ROBERT S. SHERWIN
YCCI ALL SCHOLAR DAY

Abstracts

Monday, May 13, 2024

The Anlyan Center, N107

Yale School of Medicine

300 Cedar St.

New Haven, CT 06519

Selected Oral Presentation Abstracts

Speaker 1 Abstract

Title: Causal and Systems-Based Epigenetic Clocks Demonstrate Accelerated Aging in Patients with Schizophrenia

Authors: Zachary M. Harvanek, Raghav Sehgal, Albert Higgins-Chen

Background/Significance: Schizophrenia is a severe, chronic psychiatric disorder associated with premature death, in some studies up to 20 years earlier than age-matched controls, which is not entirely explained by behavioral factors. Prior epigenetic studies have suggested there are accelerated aging phenotypes associated with schizophrenia, but these have depended on the specific epigenetic clock used. New epigenetic clocks may allow insight into mechanistic relationships between schizophrenia, epigenetic aging, and premature morbidity and mortality.

Methods: In this study, we analyzed causality-enriched epigenetic clocks[2] as well as systems-based epigenetic clocks[3] in publicly available datasets of patients with Schizophrenia and controls. Seven cross-sectional datasets containing DNA methylation data were available for this study, with a total samples size of 4,146 individuals, including 2,210 patients with schizophrenia and 1,936 controls. Meta-analyses utilized fixed effects models and accounted for age and reported sex.

Results: In meta-analyses across all three causality-enriched clocks (CausAge, DamAge, and AdaptAge), patients with schizophrenia had accelerated epigenetic aging compared to controls. SystemsAge also demonstrated accelerated epigenetic aging in patients with schizophrenia ($p < 1e-117$). This age acceleration was seen in ten of the eleven individual system clocks, with the most prominent acceleration in the Heart, Lung, and Inflammation clocks. Further analyses assessed associations with these clocks and exposure to Clozapine use and found age acceleration in the Heart, Metabolic, Inflammation, and Lung clocks.

Discussion: These are the first analyses of causality- and systems-based clocks in patients with schizophrenia. They demonstrate broad evidence of accelerated aging, including in both harmful (e.g., DamAge) and adaptive (e.g., AdaptAge) methylation sites, and across a wide range of physiological systems. Future work may examine whether other medications or specific symptoms are related to age acceleration.

Speaker 2 Abstract

Title: Ablation of fibroblast activation protein (FAP+) cells results in thinner intra-abdominal adhesions which lack cells of mesothelial origin.

Authors: Blackburn, HN[1,2]; Roulis, M[1]; Lewis, W[3,4]; Qu, R[1,3,4]; Kluger, Y[3,4]; Flavell, RA[1].

[1]Dept of Immunobiology, Yale Sch of Med
[2]Dept of Surgery, Yale Sch of Med
[3]Program of Computational Biology and Bioinformatics, Yale Univ
[4]Dept of Pathology, Yale Sch of Med

Fibrosis evolved as a fundamental property of multicellular life and, as such, fibrotic diseases and complications affect every organ system. Despite this, there are limited effective anti-fibrotic therapies. Intra-abdominal adhesions are a common and severe fibrotic complication of abdominal surgery, and the underlying cells and mechanisms driving adhesion development remain unclear. Here, we sought to understand the role of mesothelial-to-mesenchymal transition (MMT) and FAP+ cells in the development and cellular origin of intra-abdominal adhesions.

First, we employed the creER-loxP genetic tool to selectively label cell types within the abdomen. These mice underwent either adhesion-promoting or sham procedures and tissue was evaluated for cellular origins. Lineage-tracing results demonstrated that mesothelial cells are a primary source of cells within adhesions through MMT. To further interrogate our hypothesis of MMT, we performed high resolution single cell RNA sequencing of sorted mesothelial and mesenchymal cells from lineage-traced adhesions. These analyses identified distinct clusters of transitioning cells—unique to adhesions—that were lineage-traced to mesothelial origin, and defined by a combination of known mesothelial, mesenchymal, and pro-fibrotic markers.

