Division of Intramural Research

NAEHS Council Update

February 2021

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. This recruitment has been temporarily placed on hold.

Chief of the Comparative Medicine Branch
The National Institute of Environmental Health Sciences is searching for an Animal Program Director, Attending Veterinarian and Chief of the Comparative Medicine Branch (CMB). CMB provides a broad range of services and collaborative support for NIEHS intramural research programs. The incumbent will be responsible for an AAALAC accredited animal care and use program and for support of NIEHS animal research programs that engage in molecular, reproductive, neurological and immunological research as well as studying the effects of environmental agents in order to develop methods of disease prevention and treatment.
The incumbent actively support the NIEHS mission, participate in ongoing planning and management discussions to successfully resolve pertinent issues and challenges, participate in long range strategic planning processes to develop and implement effective goals and directions for the animal care program and provide information and recommendations to the Scientific Director and will conduct/collaborate in research relative to the mission of CMB and the institute. Applicants must have a DVM/VMD degree from an AVMA-accredited or approved college, a current license to practice veterinary medicine in any state in the United States and board certification by the American College of Laboratory Animal Medicine. Dr. Donald Cook,

Senior Investigator in the Immunity, Inflammation and Disease Laboratory and Chair of the NIEHS Animal Care and Use Committee serves as chair of the search committee which was launched on August 21, 2020.

Senior Clinician in the Clinical Research Branch

The National Institute of Environmental Health Sciences (NIEHS) is inviting applications for a Senior Clinician in the Environmental Autoimmunity Group (EAG) in the Clinical Research Branch within the NIEHS Division of Intramural Research in Bethesda, MD. 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. Research areas may include understanding mechanisms of human disease, developing disease assessment tools, therapeutic interventions and/or clinical trials. The Clinical Research Branch is interested in candidates with expertise in pediatric rheumatology. Research experience in the risk factors, pathogenesis, immunology, assessment, and treatment of the idiopathic inflammatory myopathies is of particular interest, but not required. Applicants should have an M.D. or equivalent doctoral degree with direct clinical research experience. The individual must possess a current, active, full, and unrestricted license or registration as a Physician to practice medicine in the United States and be eligible to be credentialed for patient care by the National Institutes of Health Clinical Center. Applicants should have Board Certification or Eligibility in Pediatric Rheumatology, with five or more years of experience in clinical research, and publications and other evidence of the ability to design and carry out original, innovative patient-oriented research. The ideal candidate will have experience leading national and international scientific collaborations. The successful candidate will be expected to develop an outstanding independent clinical research program that mentors trainees and complements and benefits from the other research programs within the Environmental Autoimmunity Group, the Clinical Research Branch, and the Division of Intramural Research. Dr. Edward Cowen, Senior Clinician National Institute of Arthritis and Musculoskeletal and Skin Diseases serves as chair of the search committee that was launched on August 31, 2020.

Recruitment of NIH Earl Stadtman Investigator Finalists

In addition to targeted recruitment, DIR is actively seeking outstanding scientists through the central NIH Stadtman recruitment mechanism. Seven outstanding candidates from the 2019-2020 Stadtman search representing a range of disciplines central to the NIEHS mission were interviewed in January and February 2020. Two candidates were offered positions at NIEHS with one declining and the second pending. Eight candidates were selected from the 2020-2021 cohort of Stadtman finalists for interviews. Due to the COVID-19 pandemic these were conducted virtually in January 2021. Offers will be extended to top candidates in February and March 2021 following discussions among DIR and NIEHS leadership.

DIR STAFF UPDATES

Masahiko Negishi, Ph.D., Senior Investigator, Reproductive and Developmental Biology Laboratory, was unanimously approved by the Board of Scientific Directors as an NIH Scientist Emeritus and assumed the position following his retirement in December 31, 2020. Dr. Negishi has distinguished himself in 37 years at NIEHS for his pioneering studies on the structure and function of xenobiotic-metabolizing enzymes and the xenobiotic-induced activation of genes that encode these enzymes. This fundamental research has led to new insights into how we respond to environmental exposures. His work has been recognized by numerous awards from prestigious organizations. The trainees he has mentored over his distinguished NIEHS career now occupy positions as independent investigators all over the world.

Dmitri Zaykin, Ph.D., Senior Investigator, Biostatistics and Computational Biology Branch died unexpectedly on December 28, 2020. Dr. Zaykin was an internationally recognized statistical geneticist. He has been a valuable member of NIEHS since 2004. His previous positions in statistical and population genetics were at the Institute of Marine Biology in Vladivostok, Russia, North Carolina State University's Statistics Department, and at GlaxoSmithKline Inc. His scientific interests were at the interface of mathematics, statistics, and biology with applications to the genetics of human diseases and pharmacogenetics. Some of his most impactful work related to understanding and modeling the balance between spurious and real findings in high throughput genetic data, such as genome-wide association studies. His innovative methods allowed for flexibility in specifying effect size distributions for estimating the credibility of hypotheses, that was not limited to traditional parametric distributions. As part of the evaluation of his methods, he developed theory that predicts the expected behavior of these posterior estimates. In particular, he derived quantifications of the relation between the number of tests in a study and the proportion of real signals expected to be contained in a set of the smallest P-values. Most recently, he had been working on methods development for inferring potential gene-environment interactions in genome-wide association studies, by testing for the association of genetic variants with the covariance of quantitative traits. His trainees and collaborators will help carry forward this work.

