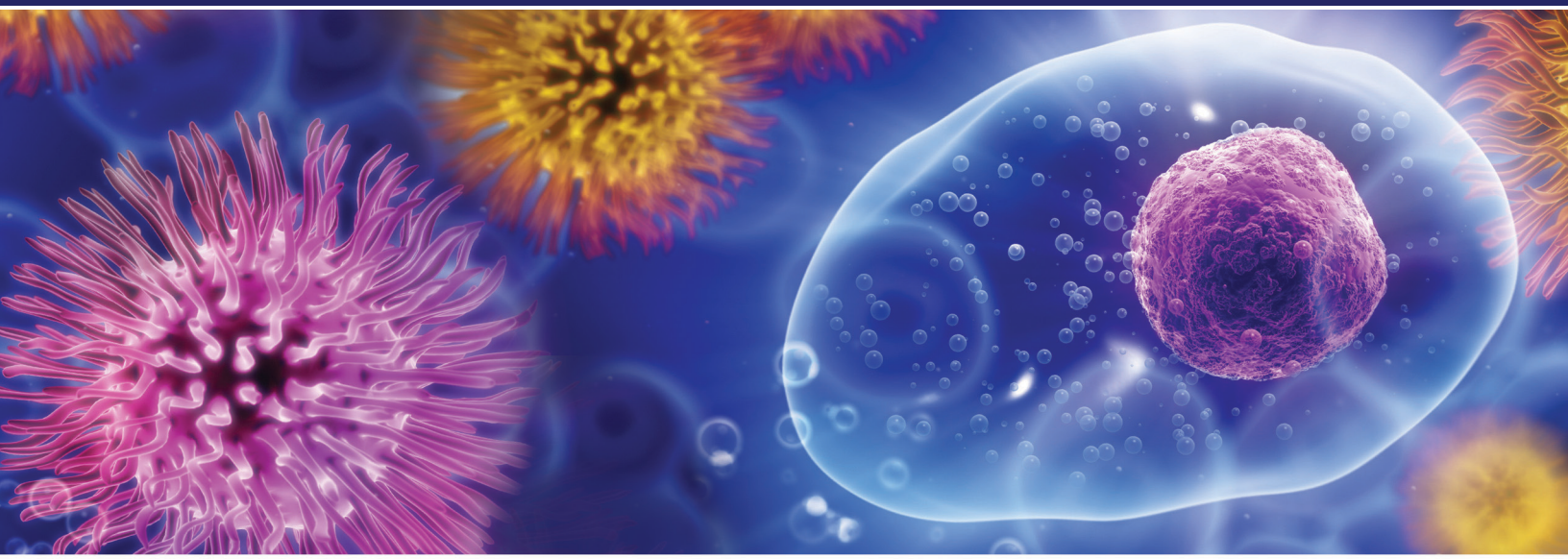
National Institute of Environmental Health Sciences



18TH ANNUAL

NIEHS Science Day

November 20, 2020

National Institutes of Health • U.S. Department of Health and Human Services

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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National Institute of
Environmental Health Sciences
Division of Intramural Research
Bldg. 101, Room A208
P. O. Box 12233, Mail Drop A2-09
Research Triangle Park, NC 27709

November 20, 2020

Dear Fellow NIEHS scientists and guests:

On behalf of Dr. Rick Woychik, Director of NIEHS and NTP, I would like to welcome you to Science Day. This event is a celebration of our research achievements, and is a way to recognize and honor some of our outstanding scientists. This year we are holding Science Day as a virtual event due to the COVID-19 pandemic

I especially wish to thank the outstanding members of the NIEHS IT community for their help in transforming Science Day into a virtual event that hopefully maintains many aspects of past in-person Science Day events.

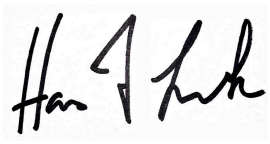
We have invited environmental health scientists from across North Carolina to join us today and participate as judges. We appreciate their efforts and welcome them to the to our virtual NIEHS world. Hopefully we will be able to see you on campus in future events.

We are also grateful to the DIR and DNTP Principal Investigators and Staff Scientists who are serving as judges for the recorded 3-minute elevator pitch competition.

Finally, I would also like to acknowledge the members of the NIEHS Science Day Steering Committee, Drs. Joel Abramowitz, Abee Boyles, Heather Henry, Thanh Hoang, Anton Jetten, Joseph Kolb, Leping Li, Negin Martin, Alex Merrick, Arun Pandiri, Thad Schug, Erik Tokar, Jack Taylor, and Karina Rodriguez. Without their Science Day would not have been possible.