Next, we selectively ablated proliferating FAP+ cells prior to adhesion induction and found that without FAP+ cells, mice develop fewer adhesions and thinner adhesions. To interrogate the cellular origin of adhesions which lack FAP+ cells, we ablated proliferating FAP+ cells within lineage tracing mice. Here we found that ablation of FAP+ cells results in the complete absence of mesothelial origin cells within adhesions.

Thus, ablation of FAP+ cells results in thinner intra-abdominal adhesions which lack a component of mesothelial-to-mesenchymal transition. Treatments that target FAP+ cells could be valuable in decreasing the burden of adhesions in humans.

Speaker 3 Abstract

Title: Longitudinal assessment of adverse family outcomes in children with standard-risk b-acute lymphoblastic leukemia from Children's Oncology Group AALL0932

Rozalyn L. Rodwin, MD, MHS,[1,2] John A. Kairalla, PhD,[3] Emily Hibbitts, PhD, [3] Lyn M. Balsamo, PhD,[1] Meenakshi Devidas, PhD, MBA,[4] Alexandra Dreyzin, MD,[5] Moira K. Whitley,[1] Naomi J. Winick, MD,[6] William L. Carroll, MD,[7] Stephen P. Hunger, MD,[8] Elizabeth Raetz, MD,[7] Reuven J. Schore, MD,[5,9] Mignon L. Loh, MD,[10] Kirsten K. Ness, PhD, FAPTA,[11] Anne L. Angiolillo, MD,[5,9,12] Nina S. Kadan-Lottick, MD MSPH [13]

1. Department of Pediatrics, Yale University School of Medicine, New Haven, CT
2. Yale Cancer Center, New Haven, CT
3. Department of Biostatistics, College of Medicine & Public Health Professions, University of Florida, Gainesville, FL
4. Department of Global Pediatric Medicine, St. Jude Children's Research Hospital, Memphis, TN
5. Division of Oncology, Center for Cancer and Blood Disorders, Children's National Hospital, Washington, DC
6. Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX
7. Perlmutter Cancer Center, Department of Pediatrics, NYU Langone Medical Center, New York, NY
8. Department of Pediatrics, Children's Hospital of Philadelphia and the Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA
9. Department of Pediatrics and Clinical and Translational Oncology Program, George Washington University School of Medicine and Health Sciences, Washington, DC
10. Ben Towne Center for Childhood Cancer Research, Seattle Children's Research Institute and Department of Pediatrics, Seattle Children's Hospital, University of Washington, Seattle, WA
11. Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Memphis, TN
12. Servier Pharmaceuticals, Boston, MA
13. Georgetown University Lombardi Comprehensive Cancer Center, Washington, DC

Background/Purpose: Acute lymphoblastic leukemia (ALL) survivors experience impaired quality of life, but less is known about family outcomes. Children's Oncology Group AALL0932 randomized reduction in vincristine/dexamethasone to every 4 (VCR/DEX4) vs. 12 (VCR/DEX12) weeks in the average risk subset of National Cancer Institute standard-B-ALL (SR AR B-ALL). We measured family outcomes longitudinally, and by treatment arm.

Methods: SR AR B-ALL patients from AALL0932, ≥4 years old, with an English-speaking parent, were evaluated at end-consolidation (T1), maintenance cycles one and four (T2, T3), maintenance cycle seven/girls' end-of-therapy (T4), and boys only end-of-therapy (T5). Surveys assessed parent-reported adverse household events since diagnosis, unhealthy family function (Family Assessment Device scores >2), and perceived child vulnerability (Child Vulnerability Scale score ≥10). Outcomes were measured longitudinally and compared between treatment groups.

Results: There were 555 participants (47.0% female, 81.1% White, 15.9% Hispanic, 58.4% age <6 years). By T1, 61.7% of responding participants had at least one parent-reported adverse household event (no longer employed [18.8%], reduced work hours [39.6%], loss of job-related opportunity [14.4%], separation/divorce [0.8%]); 56.0% were perceived vulnerable, and 20.6% had unhealthy family function. Most outcomes occurred early, but the cumulative proportion

increased slightly by T4 (76.8% any parent-reported event, 71.0% perceived vulnerable, 30.5% unhealthy function). When comparing post-randomization VCR/DEX4 vs. VCR/DEX12 among those without baseline issues, there was no difference in the cumulative proportion of participants with household events (44.3% vs. 37.2%), perceived vulnerability (55.4% vs. 67.3%), or unhealthy family function (12.7% vs. 21.7%) by T4 (all $p>0.05$). When adjusting for participant age, sex, race, ethnicity, and insurance, there was no association between randomization arm and any outcomes.