New Tenure-Track Investigator

Dr. Stavros Garantziotis the Medical Director of the NIEHS Clinical Research Unit and head of the Matrix Biology Group has accepted an offer to join the Immunity, Inflammation and Disease Laboratory as a Tenure Track Investigator. Dr. Garantziotis will continue and expand his independent research program focused on extracellular matrix biology, innate immunity, lung inflammatory diseases, and airway remodeling triggered by the environment. He is expected to start as a Tenure Track Investigator in 2021.

BSC REVIEW OF THE NEUROBIOLOGY LABORATORY

The NIEHS DIR Board of Scientific Counselors reviewed the Neurobiology Laboratory and Dr. Robin Stanley from the Signal Transduction Laboratory, November 1-3, 2020

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 and 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:

- Michelle L. Block, Ph.D., Paul Stark Professor of Pharmacology, Department of Pharmacology and Toxicology, Indiana University School of Medicine and The Stark Neuroscience Research Institute, Indianapolis, IN
- Evan Deneris, Ph.D., Professor and Vice Chair, Department of Neurosciences, Case Western Reserve University School of Medicine, Cleveland, OH
- Frederick Dyda, Ph.D., Chief, Structural Biochemistry Section, Laboratory of Molecular Biology, National Institute of Diabetes, Digestive, and Kidney Diseases, National Institutes of Health, Bethesda, MD

- Arlen W. Johnson, Ph.D., Professor, Molecular Biosciences, The University of Texas, College of Natural Sciences, Austin, TX
- Frances Leslie, Ph. D., Professor Emerita, Pharmaceutical Sciences and Pharmacology and Dean of the Graduate Division, School of Medicine, University of California, Irvine, CA
- Lori L. McMahon, Ph. D., Dean, UAB Graduate School, Jarman F. Lowder Professor of Neuroscience, Director, Comprehensive Neuroscience Center and Co-Director, Roadmap Scholars Program, University of Alabama at Birmingham, Birmingham, AL
- Gary W. Miller, Ph.D., Vice Dean for Research Strategy and Innovation and Professor, Department of Environmental Health Sciences, Columbia University School of Public Health, New York, NY
- Lisa M. Monteggia, Ph.D., Professor of Pharmacology and Barlow Family Director of the Vanderbilt Brain Institute, Vanderbilt School of Medicine, Nashville, TN
- Joaquin Ortega, Ph.D., Professor and Research Director FEMR, Department of Anatomy and Cell Biology and the Centre for Structural Biology, McGill University, Montreal QC, Canada
- Patrick Sinn, Ph.D., Faculty Director, Viral Vector Core and Associate Professor of Pediatrics, Pulmonary Medicine and Microbiology and Immunology, University of Iowa, Carver College of Medicine, Iowa City, IA
- Judith R. Walters, Ph.D., Senior Investigator, Neurophysiological Pharmacology Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD 20892-3702
- Anne E. West, M.D., Ph.D., Professor, Department of Neurobiology and Member of the Duke Institute for Brain Sciences and Duke Cancer Institute, Duke University School of Medicine, Durham, NC
- William C. Wetsel, Ph.D., Director, Mouse Behavioral and Neuroendocrine Analysis Core Facility, Department of Psychiatry and Behavioral Sciences and Associate Professor in Neurobiology, Duke University School of Medicine, Durham, NC
- Hermes H. Yeh, Ph.D., William W. Brown 1835 Memorial Professor of Physiology and Neurobiology, Department of Molecular and Systems Biology, Geisel School of Medicine at Dartmouth University, Hanover, NH
- Henry Yin, Ph.D., Professor, Department of Neurobiology and Director of Graduate Studies Duke Neurobiology, Duke University School of Medicine, Durham, NC
- Xiaoxi Zhuang, Ph.D., Professor of Neurobiology, The University of Chicago, Chicago, IL

Agenda

Sunday, November 1 – Zoom meeting
Closed Evening Session

4:00 - 4:30 p.m.	Welcome and Discussion of Past Board Reviews, Drs. Rick Woychik, Darryl Zeldin, Jerrel Yakel and John Cidlowski
4:30 – 6:00 p.m.	BSC Discussion of Review, Dr. Kathleen Caron and panel

Monday, November 2 - Zoom meeting
Morning Session

8:30 - 8:45 a.m.	Welcome, Drs. Kathleen Caron and Richard Woychik
8:45 - 9:05	Overview, Neurobiology Laboratory, Jerrel Yakel, Ph.D.
9:05 - 9:55	Ion Channel Physiology Group, Jerrel Yakel, Ph.D.
9:55 - 10:05	Coffee Break
10:05 - 10:55	Synaptic and Developmental Plasticity Group, Serena Dudek, Ph.D.
10:55 - 11:45	Developmental Neurobiology Group, Patricia Jensen, Ph.D.
11:45 - 12:45	Closed Working Lunch
12:50 - 1:35	Closed 1:1 Sessions with Investigators, Drs. Yakel, Dudek and Jensen