Please enjoy the Science Day events and join me in celebrating some of our scientific achievements.

Sincerely,



Hans Luecke, Ph.D.

Extramural Judges

David Aylor North Carolina State University	Megen Culpepper Appalachian State University
Liping Feng Duke University	Kymberly Gowdy Ohio State College of Medicine
Jack D. Griffith University of North Carolina	Samir Kelada University of North Carolina
Wolfgang Liedtke Duke University	Shuang Lim North Carolina State University
Alex Marshall North Carolina Central University	Krista McCoy East Carolina University
Fernando Pardo-Manuel De Villena University of North Carolina, Chapel Hill	Heather Patisaul North Carolina State University
David Reif North Carolina State University	Xiaohe Yang North Carolina Central University

Intramural Judges

Trevor Archer	Donna Baird
Francesco Demayo	Paul Doetsch
Janet Hall	Traci Hall
Guang Hu	Geoff Mueller
Arun Pandiri	Roel Schaaper
Natalie Shaw	Robin Stanley
Erik Tokar	Alexandra White
Carmen Williams	Humphrey Yao
Dale Sandler	

NIEHS Science Day
November 20, 2020

Zoom
https://bit.ly/337mK8T

9:00-9:15 am Introduction and Welcoming Remarks, Rick Woychik, Ph.D., NIEHS Director, Hans Luecke, Ph.D., Chair, Science Day Committee

Oral Presentations Session 1:

9:15-10:30 am — 5 Oral Presentations by Fellows/Students/Technicians

9:15-9:30 am — #1. McCann KL, and Hall TMT. **Investigation of *Snora27* as a key determinant of stem cell identity**. (ESCBL, DIR)

9:30-9:45 am — #2. Shekhar S, Tonleu JT, Okigbo C, Leka HF, Kim AE, Purse BP, Hirsch KR, Wei B, Stolze B, McGrath JA, Smith-Ryan AE, Soldin SJ, and Hall JE. **The Impact of Energy Restriction on Thyroid Hormone Dynamics**. (CRB, DIR)

9:45-10:00 am — #3. Nodzenski MT, Shi M, Umbach D, Krahn J, Wise AS, Li L, Li Y, and Weinberg CR. **GADGETS: A stochastic search tool for detecting genetic epistasis using nuclear families**. (BCBB, DIR)

10:00-10:15 am — #4. Amato CM, and Yao HH. **Our differences make us complete: The identification of novel cell populations in penis development and their involvement in hypospadias**. (RDBL, DIR)

10:15-10:30 am — #5. Chen I, Birla S, and Tokar EJ. **A human embryonic stem cell-based high-throughput platform with AI technology to screen for developmental toxicants**. (NTPL, DNTP)

10:30-11:00 pm — Break

Oral Presentations Session 2:

11:00 am-12:15 pm — 5 Oral Presentations by Fellows/Students/Technicians

11:00-11:15 am — #6. Klemm B, Sikkemma AP, Hsu A, Horng J, Hall TM, Borgnia M, and Schaaper RM. **High resolution cryo-EM structures of a new dGTPase from L. blandensis reveal a novel mode of allosteric activation by dATP**. (GISBL, DIR)

11:15-11:30 am — #7. Hoang TT, Qi C, Paul KC, Lee M, White JD, Richards M, Auerbach SS, Long S, Shrestha S, Wang T, Beane Freeman LE, Parks C, BIOS Consortium, Xu C, Ritz B, Koppelman GH, and

	London SJ. **Epigenome-wide DNA methylation in relation to pesticide use among U.S. farmers**. (EB, DIR)
11:30-11:45 am	#8. Lozoya OA, Pappas B, and Bell DA. **Hyperplexed Sample Barcoded Screening for SARS-CoV-2 by LeaSH RNA-seq**. (IIDL, DIR)
11:45 am-12:00 pm	#9. Nicholson CO, Gevers K, de Groof A, and Blackshear PJ. **Scale drop disease virus encodes an mRNA decay factor that potentially suppresses the host's antiviral response**. (STL, DIR)
12:00-12:15 pm	#10. Mazzone CM, Liang-Guallpa J, Li C, Wolcott NS, Boone MH, Southern M, Kobzar NP, de Araujo Salgado I, Reddy DM, Sun F, Zhang Y, Li Y, Cui G, and Krashes MJ. **High-fat diet consumption tunes hypothalamic feeding circuits to calorically dense food**. (NL, DIR)
12:15-4:00 pm	Break (viewing of recorded 3-minute Elevator Pitch presentations)
4:00-5:00 pm	Science Day Award Ceremony and Closing Remarks