Conclusions: SR AR B-ALL survivors experience adverse family outcomes, even with reduction in maintenance vincristine/dexamethasone. Since most family outcomes occur early in treatment, focused interventions should be provided at therapy initiation and throughout survivorship care.

Speaker 4 Abstract

Title: Elucidating the Kinetics and Dynamics of Growth-inhibitory Immune Responses to *Plasmodium falciparum* Strains

Authors: Kelly A Hagadorn[1], Mouhamad Sy[2,3], Awa B. Deme[2,3], Ibrahima Mbaye Ndiaye[2,3], Younous Diedhiou[2,3], Amadou Moctar Mbaye[2,3], Sarah K. Volkman[4], Dyann F. Wirth[4], Carole A. Long[5], Kazutoyo Miura[5], Ababacar Diouf[5], Daouda Ndiaye[2,3]* & Amy K. Bei[1,2]*

[1]Department of Epidemiology of Microbial Diseases, Yale School of Public Health, New Haven, CT, USA.
[2]Laboratory of Parasitology and Mycology, Cheikh Anta Diop University, Aristide le Dantec Hospital, Dakar, Senegal.
[3]International Research and Training Center for Applied Genomics and Health Surveillance (CIGASS) at UCAD, Dakar, Senegal (Current address).
[4]Department of Immunology and Infectious Diseases, Harvard T. H. Chan School of Public Health, Boston, MA, USA.
[5] Laboratory of Malaria and Vector Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA

*These authors contributed equally

Abstract:
Malaria, caused by *Plasmodium spp.,* specifically *Plasmodium falciparum*, is a major global health threat. Identification of highly conserved antigen targets that prove to be true correlates of immune protection could be transformational in malaria research. To do this, there is need to better understand the mechanisms underlying the development of natural immunity to malaria. We performed *in vitro* growth inhibition assays (GIA) using field-isolated *P. falciparum* isolates to better understand the kinetics and dynamics of functional immune responses to merozoite antigens longitudinally and with consideration to natural genetic diversity of currently circulating parasite genotypes. This study used samples from a longitudinal study in Thiès, Senegal, a low transmission setting with majority monogenomic infections, that enrolled 70 patients between 2014-2017. Patients were followed for two years after enrollment and plasma were collected at eight timepoints after detection of a malaria infection. *P. falciparum* parasite isolates from day 0 infections were preserved and have been genomically characterized by both 24-SNP barcode and Whole Genome Sequencing. GIAs were performed with homologous (0 SNP) parasite strains from the individual's day 0 malaria infection (n=21) and heterologous (8 SNP) parasite strains (n=17). Three distinct neutralizing antibody patterns for homologous strains longitudinally were identified, 1) long persisting high inhibitory responses, 2) inhibition that peaks at week 2/week 4 and declines to baseline, and 3) long persisting low inhibitory responses. Neutralizing antibody patterns for heterologous strains were found to be decreased or identical as compared to homologous parasite strains. Future work will be dedicated to identifying merozoite antigens and antibody biophysical features that are associated with these functional neutralizing immune responses. Understanding determinants of functional immune responses and the ability to generate strain-transcending immune responses will ultimately help to define immune correlates of protection in malaria and aid in vaccine development.