Afternoon Session

1:35 - 2:25 p.m.	In Vivo Neurobiology Group, Guohong Cui, M.D., Ph.D.
2:25 - 3:00 p.m.	Neuroepigenomics Group, Elizabeta Gjoneska, Ph.D.
3:00 - 3:15 p.m.	Coffee Break
3:15 - 3:45 p.m.	Closed 1:1 Sessions with Investigators, Drs. Cui and Gjoneska
3:45 - 4:25 p.m.	Closed Sessions with Fellows and Staff Scientists
4:25 - end	Closed BSC Discussion and completion of individual review assignments by each member

Tuesday November 19 - Zoom Meeting
Morning Session

8:30 - 9:20 a.m.	Nucleolar Integrity Group, Robin Stanley, Ph.D.
9:20 - 9:45 a.m.	Closed 1:1 Sessions with Investigator, Dr. Stanley
9:45 - 10:00 a.m.	Coffee Break
10:00 - 12:00 p.m.	Poster Session
12:00 - 12:45 p.m.	Lunch
12:45 - 1:45 p.m.	Closed: Sessions with Core Managers, Neurobehavioral Core and Viral Vector Core, Jesse D. Cushman, Ph.D., and Negin P. Martin, Ph.D.
1:45 - 3:45 p.m.	Closed BSC Discussion and completion of individual review assignments by each member
3:45 - 5:15 p.m.	Closed Session and Debriefing to NIEHS/DIR Leadership
5:15 p.m.	Adjourn

NIEHS SCIENCE DAYS

The Eighteenth Annual NIEHS Science Day was held on November 20, 2020 as a virtual event due to the COVID-19 pandemic. This "One NIEHS" event is held annually to celebrate the achievements of NIEHS scientists from all of our Divisions. The virtual event was attended by at least 250 individuals from NIEHS and academic centers across North Carolina. The NIEHS Science Day program consisted of 10 oral presentations given by fellows, students, and technicians from DIR and DNTP, as well as 30 recorded elevator presentations. Judging for the awards was performed by extramural scientists from universities located across North Carolina and NIEHS Intramural Scientists.

Mentor of the Year: Douglas Bell, Ph.D., Senior Investigator, Environmental Epigenomics and Disease Group, Immunity, Inflammation and Disease Laboratory

Fellow of the Year: Oswaldo Lozoya, Ph.D., IRTA Postdoctoral Fellow, Environmental Epigenomics and Disease Group, Immunity, Inflammation and Disease Laboratory

Best Oral Presentation: Ciro Amato III, Ph.D., IRTA Postdoctoral Fellow, Reproductive Developmental Biology Group, Reproductive and Developmental Biology Laboratory

Best Elevator Pitch Presentations:

1. Alicia Chi, Ph.D., IRTA Postdoctoral Fellow, Pregnancy and Female Reproduction Group, Reproductive and Developmental Biology Laboratory
2. Mandy Goldberg, Ph.D., IRTA Postdoctoral Fellow, Chronic Disease Epidemiology Group, Epidemiology Branch
3. Victoria Placentra, IRTA Postbaccalaureate Fellow, Mutagenesis and DNA Repair Regulation Group, Genome Integrity and Structural Biology Laboratory

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DIR PAPERS OF THE YEAR FOR 2020

McCann KE, Lustberg DJ, Shaughnessy EK, Carstens KE, Farris S, Alexander GM, Radzicki D, Zhao M, Dudek SM. Novel role for mineralocorticoid receptors in control of a neuronal phenotype. *Mol Psychiatry*. 2021 Jan;26(1):350-364. doi: 10.1038/s41380-019-0598-7. Epub 2019 Nov 19. PMID: 31745235; PMCID: PMC7234915.

> Mineralocorticoid receptors (MRs) in the brain play a role in learning and memory, neuronal differentiation, and regulation of the stress response. Within the hippocampus, the highest expression of MRs is in area CA2. CA2 pyramidal neurons have a distinct molecular makeup resulting in a plasticity-resistant phenotype, distinguishing them from neurons in CA1 and CA3. Thus, we asked whether MRs regulate CA2 neuron properties and CA2-related behaviors. Using three conditional knockout methods at different stages of development, we found a striking decrease in multiple molecular markers for CA2, an effect mimicked by chronic antagonism of MRs. Furthermore, embryonic deletion of MRs disrupted afferent inputs to CA2 and enabled synaptic potentiation of the normally LTP-resistant synaptic currents in CA2. We also found that CA2-targeted MR knockout was sufficient to disrupt social behavior and alter behavioral responses to novelty. Altogether, these results demonstrate an unappreciated role for MRs in controlling CA2 pyramidal cell identity and in facilitating CA2-dependent behaviors.

Shats I, Williams JG, Liu J, Makarov MV, Wu X, Lih FB, Deterding LJ, Lim C, Xu X, Randall TA, Lee E, Li W, Fan W, Li JL, Sokolsky M, Kabanov AV, Li L, Migaud ME, Locasale JW, Li X. Bacteria Boost Mammalian Host NAD Metabolism by Engaging the Deamidated Biosynthesis Pathway. *Cell Metab*. 2020 Mar 3;31(3):564-579.e7. doi: 10.1016/j.cmet.2020.02.001. PMID: 32130883; PMCID: PMC7194078.