Oral Presentation 1

Investigation of *Snora27* as a key determinant of stem cell identity

McCann KL, and Hall TM
Macromolecular Structure, ESCBL, DIR, NIEHS

The most abundant RNA modification, pseudouridine, is found in both coding and noncoding RNAs where it regulates RNA stability and function. H/ACA small nucleolar RNAs (snoRNAs) guide pseudouridylation within a small nucleolar ribonucleoprotein complex (snoRNP). H/ACA snoRNA-guided pseudouridylation is essential as dysregulation of H/ACA snoRNAs is a hallmark of developmental disorders and cancer. Yet, it remains largely unknown how H/ACA snoRNA levels are regulated, how changes in snoRNA levels affect pseudouridylation of their target RNAs and ultimately how changes in pseudouridylation affect RNA expression and cell fate. To begin to address these questions, we quantified H/ACA snoRNA abundance during stem cell differentiation. We determined that H/ACA snoRNA abundance is regulated during differentiation and one specific snoRNA, *Snora27*, is significantly downregulated during differentiation in three different cellular model systems: differentiation of mouse embryonic stem cells (mESCs) by retinoic acid treatment, differentiation of mESCs into cardiomyocytes and mouse myoblast differentiation into myotubes. *Snora27* is known to direct pseudouridylation of the ribosomal RNA. Importantly, the level of pseudouridylation of the *Snora27* target nucleotide is also downregulated during differentiation. To discern the function of *Snora27* during myogenesis, we used CRIPSR/Cas9 to generate a functional null cell line. Strikingly, loss of *Snora27* function inhibited myogenesis and the generation of myotubes, demonstrating the significance of a single H/ACA snoRNA for cellular differentiation and development. As *Snora27* is known to guide pseudouridylation of the ribosomal RNA, we are working to determine how loss of *Snora27* alters ribosome assembly and function, how changes in ribosome function contribute to changes in gene expression, and how this ultimately drives a change in cell identity and a failure to differentiate into myotubes.

Oral Presentation 2

The Impact of Energy Restriction on Thyroid Hormone Dynamics

Shekhar S, Tonleu JT, Okigbo C, Leka HF, Kim AE, Purse BP, Hirsch KR, Wei B, Stolze B, McGrath JA, Smith-Ryan AE, Soldin SJ, and Hall JE
Neuro-Endocrine Reproductive Medicine, CRB, DIR, NIEHS and Department of Exercise and Sport Science, UNC-Chapel Hill and Department of Laboratory Medicine, Clinical Center, NIH

Background: Intermittent energy restriction (IER) is gaining popularity as a weight-loss strategy. However, the effect of short-term energy restriction on thyroid hormone dynamics is not well characterized.

Methods: Nineteen healthy women (mean age ± SD: 23.36± 2.08 yr) with normal baseline thyroid function and negative anti-thyroid antibodies underwent two 5-day interventions of a prescribed diet and identical standardized exercise in the early follicular phase of two menstrual cycles - neutral energy availability (NEA) 45 kCal/kg*LBM/d followed by deficient energy availability (DEA) 20 kCal/kg*LBM/d. Energy requirements were estimated as previously described (doi.org/10.1210/jendso/bvaa046.1468) and were used to generate a diet and exercise regimen for each participant. On day 5 of both interventions, body composition was assessed by BodPod®. Standardized NEA or DEA breakfast and lunch were provided as appropriate as well as a standardized NEA snack on both sampling visits. Blood sampling was performed for 8 hours starting at ~0800 h with measurement of TSH and growth hormone (GH) every 10 min, cortisol every 30 min, total T3 (TT3), reverse T3 (rT3) and total T4 (TT4) every 60 min, free T3 (FT3), free T4 (FT4) and TBG at the beginning and end of sampling. Liquid chromatography-tandem mass spectrometry (LC-MS) was used for measurements of all thyroid hormones, with the exception of TSH and TBG which were measured by ELISA as were GH and cortisol. Data were analyzed using ANOVA-RM and linear mixed models. Results are presented as mean or least squared mean ± sem.

