genetics of the National Cancer Institute.

Named Professorships/Lectures

Dr. Francesco DeMayo (Chief, Reproductive and Developmental Biology Laboratory) presented the Presidents Lecture at the Society for Reproductive Biology Annual Meeting in Adelaide, Australia and the State of the Art Lecture at the Society for Pelvic Research annual meeting in New Orleans, LA.
Dr. William Copeland (Chief, Genome Integrity and Structural Biology Laboratory) presented the Keynote address at the '5th DNA Polymerase meeting' in Leiden, The Netherlands.
Dr. Raja Jothi (Epigenetics and Stem Cell Biology Laboratory) presented the Khairallah Lecture at the University of Connecticut.
Dr. Kenneth Korach (Reproductive and Developmental Biology Laboratory) presented the Presidential Keynote Address at the annual meeting of the Society for the Study of Reproduction.
Dr. Stephanie London (Epidemiology Branch) presented a plenary talk at the Airway Vista 2018 international conference in Seoul, Korea.
Dr. Lisa Rider (Clinical Research Branch) presented Keynote Lectures at 9th Myositis Workshop in Tokyo, Japan and the 5th National Myositis Conference in Beijing, PR China.
Dr. Allen Wilcox (Epidemiology Branch) presented the Keynote Address at the 2018 annual meeting of the Society for Epidemiologic Research.
Dr. Carmen Williams (Reproductive and Developmental Biology Laboratory) presented the Dr. Yves Clermont Lecture in Reproduction at the 11th Annual Research Day of the McGill Centre for Research in Reproduction and Development in Montreal, Canada.

Dr. Samuel Wilson (Genome Integrity and Structural Biology Laboratory) Keynote Lectures at the Smerdon-Reeves Symposium, Washington State University and the Van Houten Symposium, Duke University.

Dr. Humphrey Yao was selected by the President of the Society for the Study of Reproduction as the Exchange Lecturer to present a plenary lecture at the 2018 annual meeting for the Australian Society for Reproductive Biology in, Adelaide, Australia.

Dr. Darryl Zeldin (Scientific Director and Immunity, Inflammation and Disease Laboratory) gave the Keynote Lecture at the First Allergy and Clinical Immunology International Summit Forum, University of the Chinese Academy of Sciences, Beijing, PR China. He also gave the Keynote Lecture at the International Symposium on the Environment and Reproduction, Nanjing, PR China.

Advisory/Editorial Boards

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

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

Dr. Serena Dudek (Neurobiology Laboratory) was elected treasurer of the Society for Neuroscience.

Dr. Stavros Garantziotis (Immunity, Inflammation and Disease Laboratory) was appointed to the editorial board of *Matrix Biology*.

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) was selected as a faculty member of *F1000 Prime* in the *Structure: RNA & DNA section*.

Dr. Chandra Jackson (Epidemiology Branch) served as an Invited Guest Editor for the *International Journal of Environmental Research and Public Health*

Dr. Anne Marie Jukic (Epidemiology Branch) served on the Editorial Board of *Environmental Health Perspectives.*

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

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

Dr. Lisa Rider (Clinical Research Branch) served as an Associate Editor for *Associate Editor, Autoimmune and Autoinflammatory Disorders, Frontiers in Immunology*, and served on the Editorial Boards of *Journal of Neuromuscular Diseases* and *International Journal of Rheumatology*.

Dr. Robin Stanley (Signal Transduction Laboratory) was appointed to the Editorial Board of appointed to the editorial board of the *Journal of Visualized Experiments.*

Dr. R. Scott Williams (Genome Integrity and Structural Biology Laboratory) served on the Editorial Board of the *Journal of Biological Chemistry* and as a guest editor for *Cell Molecular Life Sciences.*

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*, *Molecular and Cellular Pharmacology* and the *Journal of Lipid Research.*

Dr. Shanshan Zhao (Biostatistics and Computational Biology Branch) was appointed as an associate editor of *Biometrics*.

Training and Mentoring

NIEHS Trainee Alumni

DIR has recently analyzed where recent postdoctoral trainees have gone upon completing their training, what they are doing and the level of the positions they took. Below is a summary of the analysis of 50 postdoctoral trainees that left NIEHS from January 1, 2018 through December 31, 2018.

What are they doing?

Additional postdoctoral training	5
Internship	0
Additional advanced degree	0
Primarily teaching	2
Primarily basic research	17
Primarily clinical research	2
Primarily clinical practice	0
Primarily applied research	14
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	4
Grants management	0
Business development or Operations	0
Computation/informatics	0
Sales/marketing	0
Technical/customer support	1
Unknown or Undecided	3
Other	0
Unemployed	1
TOTAL	50

Where did they go?

Academic institution	16
Government agency	4
For-profit company	24
Non-profit organization	2
Private medical practice	0
Independent/self-employed	0
Unknown or Undecided	3
Unemployed	1
TOTAL	50

What is the level of their position?

Tenure track faculty	8
Non-tenure track faculty	0
Professional staff	32
Support staff	0
Management	0
Trainee	6
Unknown or Undecided	3
Unemployed	1
TOTAL	50