> Nicotinamide adenine dinucleotide (NAD), a cofactor for hundreds of metabolic reactions in all cell types, plays an essential role in metabolism, DNA repair, and aging. However, how NAD metabolism is impacted by the environment remains unclear. Here, we report an unexpected trans-kingdom cooperation between bacteria and mammalian cells wherein bacteria contribute to host NAD biosynthesis. Bacteria confer resistance to inhibitors of NAMPT, the rate-limiting enzyme in the amidated NAD salvage pathway, in cancer cells and xenograft tumors. Mechanistically, a microbial nicotinamidase (PncA) that converts nicotinamide to nicotinic acid, a precursor in the alternative deamidated NAD salvage pathway, is necessary and sufficient for this protective effect. Using stable isotope tracing and microbiota-depleted mice, we demonstrate that this bacteria-mediated deamidation contributes substantially to the NAD-boosting effect of oral nicotinamide and nicotinamide riboside supplementation in several tissues. Collectively, our findings reveal an important role of bacteria-enabled deamidated pathway in host NAD metabolism.

Qin Y, Grimm SA, Roberts JD, Chrysovergis K, Wade PA. Alterations in promoter interaction landscape and transcriptional network underlying metabolic adaptation to diet. *Nat Commun*. 2020 Feb 19;11(1):962. doi: 10.1038/s41467-020-14796-x. PMID: 32075973; PMCID: PMC7031266.

Metabolic adaptation to nutritional state requires alterations in gene expression in key tissues. Here, we investigated chromatin interaction dynamics, as well as alterations in cis-regulatory loci and transcriptional network in a mouse model system. Chronic consumption of a diet high in saturated fat, when compared to a diet high in carbohydrate, led to dramatic reprogramming of the liver transcriptional network. Long-range interaction of promoters with distal regulatory loci, monitored by promoter capture Hi-C, was regulated by metabolic status in distinct fashion depending on diet. Adaptation to a lipid-rich diet, mediated largely by nuclear receptors including Hnf4α, relied on activation of preformed enhancer/promoter loops. Adaptation to carbohydrate-rich diet led to activation of preformed loops and to de novo formation of new promoter/enhancer interactions. These results suggest that adaptation to nutritional changes and metabolic stress occurs through both de novo and pre-existing chromatin interactions which respond differently to metabolic signals.

Dinse GE, Parks CG, Weinberg CR, Co CA, Wilkerson J, Zeldin DC, Chan EKL, Miller FW. Increasing Prevalence of Antinuclear Antibodies in the United States. *Arthritis Rheumatol*. 2020 Jun;72(6):1026-1035. doi: 10.1002/art.41214. Epub 2020 Apr 30. PMID: 32266792; PMCID: PMC7255943.

OBJECTIVE: Growing evidence suggests increasing frequencies of autoimmunity and certain autoimmune diseases, but findings are limited by the lack of systematic data and evolving approaches and definitions. This study was undertaken to investigate whether the prevalence of antinuclear antibodies (ANA), the most common biomarker of autoimmunity, changed over a recent 25-year span in the US.
METHODS: Serum ANA were measured by standard indirect immunofluorescence assays on HEp-2 cells in 14,211 participants age ≥12 years from the National Health and Nutrition Examination Survey, with approximately one-third from each of 3 time periods: 1988-1991, 1999-2004, and 2011-2012. We used logistic regression adjusted for sex, age, race/ethnicity, and survey design variables to estimate changes in ANA prevalence across the time periods.
RESULTS: The prevalence of ANA was 11.0% (95% confidence interval [95% CI] 9.7-12.6%) in 1988-1991, 11.5% (95% CI 10.3-12.8%) in 1999-2004, and 15.9% (95% CI 14.3-17.6%) in 2011-2012 (P for trend < 0.0001), which corresponds to ~22 million, ~27 million, and ~41 million affected individuals, respectively. Among adolescents age 12-19 years, ANA prevalence increased substantially, with odds ratios (ORs) of 2.02 (95% CI 1.16-3.53) and 2.88 (95% CI 1.64-5.04) in the second and third time periods relative to the first (P for trend < 0.0001). ANA prevalence increased in both sexes (especially in men), older adults (age ≥50 years), and non-Hispanic whites. These increases in ANA prevalence were not explained by concurrent trends in weight (obesity/overweight), smoking exposure, or alcohol consumption.
CONCLUSION: The prevalence of ANA in the US has increased considerably in recent years. Additional studies to determine factors underlying these increases in ANA prevalence could elucidate causes of autoimmunity and enable the development of preventative measures.

Schellenberg MJ, Appel CD, Riccio AA, Butler LR, Krahn JM, Liebermann JA, Cortés-Ledesma F, Williams RS. Ubiquitin stimulated reversal of topoisomerase 2 DNA-protein crosslinks by TDP2. *Nucleic Acids Res*. 2020 Jun 19;48(11):6310-6325. doi: 10.1093/nar/gkaa318. PMID: 32356875; PMCID: PMC7293035.