Results: Body mass index, bodyweight and % fat mass were not different between interventions. GH and cortisol were unaffected by DEA ($p=0.46$, $p=0.63$). TBG was not affected by time of day or dietary intervention ($p=0.95$, $p=0.41$). However, compared with NEA, TT3 (89.15 ± 2.89 vs 95.55 ± 2.89 ng/dL for DEA and NEA, respectively; $p<0.0001$) and TSH (0.92 ± 0.08 vs 1.03 ± 0.09 mIU/mL; $p=0.0011$) were lower after DEA, while TT4 (6.26 ± 0.25 vs 6.06 ± 0.25 mg/dL; $p=0.04$), FT4 (3.37 ± 0.26 vs 2.94 ± 0.25 ng/d;, $p=0.0052$) and rT3 (11.77 ± 0.58 vs 8.85 ± 0.51 ng/dL; $p<0.0001$) were higher. Regardless of dietary intervention, FT3 ($p=0.0005$), TT3 ($p<0.0001$), TT4 ($p<0.0001$) and TSH ($p<0.0001$) decreased across the day.

Conclusion: Using LC-MS for as a more robust measure of thyroid hormones, we have now shown that changes in thyroid hormone dynamics occur after only 5 days of 55% energy restriction in the absence of alterations in body composition, cortisol, GH, TBG or the circadian pattern of thyroid hormone secretion. The decrease in TSH combined with the decrease in TT3 and increase in rT3 support the contribution of both central and peripheral mechanisms to these changes. Taken together these results provide support for a multi-level adaptation in thyroid hormone dynamics to conserve energy expenditure in response to short-term energy restriction.

Oral Presentation 3

GADGETS: A stochastic search tool for detecting genetic epistasis using nuclear families

Nodzenski MT, Shi M, Umbach D, Krahn J, Wise AS, Li L, Li Y, and Weinberg CR
Methods and Applications in Epidemiology, BCBB, DIR, NIEHS

We propose an evolutionary algorithm for detecting genetic epistasis based on case-parent triads or case-sibling pairs. Our approach, GADGETS (Genetic Algorithm for Detecting Genetic Epistasis using Triads or Siblings), efficiently explores huge search spaces to find multi-SNP interactions, allowing much larger candidate SNP sets than do existing methods. GADGETS first randomly samples a “population” of fixed-size sets of SNPs, and then assigns a fitness score to each “individual” (set) in that population based on paired comparisons between siblings. For triads, the disease-free pseudo-sibling is the hypothetical genome formed by the untransmitted parental SNPs. We initially randomly partition the sets into distinct clusters of individuals, as ‘island’ subpopulations, and allow those to separately evolve with limited cross-migration. Passage of individual SNP sets to the next generation is proportional to the fitness score, with modifications introduced by mutation and crossover. Island populations evolve over a pre-defined number of generations, with the highest scoring sets at termination considered potentially epistatic. We use permutation tests to assess collective evidence for joint association and a graphics procedure to divulge clusters of interacting SNPs. We document performance of GADGETS by applying it to simulated scenarios with multiple risk-associated SNP-sets embedded among 10,000 candidate SNPs. We further demonstrate that GADGETS outperforms competitors even after substantially reducing the number of SNPs considered to accommodate their limitations. Finally, we apply GADGETS to dbGaP case-parent triad data on oral clefting and identify sets of SNPs that appear to interact synergistically in Asians.

Oral Presentation 4

Our differences make us complete: The identification of novel cell populations in penis development and their involvement in hypospadias

Amato CM and Yao HH
Reproductive Developmental Biology, RDBL, DIR, NIEHS

Increasing prevalence of exposure to environmental estrogens and antiandrogens have amplified the incidence of male reproductive diseases. The cases of hypospadias, or incomplete closure of the urethra along the penis, has steadily increased over the past several decades and is the second most common birth defect in the United States. This defect often requires surgical interventions and if not corrected, it can lead to difficult urination and intercourse, leaving lasting psychological and physical impacts. In the male embryo, urethral closure relies on androgens, and disruption of androgen signaling with anti-androgens or estrogens at any time during urethral closure results in hypospadias. In mice, anti-androgens and estrogens differentially impact the severity of hypospadias that exhibit various phenotypes in different cell types of the penis. Therefore, we hypothesized that different cell types in the penis have different responses to androgens and estrogens. Using mouse as the model organism, we identified 2 new cell populations in the penis with cell lineage tracing method and single cell sequencing. These two cell types express either Forkhead box L2 (*Foxl2)* or Steroidogenic Factor 1 *(Sf1),* both hypospadias-related transcription factors. To investigate the importance of these two cell types, we ablated them by inducing cell death in respective cell types and found that the FOXL2+ and SF1+ cell populations have essential, but distinct roles in urethra closure and occurrence of hypospadias. Single-cell RNA sequencing on fetal penis further revealed that the FOXL2+ and SF1+ cell populations have unique transcriptomic profiles during the hormone sensitive window of development. They both express androgen and estrogen receptors and distinct patterns of androgen- and estrogen-responsive genes. In summary, we uncovered two novel cell populations that play essential roles in urethra closure and their different responsiveness to androgens and estrogens. These data provide new entry points to understand not only the basic biology of urethra closure but also the potential influences of anti-androgenic and estrogenic endocrine disruptors on penis development.