Poster Abstracts

Poster Abstract 1

Title: Distinct pattern of synaptic loss in Parkinson's disease depression and initial findings from the Yale Ketamine PD (KET-PD) trial

Authors: Mina Ansari[1], Yanghong Yang[1], Mika Naganawa[1], Mark Dias[1], Shannan Henry$_1$, Jim Ropchan[1], Robert A. Comley[2], Nabeel Nabulsi[1], Yiyun Huang[1], Richard E. Carson[1], Sjoerd J. Finnema[2], Sina Nikayin[1], Sule Tinaz[1], David Matuskey[1], Gerard Sanacora[1], Sophie E Holmes[1]

[1]Yale University, New Haven, CT [2] Abbvie, Chicago, IL

Background: Depression is common in Parkinson's disease (PD). We hypothesize that synaptic loss underpins depression and that ketamine will effectively treat depression in PD. We investigated synaptic loss in PD depression (PDd) using PET and presented the initial blinded findings of the first clinical trial investigating ketamine's antidepressant effects in PDd.

Methods: Ten people with PDd (age: 61 ± 7 years; 4 men) and twelve people with PD but without depression (age: 62 ± 6 years; 5 men) were imaged with [^{11}C]UCB-J PET. The primary outcome measure was binding potential (BP_{ND}: calculated from SRTM2), calculated using the centrum semiovale as the reference region. Two-tailed t-tests were used to determine between-group differences in BP_{ND}, and Pearson's correlation was used for association with depressive symptoms, assessed using the Montgomery-Asberg depression rating scale (MADRS). We present preliminary data from a separate ongoing clinical trial, in which 24 people with PDd (62 ± 9), 11 men, 13 women, mean MADRS: 25± 4), were randomized to receive six infusions of either ketamine (0.5mg/kg) or placebo, with MADRS score being the primary outcome measure.

Results: We observed significantly lower synaptic density in the PDd vs. PD group in the dorsolateral prefrontal cortex (dlPFC), anterior cingulate and hippocampus (p<0.05); and a significant negative correlation between MADRS and [^{11}C]UCB-J in the dlPFC (r= -0.64, p=0.004). Initial blinded results from the clinical trial indicate robust reductions in depression severity following ketamine or placebo (66% responders, 54% in remission), with evidence of sustained effects at 1 month follow-up (50% responders, 38% in remission).

Conclusions: A lower synaptic density in PDd we observed, which could represent a target for synaptogenic interventions such as ketamine. Although blinded, the preliminary findings of our clinical trial show a robust reduction in depression symptoms suggesting that ketamine is a promising intervention for PDd.

Poster Abstract 2

Lower SV2A Synaptic Density following Chronic Stress and Relationships with Cognitive impairment: an *In Vivo* [^{18}F]SynVesT-1 and Pet Study in Male and Female Rats

Ruth H. Asch[1], Zhengxin Cai[2,3], Ralph J. DiLeone[1], Richard E. Carson[2,4], Conor M. Liston[5], and Irina Esterlis[1,2,6]

[1]Department of Psychiatry, Yale School of Medicine, New Haven, CT, 06511
[2]Department of Radiology & Biomedical Imaging, Yale School of Medicine, New Haven, CT, 06520
[3]Department of Pharmachology, Yale School of Medicine, New Haven, CT, 06520
[4]Department of Biomedical Engineering, Yale School of Engineering & Applied Science, New Haven, CT, 06520
[5] Weill Cornell Graduate School of Medical Sciences, New York, NY, 10065
[6]U.S. Department of Veteran Affairs National Center for Posttraumatic Stress Disorder, Clinical Neurosciences Division, VA Connecticut Healthcare System, West Haven, CT, 06516, USA

Background: Stress is well recognized risk factor for developing neuropsychiatric conditions. Converging evidence indicates chronic stress can induce synaptic loss in prefrontal cortex (PFC) and hippocampus- key mediators of mood and cognition. Past studies of synaptic density relied mostly on postmortem measures, however, it is now possible to measure synaptic density *in vivo* using radioligands targeting synaptic vesicle protein 2A (SV2A) and positron emission tomography (PET). Therefore, this study used *in vivo* PET to investigate synaptic SV2A density following chronic stress in male and female rats and explored relationships with behavior.

Methods: Male and female Long-Evans rats were exposed to 23 days of chronic unpredictable stress (CUS; n=16/sex) and compared to control (CON) rats (*n*=8/sex). Following CUS, Novel Object Recognition was employed to test cognitive function. In a subset rats (*n*=6/sex/group), PET with [^{18}F]SynVesT-1 was used to measure synaptic density in PFC and hippocampus.