> Tyrosyl-DNA phosphodiesterase 2 (TDP2) reverses Topoisomerase 2 DNA-protein crosslinks (TOP2-DPCs) in a direct-reversal pathway licensed by ZATTZNF451 SUMO2 E3 ligase and SUMOylation of TOP2. TDP2 also binds ubiquitin (Ub), but how Ub regulates TDP2 functions is unknown. Here, we show that TDP2 co-purifies with K63 and K27 poly-Ubiquitinated cellular proteins independently of, and separately from SUMOylated TOP2 complexes. Poly-ubiquitin chains of ≥ Ub3 stimulate TDP2 catalytic activity in nuclear extracts and enhance TDP2 binding of DNA-protein crosslinks in vitro. X-ray crystal structures and small-angle X-ray scattering analysis of TDP2-Ub complexes reveal that the TDP2 UBA domain binds K63-Ub3 in a 1:1 stoichiometric complex that relieves a UBA-regulated autoinhibitory state of TDP2. Our data indicates that that poly-Ub regulates TDP2-catalyzed TOP2-DPC removal, and TDP2 single nucleotide polymorphisms can disrupt the TDP2-Ubiquitin interface.

Gambini A, Stein P, Savy V, Grow EJ, Papas BN, Zhang Y, Kenan AC, Padilla-Banks E, Cairns BR, Williams CJ. Developmentally Programmed Tankyrase Activity Upregulates β-Catenin and Licenses Progression of Embryonic Genome Activation. *Dev Cell*. 2020 Jun 8;53(5):545-560.e7. doi: 10.1016/j.devcel.2020.04.018. Epub 2020 May 21. PMID: 32442396; PMCID: PMC7335218.

> Embryonic genome activation (EGA) is orchestrated by an intrinsic developmental program initiated during oocyte maturation with translation of stored maternal mRNAs. Here, we show that tankyrase, a poly(ADP-ribosyl) polymerase that regulates β-catenin levels, undergoes programmed translation during oocyte maturation and serves an essential role in mouse EGA. Newly translated TNKS triggers proteasomal degradation of axin, reducing targeted destruction of β-catenin and promoting β-catenin-mediated transcription of target genes, including Myc. MYC mediates ribosomal RNA transcription in 2-cell embryos, supporting global protein synthesis. Suppression of tankyrase activity using knockdown or chemical inhibition causes loss of nuclear β-catenin and global reductions in transcription and histone H3 acetylation. Chromatin and transcriptional profiling indicate that development arrests prior to the mid-2-cell stage, mediated in part by reductions in β-catenin and MYC. These findings indicate that post-transcriptional regulation of tankyrase serves as a ligand-independent developmental mechanism for post-translational β-catenin activation and is required to complete EGA.

Hayne CK, Schmidt CA, Haque MI, Matera AG, Stanley RE. Reconstitution of the human tRNA splicing endonuclease complex: insight into the regulation of pre-tRNA cleavage. *Nucleic Acids Res*. 2020 Aug 20;48(14):7609-7622. doi: 10.1093/nar/gkaa438. PMID: 32476018; PMCID: PMC7641302.

> The splicing of tRNA introns is a critical step in pre-tRNA maturation. In archaea and eukaryotes, tRNA intron removal is catalyzed by the tRNA splicing endonuclease (TSEN)

complex. Eukaryotic TSEN is comprised of four core subunits (TSEN54, TSEN2, TSEN34 and TSEN15). The human TSEN complex additionally co-purifies with the polynucleotide kinase CLP1; however, CLP1's role in tRNA splicing remains unclear. Mutations in genes encoding all four TSEN subunits, as well as CLP1, are known to cause neurodegenerative disorders, yet the mechanisms underlying the pathogenesis of these disorders are unknown. Here, we developed a recombinant system that produces active TSEN complex. Co-expression of all four TSEN subunits is required for efficient formation and function of the complex. We show that human CLP1 associates with the active TSEN complex, but is not required for tRNA intron cleavage in vitro. Moreover, RNAi knockdown of the Drosophila CLP1 orthologue, cbc, promotes biogenesis of mature tRNAs and circularized tRNA introns (tricRNAs) in vivo. Collectively, these and other findings suggest that CLP1/cbc plays a regulatory role in tRNA splicing by serving as a negative modulator of the direct tRNA ligation pathway in animal cells.

Borrel A, Auerbach SS, Houck KA, Kleinstreuer NC. Tox21BodyMap: a webtool to map chemical effects on the human body. *Nucleic Acids Res*. 2020 Jul 2;48(W1):W472-W476. doi: 10.1093/nar/gkaa433. PMID: 32491175; PMCID: PMC7319561.

To support rapid chemical toxicity assessment and mechanistic hypothesis generation, here we present an intuitive webtool allowing a user to identify target organs in the human body where a substance is estimated to be more likely to produce effects. This tool, called Tox21BodyMap, incorporates results of 9,270 chemicals tested in the United States federal Tox21 research consortium in 971 high-throughput screening (HTS) assays whose targets were mapped onto human organs using organ-specific gene expression data. Via Tox21BodyMap's interactive tools, users can visualize chemical target specificity by organ system, and implement different filtering criteria by changing gene expression thresholds and activity concentration parameters. Dynamic network representations, data tables, and plots with comprehensive activity summaries across all Tox21 HTS assay targets provide an overall picture of chemical bioactivity.