Oral Presentation 5

A human embryonic stem cell-based high-throughput platform with AI technology to screen for developmental toxicants

Chen I, Birla S, and Tokar EJ
Stem Cell Toxicology, NTPL, DNTP, NIEHS

Environmental factor-induced birth defects raise the risk for lifelong disabilities to those who survive and increases the economic burden to their families and society. While over 80,000 chemicals are registered for use in the United States, many of them have undergone little safety testing. Therefore, a rapid and accurate method for predicting environmental developmental toxicants in humans is strongly desired. In this study, we aim to develop a high-throughput platform with human embryonic stem cells (hESCs) and machine learning techniques to screen for environmental teratogens. Three-dimensional embryoid bodies (EBs) generated from hESCs were utilized as the model since their formation recapitulates many early embryogenic processes. Thirty-five chemicals with confirmed teratogenicity at four different levels (none, minimal, moderate, and high) were employed as the standards for model training. After a 10-day exposure, the expression of 20 hallmark genes related to germ layer formation in EBs was measured for training the prediction model in 10 different machine learning algorithms. With feature selection, the Random Forest-based model showed the best accuracy (mean: 53%) and reliability (mean: 0.37) to categorize chemicals into their corresponding risk levels. To enhance and further validate the prediction accuracy, the teratogenicity of an additional 19 chemicals with limited toxicity information was assessed by this model and the results were largely consistent with previous studies. Furthermore, a complementary system using fluorescent imaging to assess chemical-elicited structural alterations in EBs was also built with convolutional neural network (CNN) deep learning technique to help predict chemical teratogenicity. This pilot CNN model showed a high prediction accuracy (mean: 97%) and indicated a potential developmental toxicity of Bisphenol A. Together, these results present a promising potential of our screening platform in identifying human developmental toxicants and understanding their etiology.

Oral Presentation 6

High resolution cryo-EM structures of a new dGTPase from L. blandensis reveal a novel mode of allosteric activation by dATP

Klemm B, Sikkemma AP, Hsu A, Horng J, Hall TM, Borgnia M, and Schaaper RM
Mechanisms of Mutation, GISBL, DIR, NIEHS

dNTP triphosphohydrolases (dNTPases) are an important group of enzymes that perform multiple functions in the cell, including regulation of the dNTP pools and protection against invading DNAs, like viruses. These includes human SAMHD1 and *E. coli* dGTPase, which regulate dNTP pools in their respective organisms and are capable of restricting growth of certain viruses, such as HIV in humans or T7 bacteriophage in *E. coli*. In the present work, we have investigated a putative dNTPase from the marine organism *Leeuwenhoekiella blandensis* and show that the enzyme hydrolyzes, specifically, the critical DNA precursor dGTP (dGTPase). We also find that the enzyme is subject to allosteric activation by dATP, specifically. We have obtained high-resolution cryo-EM structures of the enzyme bound to the dGTP substrate and/or the dATP effector. The structures reveal detailed insights into the precise mode of catalysis, as well as the mode by which the allosteric activator dATP influences the activity. The structures represent the highest resolution cryo-EM structures of any SAMHD1-like dNTPase or, for that matter, any HD-domain protein to date. Allosteric regulation mediated by dATP represents a new regulatory feature among the studied dNTPases. We propose that allosteric regulation of a dGTPase by dATP represents a relevant feature for controlling the cellular dNTP pools, in particular in conjunction with the unusual Ribonucleotide Reductase found in *L. blandensis*.