Results: Overall, CUS was associated with lower synaptic density (η_p^2=0.43, p=0.005). Specifically, synaptic density was lower in CUS male PFC (5.7%, p<0.001) and CUS female hippocampus (4.6%, p=0.055) relative to same-sex CON rats. Further, in CUS rats, cognitive impairment was associated with synaptic density in PFC (r=0.666, p=0.025) and hippocampus (r=0.774, p=0.005).

Conclusions: We demonstrate for the first time that [^{18}F]SynVesT-1 and PET can be used for the *in vivo* quantification of synaptic density in a rodent model of chronic stress and relationships with stress-related behavioral deficits. Studies such as this are critical for facilitating translational research needed to elucidate synaptic mechanisms in disease and treatment response.

Funding Sources: KL2 GR119980; T32 MH014276; U.S. Department of Veterans Affairs National Center for PTSD

Poster Abstract 3

Coupling of osteocytic osteolysis and functional osteoclasts in lactation

Diana Athonvarangkul, MD-PhD and John Wysolmerski, MD

Osteocytic osteolysis may contribute to bone loss in lactation. The connection between osteocytes and osteoclasts to regulate lactational bone resorption is not understood. In this study, we provide novel evidence that bone resorption in lactation is coordinated between osteocytes and osteoclasts. In particular, loss of functional osteoclasts prevents osteocytic osteolysis during lactation.

We initially hypothesized that inhibition of osteoclast activity would lead to a compensatory increase in osteocytic osteolysis during lactation. We treated 10 week-old lactating CD1 mice with recombinant osteoprotegerin (OPG, 10mg/kg) to block RANKL signaling, zoledronic acid (ZA,100 ug/kg) to inhibit osteoclasts or vehicle, from delivery through mid-lactation (day 12). Eliminating osteoclast function with either OPG or ZA prevented lactational trabecular BMD loss measured by microCT. The average osteocyte lacunar area, measured by backscatter electron microscopy, did not significantly differ among the groups. However, OPG and ZA tended to prevent the shift to large osteocyte lacunae (30-60 uM) that was observed in the lactation group, reflecting loss of osteocytic osteolysis and presence of osteocyte heterogeneity. Lactational increases in gene expression of the key resorptive enzymes tartrate-resistant acid phosphatase, cathepsin K, and matrix metallopeptidase 13 were not observed in osteocyte-enriched RNA samples from OPG and ZA groups, suggesting that loss of active osteoclasts interferes with the phenotypic switch in osteocytes.

Since the above results suggested that osteocytic osteolysis depends on RANKL signaling, we asked whether osteocytes might express RANK during lactation. We crossed the mT/mG reporter mouse with the RANK-Cre mouse to identify cells expressing RANK by their switch from red to green fluorescence. All osteocytes remained red, which indicated that RANK is not expressed on osteocytes. Therefore, the inhibition of osteocytic osteolysis by OPG must be mediated indirectly by osteoclasts or another RANK-expressing cell.

Here we showed that osteoclastic resorption is coordinated with osteocytic osteolysis in lactation. Our working theory is osteocytes are stimulated by RANKL-dependent coupling factor(s) from active osteoclasts to induce a bone resorption gene program. Identifying clastokines that couple the activity of osteoclasts and osteocytes could be important for pathophysiology outside of lactation and may lead to therapeutic targets for pathologic bone turnover.

Poster Abstract 4

eGFR Variability in Heart Failure (HF) Patients with CardioMEMS Monitoring

Authors: Lawrence Ullman Jr.[1], Gabriel Barsotti[1], Paige Beaudry[1], Jeffrey Turner[1]

Author Affiliations: 1. Yale School of Medicine, Department of Internal Medicine, Section of Nephrology

Introduction: Increased estimated glomerular filtration rate (eGFR) variability has been associated with an increased risk of stroke, myocardial infarction, and all-cause mortality.[1,2] Chronic heart failure (CHF) patients are a subset of patients that are commonly associated with variable eGFR.[3] One approach to HF management is CardioMEMS implantation, which allows patients' providers to remotely monitor their pulmonary artery pressure (PAP) to guide care in real-time. Therefore, we hypothesized that HF management guided by CardioMEMS may improve eGFR variability due to treatment adjustments aiding in volume regulation.