Welch BM, Keil AP, van 't Erve TJ, Deterding LJ, Williams JG, Lih FB, Cantonwine DE, McElrath TF, Ferguson KK. Longitudinal profiles of plasma eicosanoids during pregnancy and size for gestational age at delivery: A nested case-control study. *PLoS Med*. 2020 Aug 14;17(8):e1003271. doi: 10.1371/journal.pmed.1003271. PMID: 32797061; PMCID: PMC7428021.

BACKGROUND: Inflammation during pregnancy is hypothesized to influence fetal growth. Eicosanoids, an important class of lipid mediators derived from polyunsaturated fatty acids, can act as both direct influences and biomarkers of inflammation through a variety of biological pathways. However, quantifying these distinct inflammatory pathways has proven difficult. We aimed to characterize a comprehensive panel of plasma eicosanoids longitudinally across gestation in pregnant women and to determine whether levels differed by infant size at delivery.

METHODS AND FINDINGS: Our data come from a case-control study of 90 pregnant women nested within the LIFECODES prospective birth cohort study conducted at Brigham and Women's Hospital in Boston, Massachusetts. This study included 31 women who delivered small for gestational age (SGA) babies (SGA, ≤10th percentile), 28 who delivered large for gestational age (LGA) babies (≥90th percentile), and 31 who delivered appropriate for gestational age (AGA) babies (controls, >10th to <90th percentile). All deliveries occurred between 2010 and 2017. Most participants were in their early 30s (median age: 33 years), of white (60%) or black (20%) race/ethnicity, and of normal pre-pregnancy BMI (median BMI: 23.5 kg/m2). Women provided non-fasting plasma samples during 3 prenatal study visits (at median 11, 25, and 35 weeks gestation) and were analyzed for a panel of eicosanoids. Eicosanoids were grouped by biosynthetic pathway, defined by (1) the fatty acid precursor, including linoleic acid (LA), arachidonic acid (AA), docosahexaenoic acid (DHA), or eicosapentaenoic acid (EPA), and (2) the enzyme group, including cyclooxygenase (COX), lipoxygenase (LOX), or cytochrome P450 (CYP). Additionally, the concentrations of the 4 fatty acids (LA, AA, DHA, and EPA) were measured in maternal plasma. Analytes represent lipids from non-esterified plasma. We examined correlations among eicosanoids and trajectories across pregnancy. Differences in longitudinal concentrations between case groups were examined using Bayesian linear mixed effects models, which included participant-specific random intercepts and penalized splines on gestational age. Results showed maternal plasma levels of eicosanoids and fatty acids generally followed U-shaped curve patterns across gestation. Bayesian models showed that associations between eicosanoids and case status varied by biosynthetic pathway. Eicosanoids derived from AA via the CYP and LOX biosynthetic pathways were positively associated with SGA. The adjusted mean concentration of 12-HETE, a LOX pathway product, was 56.2% higher (95% credible interval 6.6%, 119.1%) among SGA cases compared to AGA controls. Eicosanoid associations with LGA were mostly null, but negative associations were observed with eicosanoids derived from AA by LOX enzymes. The fatty acid precursors had estimated mean concentrations 41%-97% higher among SGA cases and 33%-39% lower among LGA cases compared to controls. Primary limitations of the study included the inability to explore the potential periods of susceptibility of eicosanoids on infant size due to limited sample size, along with the use of infant size at delivery instead of longitudinal ultrasound measures to estimate fetal growth.

CONCLUSIONS: In this nested case-control study, we found that eicosanoids and fatty acids systematically change in maternal plasma over pregnancy. Eicosanoids from specific inflammation-related pathways were higher in mothers of SGA cases and mostly similar in mothers of LGA cases compared to controls. These findings can provide deeper insight into etiologic mechanisms of abnormal fetal growth outcomes.

Mazzone CM, Liang-Guallpa J, Li C, Wolcott NS, Boone MH, Southern M, Kobzar NP, Salgado IA, Reddy DM, Sun F, Zhang Y, Li Y, Cui G, Krashes MJ. High-fat food biases hypothalamic and mesolimbic expression of consummatory drives. *Nat Neurosci*. 2020 Oct;23(10):1253-1266. doi: 10.1038/s41593-020-0684-9. Epub 2020 Aug 3. PMID: 32747789; PMCID: PMC7529959.

Maintaining healthy body weight is increasingly difficult in our obesogenic environment. Dieting efforts are often overpowered by the internal drive to consume energy-dense foods. Although the selection of calorically rich substrates over healthier options is identifiable across species, the mechanisms behind this choice remain poorly understood. Using a passive devaluation paradigm, we found that exposure to high-fat diet (HFD) suppresses the intake of nutritionally balanced standard chow diet (SD) irrespective of age, sex, body mass accrual and functional leptin or melanocortin-4 receptor signaling. Longitudinal recordings revealed that this SD devaluation and subsequent shift toward HFD consumption is encoded at the level of hypothalamic agouti-related peptide neurons and mesolimbic dopamine signaling. Prior HFD consumption vastly diminished the capacity of SD to alleviate the negative valence associated with hunger and the rewarding properties of food discovery even after periods of HFD abstinence. These data reveal a neural basis behind the hardships of dieting.