Oral Presentation 7

Epigenome-wide DNA methylation in relation to pesticide use among U.S. farmers

Hoang TT, Qi C, Paul KC, Lee M, White JD, Richards M, Auerbach SS, Long S, Shrestha S, Wang T, Beane Freeman LE, Parks C, BIOS Consortium, Xu C, Ritz B, Koppelman GH, and London SJ
Genetics, Environment & Respiratory Disease, EB, DIR, NIEHS and the University of Groningen and the Biomolecular Screening Branch, NTP, NIEHS and the Chronic Disease Group, EB, DIR, NIEHS

BACKGROUND: Pesticide exposure is associated with various adverse health outcomes, but the underlying mechanisms are not fully understood. DNA methylation, an epigenetic modification, may play a role. DNA methylation signals likely differ by specific pesticide, but no epigenome-wide association studies have evaluated methylation signals across different pesticides. We conducted epigenome-wide analyses of DNA methylation in relation to several pesticides in the Agricultural Lung Health Study (ALHS).

METHODS: The ALHS is case-control study of current adult asthma, nested within a larger agricultural cohort. We analyzed data from blood DNA methylation generated using Illumina's MethylationEPIC array in 1,170 farmers. Pesticide use was reported within the larger agricultural cohort (past use) and the ALHS collected pesticide use in the last 12 months (current use). We evaluated 9 specific pesticides still marketed for which at least 30 farmers reporting past and current use, as well as 7 banned organochlorines with at least 30 farmers reporting past use. Using robust linear regression, we compared pesticide users to those who had never used the specific pesticide, adjusting for age, smoking status, packyears, state of residence, asthma status, and estimated cell type proportions.

RESULTS: Using family-wise error rate ($p<9\times10\text{-}8$) or false discovery rate ($p<0.05$), 162 differentially methylated CpGs were observed across eight currently marketed pesticides (acetochlor, atrazine, dicamba, glyphosate, malathion, metolachlor, mesotrione, and picloram) and one banned organochlorine (heptachlor). The 162 CpGs were unique to each pesticide. For 8 of 9 pesticides, we had information on the number of days the pesticide was used in their lifetime, and there was evidence of a dose-response at all but one CpG. Significant CpGs were enriched for transcription motifs and 28% were associated with gene expression. For picloram, associated CpGs were enriched for DNase I hypersensitivity sites in blood and fetal brain.

CONCLUSION: Our results suggest that pesticides have specific differential methylation signals. These differentially methylated patterns may be biomarkers of long-term exposures and may improve our understanding of pesticide-related health effects.

Oral Presentation 8

Hyperplexed Sample Barcoded Screening for SARS-CoV-2 by LeaSH RNA-seq

Lozoya OA, Pappas B, and Bell DA
Environmental Genomics, IIDL, DIR, NIEHS and Integrative Bioinformatics Support Group, NIEHS

During an outbreak, infectious pathogens like severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the viral pathogen responsible for Coronavirus Disease 2019 (COVID-19), can spread to pandemic levels and overwhelm healthcare systems, particularly when screening tools are lacking or scarce. As such, the ongoing global COVID-19 pandemic has rendered the current "gold standard" of care, SARS-CoV-2 nucleic acid screening by single-plex qPCR fluorometry, insufficient to fulfill growing demands for SARS-CoV-2 diagnostics worldwide. Ever since, public health networks have faced intermittent collapse of supply chains for diagnostics consumables and backlogs in COVID-19 diagnoses, leading to unchecked SARS-CoV-2 transmission, treatment delays for COVID-19 patients, and increased mortality rates overall.

The purpose of our project, supported through the NIH RADx-Rad initiative, is to develop an easily scalable and massively paralleled nucleic acid detection method that screens for both viral SARS-CoV-2 gRNA content (load) and a patient's own transcriptional response to infection (expression profile) in the same reaction, for >9,000 distinguishable patients combined, and with all of them tested at once by next generation sequencing (NGS). Next, transcriptional profiles are analyzed in the context of clinical data (electronic medical records of symptoms, treatments and outcomes) to identify and select features (biomarkers) predictive of clinical outcome using machine learning methods. These selected biomarkers are then validated in an independent clinical sample. Therefore, besides increasing testing throughput, our precision medicine approach to SARS-CoV-2 screening may provide a very early look at who may be asymptomatic but infectious, or who is about to get very sick with COVID-19.