Methods: This retrospective observational study included HF patients identified from the Yale Heart Failure and Transplant CardioMEMS registry. Patients initiated on dialysis, received a heart or kidney transplant, or died during the observation period were excluded. Creatinine measurements were taken at baseline (15-12 months before CardioMEMS implantation) and 12 months pre- and post-CardioMEMS implantation. The 2021 CKD-EPI equation was used to calculate eGFR, and eGFR variability was quantified through the coefficient of variation (CV). The primary outcomes were >40% eGFR decline, need for dialysis or transplant, and death. Outcome data was collected up to six years following CardioMEMS deployment.

Results: 431 patients received a CardioMEMS implant at Yale between 2017-2023, and we randomly sampled 160 of these patients. Of the 160 patients, 91 patients satisfied inclusion and exclusion criteria. 26% of patients had >40% eGFR decline (n=24), 7.7% initiated dialysis (n=7), 1.1% had transplantation (n=1), and 27.5% died (n=25). The CV of eGFR demonstrated a nonsignificant downward trend of 0.014 (p=0.2011) when comparing before and after CardioMEMS deployment.

Conclusion: In this subset of CardioMEMS patients, we observed a small decrease in eGFR variability when comparing pre- and post-CardioMEMS implantation. Future research investigating how changes in pharmacological treatment guided by CardioMEMS data is warranted to better understand the impact of real-time PAP data on eGFR variation.

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Poster Abstract 5

Title: Conceptualizing Experiences of Anti-Black Racism in Black American Adolescents
Author(s) and Affiliation(s): Amanda Calhoun, MD, MPH, (Yale Child Study Center), Mark Beitel, PhD (Yale Child Study Center)

Abstract:

Although there is increasing documentation of the crucial impact of racism on the mental health of Black youth, there is still a dearth of research targeting the mental health of Black youth, especially pertaining to their lived experiences of racism and its mental health sequalae. There is a need for measures that address the adverse coping behaviors that may occur because of anti-Black racism such as disordered eating[1], dysphoria[2], hypervigilance and rumination[3], substance use[4], and somatic symptoms[5] so that clinicians can understand where and how to intervene. Extant psychopathology measures are tied to DSM-5-TR diagnostic criteria and may be limited because research shows that trauma, which could describe experiences of anti-Black racism, produces subthreshold and/or diagnostically cross-cutting negative psychological effects, which may not be well characterized by current diagnostic tools. In addition, existing screeners do not provide a way to explore links between anti-Black racism and psychopathology; for example, the pressure that Black adolescents feel to lose weight to fit perceived Eurocentric ideals may facilitate disordered eating.

This work is urgently needed to fill a major gap in our approach to the mental health of Black children and adolescents. It is intended to have a significant impact on the assessment of anti-Black racism dimensions as well as eventually, behavioral sequelae of anti-Black racism experiences in Black youth, and of course, interventions that can more accurately target the specific and unique experiences of anti-Black experienced by Black youth.

This study will begin the preliminary work, through a qualitative approach, to design a future quantitative questionnaire that will more accurately and comprehensively capture a) the dimensions of anti-Black racism and b) various coping behaviors tied to psychiatric clinical endpoints, such as depression, anxiety and rumination, hypervigilance, somatic symptoms, disordered eating, and substance use.

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Poster Abstract 6

Title: **Sodium Homeostasis and the Immune Response**

Authors: Irene Chernova[1], Wenzhi Song[2], Tayyaba Ishaq[1] and Joseph Craft[1, 2]
[1]Departments of Internal Medicine and [2]Immunobiology, Yale University School of Medicine, New Haven, CT

Abstract: The production of an effective immune response is a complex endeavor that is sensitive to fluctuations and disturbances of substances as varied as hormones, cytokines, glucose and lipids. One factor whose effects on the immune response have not been explored is ion concentrations, specifically the concentration of the main extracellular ion sodium ($[Na^+]$). Disorders of sodium homeostasis, hyponatremia (low serum $[Na^+]$) and hypernatremia (high serum $[Na^+]$) are highly prevalent, yet little is known about immune responses under such conditions.