Lujan SA, Longley MJ, Humble MH, Lavender CA, Burkholder A, Blakely EL, Alston CL, Gorman GS, Turnbull DM, McFarland R, Taylor RW, Kunkel TA, Copeland WC. Ultrasensitive deletion detection links mitochondrial DNA replication, disease, and aging. *Genome Biol*. 2020 Sep 17;21(1):248. doi: 10.1186/s13059-020-02138-5. PMID: 32943091; PMCID: PMC7500033.

BACKGROUND: Acquired human mitochondrial genome (mtDNA) deletions are symptoms and drivers of focal mitochondrial respiratory deficiency, a pathological hallmark of aging and late-onset mitochondrial disease.
RESULTS: To decipher connections between these processes, we create LostArc, an ultrasensitive method for quantifying deletions in circular mtDNA molecules. LostArc reveals 35 million deletions (~ 470,000 unique spans) in skeletal muscle from 22 individuals with and 19 individuals without pathogenic variants in POLG. This nuclear gene encodes the catalytic subunit of replicative mitochondrial DNA polymerase γ. Ablation, the deleted mtDNA fraction, suffices to explain skeletal muscle phenotypes of aging and POLG-derived disease. Unsupervised bioinformatic analyses reveal distinct age- and disease-correlated deletion patterns.
CONCLUSIONS: These patterns implicate replication by DNA polymerase γ as the deletion driver and suggest little purifying selection against mtDNA deletions by mitophagy in postmitotic muscle fibers. Observed deletion patterns are best modeled as mtDNA deletions initiated by replication fork stalling during strand displacement mtDNA synthesis.

Bisogno LS, Yang J, Bennett BD, Ward JM, Mackey LC, Annab LA, Bushel PR, Singhal S, Schurman SH, Byun JS, Nápoles AM, Pérez-Stable EJ, Fargo DC, Gardner K, Archer TK. Ancestry-dependent gene expression correlates with reprogramming to pluripotency and multiple dynamic biological processes. *Sci Adv*. 2020 Nov 20;6(47):eabc3851. doi: 10.1126/sciadv.abc3851. PMID: 33219026; PMCID: PMC7679169.

Induced pluripotent stem cells (iPSCs) can be derived from differentiated cells, enabling the generation of personalized disease models by differentiating patient-derived iPSCs into disease-relevant cell lines. While genetic variability between different iPSC lines affects differentiation potential, how this variability in somatic cells affects pluripotent potential is less understood. We generated and compared transcriptomic data from 72 dermal fibroblast-iPSC pairs with consistent variation in reprogramming efficiency. By considering equal numbers of samples from self-reported African Americans and White Americans, we identified both ancestry-dependent and ancestry-independent transcripts associated with reprogramming efficiency, suggesting that transcriptomic heterogeneity can substantially affect reprogramming. Moreover, reprogramming efficiency-associated genes are involved in diverse dynamic biological processes, including cancer and wound healing, and are predictive of 5-year breast cancer survival in an independent cohort. Candidate genes may provide insight into mechanisms of ancestry-dependent regulation of cell fate transitions and motivate additional studies for improvement of reprogramming.

AWARDS AND HONORS

Scientific Awards

Dr. Francesco DeMayo (Chief, Reproductive and Developmental Biology Laboratory) was inducted as a Fellow for the American Association for the Advancement of Science.
Dr. Kelly Ferguson (Epidemiology Branch) received the inaugural Lou Guillette Jr. Outstanding Young Investigator award from the HEEDS organization.
Dr. Frederick Miller and Dr. Lisa Rider (Clinical Research Branch) received the NICHD Director's Group Award for work on the trans-NIH COVID-19 Maternal and Child Health subgroup.
Dr. Lisa Rider (Clinical Research Branch) also received the James T. Cassidy Award from the American Academy of Pediatrics Section on Rheumatology
Dr. Clarice Weinberg (Biostatistics and Computational Biology Branch) was honored as a "Changemaker," (one of 50 selected out of 11,000 alumni over 50 years) by the University of Washington School of Public Health.

Named Professorships/Lectures

Dr. Chandra Jackson (Epidemiology Branch) was invited as Keynote Speaker, at the Network of Minority Research Investigators meeting organized by the National Institute of Diabetes and Digestive and Kidney Diseases in Bethesda, MD.
Dr. Lisa Rider (Clinical Research Branch) was the Keynote speaker of the 18th Indian National Pediatric Rheumatology Conference. Dr. Rider also invited to present the Kennedy Lectureship at the University of Alabama Department of Pediatrics, Birmingham AL in November 2021.
Dr. Allen Wilcox (Scientist Emeritus, Epidemiology Branch) presented the Sholom Wacholder Distinguished Lecture in Quantitative Health Sciences at the National Cancer Institute.
Dr. Humphrey Yao (Reproductive and Developmental Biology Laboratory) presented the Keynote address at the Annual meeting American Society for Reproductive Medicine.
Dr. Darryl Zeldin (Scientific Director and Immunity, Inflammation and Disease Laboratory) gave Keynote Lectures 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.

Advisory/Editorial Boards

Dr. Trevor Archer (NIH Distinguished Investigator and Chief, Epigenetics and Stem Cell Biology Laboratory) was appointed to the Board of Reviewing Editors of *Science*.
Dr. William Copeland (Chief, Genome Integrity and Structural Biology Laboratory) served on the Mitochondrial Disease Gene Curation Expert Panel the Children's Hospital of Philadelphia, to curate mitochondrial disease genes that cause Leigh syndrome spectrum. He also served as Chair for the 25th anniversary meeting of the United Mitochondrial Disease Foundation which will be held June 2021 in Charlotte, NC.