We are currently fostering collaborative agreements with extramural parties all over the U.S. to share and collect standard (nasopharyngeal swabs) and alternative (saliva, buccal swab) types of clinical specimens from SARS-CoV-2 positive patients. Through these agreements, we can compare the efficacy of SARS-CoV-2 diagnostics and COVID-19 prognostics based on different sample types, refine the logistics to implement our technology off-site, and benchmark its robustness by cross-validating its performance in multiple diagnostics laboratories. Our ultimate goal is to make it easy to adopt this technology in clinical environments by matching its implementation at the bench level to the standard operation protocols for qPCR-based SARS-CoV-2 diagnostics used in certified testing laboratories.

Our technology is designed for versatility: it can be tailored quickly to detect entire pathogen classes. Looking ahead, methods developed during this project could apply to other infectious pathogens, which will help jump-start new epidemiological screening platforms, and exploit mass-scale volume, throughput, and versatility of NGS technologies, when facing future pandemics.

Oral Presentation 9

Scale drop disease virus encodes an mRNA decay factor that potentially suppresses the host's antiviral response

Nicholson CO, Gevers K, de Groof A, and Blackshear PJ
Post-Transcriptional Gene Expression, STL, DIR NIEHS and MSD Animal Health/Intervet International bv., Department Discovery & Technology, The Netherlands

The majority of seafood is now and for the foreseeable future farmed. Asian seabass is farmed for human consumption in a region populated by over 600 million people. The growth of Asian seabass farming has led to an increase in the lethal scale drop disease that can devastate the fish farm's population. Furthermore, scale drop disease is observed in a setting where fish population density is high; an observation that mirrors the reality of the current COVID-19 pandemic where high population densities correlate with the number of infection cases. The causative agent of scale drop disease is the scale drop disease virus (SDDV). Among the ~129 open reading frames encoded by the SDDV genome is one called ORF_096L that encodes a protein with macromolecular domains similar to the tristetraprolin (TTP) protein family of mRNA decay factors found in eukaryotes. TTP and its orthologs bind to AU-rich sequences in the 3'UTR of mRNA using their tandem CCCH zinc fingers (TZF), and use a domain in their C-termini to bind to the CNOT1 subunit of the CCR4-NOT (CNOT) deadenylation complex. The result is the subsequent removal of the poly-A tail from the bound mRNA and decay of the mRNA. This mechanism of action allows TTP and its orthologs to post-transcriptionally regulate diverse biological processes like the TNF-alpha mediated inflammatory response, hematopoiesis, and placental physiology. Interestingly, our study has uncovered that SDDV's ORF_096L promotes mRNA decay by binding RNA sequences distinct from the one bound by eukaryotic TTP orthologs. Furthermore, we have found evidence suggesting that ORF_096L suppresses the host's interferon-alpha and -gamma responsive pathways which are known innate antiviral response pathways. Therefore, our study has revealed how a virus can co-opt the macromolecular domains found in host proteins to promote its life cycle.

Oral Presentation 10

High-fat diet consumption tunes hypothalamic feeding circuits to calorically dense food

Mazzone CM, Liang-Guallpa J, Li C, Wolcott NS, Boone MH, Southern M, Kobzar NP, de Araujo Salgado I, Reddy DM, Sun F, Zhang Y, Li Y, Cui G, and Krashes MJ
In Vivo Neurobiology, NL, DIR, NIEHS and Diabetes, Endocrinology, and Obesity Branch, NIDDK, and the State Key Laboratory of Membrane Biology, Peking University School of Life Sciences

Dieting is notoriously difficult, particularly with the convenient availability of calorically dense foods, particularly those high in fat content. Despite ever-expanding dietary guidelines, sustained internal drives to consume energy rich foods over lower calorie alternatives often surmount efforts to diet. The impact of high-fat diets (HFDs) on the neural mechanisms regulating feeding remain poorly understood. Agouti-related peptide (AgRP) expressing neurons of the arcuate nucleus of the hypothalamus are activated by energy deficits and robustly drive food intake. To determine the influence of high-fat foods on these neurons, we used cutting-edge *in vivo* fiber photometry and optogenetic strategies in mice to longitudinally assess changes in activity and function of AgRP neurons during standard diet (SD) presentation following a history of HFD access. Behaviorally, we found that HFD exposure dramatically and persistently reduces SD consumption in a manner independent of sex or changes in body weight. Fiber photometry recordings revealed that HFD access suppressed AgRP neuron responses to SD presentation, or gastric infusion of calories, and these effects persisted following HFD withdrawal. While AgRP neuron responses to SD were blunted by one week of HFD exposure, effects of the gut hunger hormone ghrelin, or various gastrointestinal satiety signals, remained intact at this time point. Surprisingly, a history of HFD consumption greatly reduced AgRP neuron stimulation-evoked feeding of SD, while evoked feeding of HFD remained robust. Together, these findings uncover diet-induced alterations in primary neural feeding circuits that contribute to the challenges associated with maintaining a healthy diet.