We set out to investigate sodium's effects on B cells and recapitulate our observations in mouse models of protective immunity and autoimmunity. *In vitro* studies demonstrated that B cells have decreased survival and impaired differentiation to antibody-secreting cells when exposed to high $[Na^+]$. Pharmacologic blockade or genetic manipulation of Na^+-K^+-ATPase, a major sodium transporter, resulted in impaired B cell survival *in vitro* when exposed to high $[Na^+]$ and abrogated B cell numbers *in vivo*. Animals made hypernatremic via water deprivation had smaller spleens and fewer B lymphocytes. Moreover, the immune response to immunization, as measured by antigen-specific B cells and antibody titers, was significantly diminished when transient hypernatremia was induced at the time of antigen introduction. We are currently investigating how changes in intracellular ion concentrations lead to disruption of B cell homeostasis and induced immune responses. We hope this work will provide important insights into how to optimize an ionic environment to promote an effective immune response and have important public health implications about how to approach vaccination, infection and other immune concerns in patients with clinical disorders of sodium homeostasis.

Poster Abstract 7

Fetal Growth Associated with Maternal Rheumatoid Arthritis and Juvenile Idiopathic Arthritis.

Eugenia Y. Chock[1]; Zeyan Liew[2]; Lars Henning Pedersen[3,4,5]; Mette Oestergaard Thunbo.[5]

[1] Section of Rheumatology, Department of Internal Medicine, Yale School of Medicine, New Haven, CT, USA.
[2] Yale Center for Perinatal, Pediatric and Environmental Epidemiology, Yale School of Public Health, New Haven, CT, USA.
[3] Department of Obstetrics and Gynecology, Clinical Medicine, Aarhus University and Aarhus University Hospital, Aarhus, Denmark.
[4] Department of Biomedicine, Aarhus University, Denmark.
[5] Department of Clinical Medicine, Aarhus University, Denmark.

Introduction: Maternal chronic inflammatory arthritis, including rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA), is associated with a higher risk of preterm delivery and infants with low birth weights, but the timing and trajectory of fetal growth during pregnancy associated with these maternal conditions have not been well studied.

Methods: We conducted a population-based cohort study in Denmark from 2008-2018 which included 503,491 singleton pregnancies. Among them, 2,206 mothers have received an RA or JIA diagnosis (RA/JIA) before or during pregnancy. We analyzed 2nd trimester fetal ultrasound measurements (at 18-22 weeks' gestation) extracted from the Danish Fetal Medicine Database. We first examined the estimated fetal weight (EFW) at the 2nd trimester and the recorded birth weight separately. Then, we calculated the fetal growth gradient by computing the mean difference between the fetal weight and the birth weight Z-scores. We conducted linear regression analyses for these outcomes comparing pregnancies with or without RA/JIA adjusting for confounding factors. We further stratified the maternal RA/JIA groups by the antirheumatic therapies received during pregnancy.

Results: Maternal RA/JIA was not associated with a reduction of EFW in mid-pregnancy, but a lower birth weight (Z- scores mean difference: -0.08; 95%CI -0.13, -0.04). Maternal RA and JIA was associated with fetal growth gradient reduction computed using the 2nd trimester EFW and birth weight measures (Z-score mean difference: -0.14; 95%CI -0.08, -0.19), with the largest growth reduction observed among mothers with RA/JIA who used corticosteroids (-0.26; 95%CI -0.11, -0.41) and sulfasalazine (-0.61; 95%CI -0.45, -0.77) during pregnancy.

Conclusion: Offspring born to individuals with RA/JIA had lower birth weight; with the greatest gradient of fetal growth reduction noted during the late pregnancy period, and among corticosteroid and sulfasalazine users.