Dr. Francesco DeMayo (Chief, Reproductive and Developmental Biology Laboratory) served as Chair of the Endometriosis (EM) peer review panel of the 2020 Peer Reviewed Medical Research Program (PRMRP) for the Department of Defense Congressionally Directed Medical Research Programs (CDMRP). He also served as President of 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 and Academic Program Review panel for Georgia Institute of Technology School of Biology. He also served as an Academic Editor for *BioMed Research International, Biochemistry Research International* and on the editorial boards *Nucleic Acids Research* and *DNA Repair*.

Dr. Kelly Ferguson (Epidemiology Branch) was appointed to the Editorial Board of *Environmental Research*.

Dr. Michael Fessler (Chief, Immunity, Inflammation and Disease Laboratory) 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 of *Matrix Biology*, *American Journal of Respiratory Cell and Molecular Biology* and the *American Journal of Physiology – Lung Cellular and Molecular Physiology*. 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 external scientific reviewer for the Hauptman-Woodward Medical Research Institute.

Dr. Patricia Jensen (Neurobiology Laboratory) served on the External Advisory Committee for the Metabolic Basis of Disease Center for the Pennington Biomedical Research Center.

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.*

Dr. Kathy Laber (Comparative Medicine Branch) served as an Emeritus Council Member for AAALAC.

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

Dr. Fredrick Miller (Clinical Research Branch) served on the Editorial Board of *Annals of the Rheumatic Diseases*. He was also appointed to the Scientific Advisory Board of the Autoimmune Registry that recently published the first comprehensive list of autoimmune diseases with prevalence statistics, disease subtypes, and disease profiles.

Dr. Marcos Morgan (Reproductive and Developmental Biology Laboratory) served as an invited reviewer for the Mexican National Council of Science and Technology (CONACYT).

Dr. Alison Motsinger-Reif (Chief, Biostatistics and Computational Biology Branch) served on the External Advisory Board for the Hercules Center at Emory. She was also appointment as a Statistical Associate Editor for *Exposome* and to the Statistical Board of Reviewing Editors for *Science*.

Dr. Geoffrey Mueller (Genome Integrity and Structural Biology Laboratory) was appointed a review editor and a guest editor for a special edition topic: Activation of innate immunity by allergens and allergenic sources" for *Frontier in Allergy*.

Dr. Anant Parekh (Chief, Signal Transduction Laboratory) was appointed as Executive Editor of *Function* and served on the editorial board of *Cells*.

Dr. Lalith Perera (Genome Integrity and Structural Biology Laboratory) served on the Editorial Board of *International Journal of Molecular Sciences* and was appointed as an Associate Editor of *Frontiers in Chemistry*.

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*.

Dr. Keith Shockley (Biostatistics and Computational Biology Branch) served on the editorial boards of *Toxicologic Pathology*, *Frontiers in Toxicogenomics*, *Frontiers in Computational Toxicology and Informatics*. He also served on the Juvenile Animal Clinical Pathology Reference Data Work Group for the Health and Environmental Sciences Institute (HESI).

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.*

Dr. Steve Wu (Reproductive and Developmental Biology Laboratory) served on the editorial board of Chinese Journal of Physiology, the official publication of Chinese Physiological Society (TAIWAN).

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.* Dr. Yao was also selected as a regular member of the Cellular, Molecular and Integrative Reproduction Study Session for the NIH.

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 Federal 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

From January 1, 2020 through December 31, 2020, 3 pre-doctoral trainees left NIEHS to continue their doctoral studies in their universities. 22 post-baccalaureate trainees left NIEHS. The majority of them went to either medical school or graduate school. And 31 postdoctoral trainees left NIEHS. Below is a summary of the analysis of where the postdoctoral trainees have gone upon completing their training, what they are doing and the level of their current position.

What are they doing?

Additional postdoctoral training	**4**
Internship	**0**
Additional advanced degree	**1**
Primarily teaching	**0**
Primarily basic research	**8**
Primarily clinical research	**2**
Primarily clinical practice	**0**
Primarily applied research	**10**
Primarily patient care	**0**
Regulatory affairs	**2**
Science administration/project management	**0**
Intellectual property/ licensing and patenting	**0**
Consulting	**1**
Public policy	**0**
Science writing or communications	**0**
Grants management	**0**
Business development or Operations	**0**
Computation/informatics	**1**
Sales/marketing	**0**
Technical/customer support	**0**
Unknown or Undecided	**2**
Other	**0**
Unemployed	**0**
TOTAL	**31**

Where did they go?

Academic institution	**17**
Government agency	**6**
For-profit company	**6**
Non-profit organization	**0**
Private medical practice	**0**
Independent/self-employed	**1**
Unknown or Undecided	**1**
Unemployed	**0**
TOTAL	**31**

What is the level of their position?

Tenure track faculty	**9**
Non-tenure track faculty	**3**
Professional staff	**11**
Support staff	**0**
Management	**1**
Trainee	**5**
Unknown or Undecided	**2**
Unemployed	**0**
TOTAL	**31**