3-Minute Elevator Pitch Presentations

Pitch 1. Bhawsinghka N, Glenn KF, and Schaaper RM.
Duplex sequencing to investigate hypermutation associated with dGTP starvation(GISBL).

Pitch 2. Bridges KA, and Nicol B.
The Potential Role of Runx1 in Ovarian Pathologies (RDBL).

Pitch 3. Chi RA, Wang T, Huang C, Wu S, Young S, Lydon J, and DeMayo F.
Inside the uterus: How phosphosignaling impact pregnancy outcome(RDBL).

Pitch 4. Foo AC, Thompson PM, Chen S, Jadi R, Lupo B, Eugene DF, Arora S, Placentra VC, Premkumar L, Perera L, Pederson LC, Matrin N, and Mueller GA.
The mosquito protein AEG12 exerts broad-spectrum antiviral activity through lipid membrane disruption(NMR).

Pitch 5. Frazier MN, Pillon MC, Dillard LB, Williams JG, Kocaman S, Krahn JM, Perera L, Hayne CK, Gordon J, Stewart ZD, Sobhany M, Deterding LJ, Hsu AL, Dandey VP, Borgnia M, and Stanley RE.
U're the one I want: cryo-EM structures of the SARS-CoV-2 endoribonuclease Nsp15 reveal insight into nuclease specificity and dynamics(STL).

Pitch 6. Goldberg M, D'Aloisio AA, O'Brien KM, Zhao S, and Sandler DP.
Pubertal timing and breast cancer risk in the Sister Study cohort(EB).

Pitch 7. Gordon J, and Stanley RE.
Regulation of the Human RNasePNK pre-rRNA Processing Complex(STL).

Pitch 8. Gu T, Suen A, Jefferson W, and Williams C.
Using endometrial organoids to characterize molecular changes in uterine glands from neonatal DES-exposed mice. (RDBL).

Pitch 9. Gunn KA, Bisogno LS, and Archer TK.
Determining the role of BAF60a, an accessory BAF subunit, in the Glucocorticoid Receptor (GR) response of A549 cells(ESCBL).

Pitch 10. Hayne CK.
tRNA processing: snipping without CLP1.(STL).

Pitch 11. Hewitt SC, Lydon J, Galjart N, and DeMayo F.
The chromatin structural protein CCCTC-binding factor (CTCF) is essential for optimal endometrial development and function (RDBL).

Pitch 12. Inoue K, Ankney AJ, Pedersen LC, Mueller GA, and Shaw ND.
Epigenetic control of ACE2 by the chromatin remodeler, SMCHD1(CRB).

Pitch 13. Kar A, Degtyareva N, and Doetsch PW.
Dysregulation of NTHL1 and sensitivity to chemotherapeutic agents in human cells(GISBL).

Pitch 14. Kocaman S, and Stanley R.
Identifying the unfolding mechanism of Rix7, an essential AAA-ATPase in

ribosome biogenesis
(STL).

Pitch 15. Lawrence KG, Neihoff NM, Keil AP, Braxton JW, Christenbury K, Stewart PA, Stenzel MR, Curry MD, Engel LS, and Sandler DP.
Exposure to airborne crude oil chemicals and adult incident asthma (EB).

Pitch 16. Li R, Wang T, Wu S, and Demayo F.
TRIM28, a novel partner of PGR in regulating uterine biology (RDBL).

Pitch 17. Mellouk N, Grimm S, and Yao HH.
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Pitch 18. Moore KR, Williams DR, and Baird DD.
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Pitch 19. Niehoff NM, Keil AP, Jones RJ, Fan S, Gierach GL, and White AJ.
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Pitch 20. Ortega MT, McGrath JA, Carlson L, Flores Poccia V, Larson G, Douglas C, Sun BZ, Zhao S, Vesper HW, Duke L, Botelho JC, Filie AC, and Shaw ND.
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Pitch 22. Placentra VC, Degtyareva NP, Mueller GA, Bortner CD, and Doetsch PW.
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Pitch 24. Stewart Z, Stewart ZD, Hayne CK, and Stanley RE.
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Pitch 25. Warden MS, DeRose EF, Mueller GA, Gavis ER, and Hall TM.
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