Poster Abstract 8

Title: Nanoscale imaging of pT217-tau in aged rhesus macaque entorhinal and dorsolateral prefrontal cortex: Evidence of interneuronal trafficking and early-stage neurodegeneration

Authors: Dibyadeep Datta[1,2]*, Isabella Perone[1], Denethi Wijegunawardana[1], Feng Liang[3], Yury M. Morozov[1], Jon Arellano[1], Alvaro Duque[1], Zhongcong Xie[3], Christopher H. van Dyck[2], Mary Kate P. Joyce[1], Amy F.T. Arnsten[1]*

Affiliations:

[1]Departments of Neuroscience, Yale University, School of Medicine, 333 Cedar St., New Haven, CT USA 06510
[2] Department of Psychiatry, Yale University, School of Medicine, 333 Cedar St., New Haven, CT USA 06510
[3] Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital and Harvard Medical School, 55 Fruit Street, Boston, MA 02114

Background: Advances in Alzheimer's disease (AD) have revealed a novel fluid biomarker, tau phosphorylated at T217 (pT217-tau), in CSF and plasma, that predicts AD prior to cognitive deficits. Understanding the role of pT217-tau is important in assessing efficacy of novel treatments aimed at early-stage disease. However, it is unknown why pT217-tau is effective in predicting brain pathology, as little is known about early, soluble pT217-tau brain expression. These questions are difficult to address in humans, as soluble p-tau is rapidly dephosphorylated postmortem, and PET scans detect late-stage, fibrillated tau. However, the etiology of pT217-tau in aging brains can be probed in rhesus macaques, where perfusion fixation allows capture of phosphorylated proteins in their native state. Aging macaques naturally develop tau pathology with the same qualitative pattern and sequence as humans, including initial cortical pathology in layer II of the entorhinal cortex (ERC) evident early in aging, and later in layer III of the dorsolateral prefrontal cortex (dlPFC).

Methods: We utilized multi-label immunofluorescence and immunoelectron-microscopy to examine the subcellular localization of early-stage pT217-tau in ERC and dlPFC of aged macaques with naturally occurring tau pathology and assayed pT217-tau levels in plasma.

Results: pT217-tau labeling is primarily observed in postsynaptic compartments, accumulating in: 1) dendritic spines on the calcium-storing smooth endoplasmic reticulum spine apparatus near asymmetric glutamatergic-like synapses, and 2) in dendritic shafts, where it aggregated on microtubules, often "trapping" endosomes associated with Aβ42. The dendrites expressing pT217-tau were associated with autophagic vacuoles and dysmorphic mitochondria, indicative of early neurite degeneration. We observed trans-synaptic pT217-tau trafficking between neurons within omega-shaped bodies and endosomes, specifically near excitatory, but not inhibitory synapses. We also examined pT217-tau in blood plasma in macaques across age-span and observed a statistically significant age-related increase in pT217-tau.

Conclusions: These data provide the first direct evidence of pT217-tau trafficking between neurons near synapses to "seed" tau pathology in higher brain circuits, interfacing with the extracellular space to become accessible to CSF and blood. The expression of pT217-tau in dendrites with early signs of degeneration may help to explain why this tau species can herald future disease.

Poster Abstract 9

Title: *Pancreatic β cell-specific Gclc gene deletion causes a heterogenous diabetes phenotype in adult mice*

Authors: Davidson EA[1,2], Chen Y[1], Cardone RL[3], Inma Ruz-Maldonado[3], Kibbey RG[2,3], Zhang X[2,3], Perry RJ[2,3], Thompson DC[1], Vasiliou V[1*]

Affiliations: [1]Department of Environmental Health Sciences, Yale School of Public Health, Yale University, New Haven, CT, USA
[2]Department of Cellular & Molecular Physiology, Yale School of Medicine, New Haven, CT, USA
[3]Department of Internal Medicine, Yale School of Medicine, New Haven, CT, USA

Abstract
Oxidative stress, the imbalance of reactive oxygen species and antioxidant capacity, is implicated in type 2 diabetes (T2D)-related pancreatic islet β cell dysfunction. Glutathione (GSH) is an abundant cellular antioxidant and mitigates oxidative stress. T2D is associated with impaired islet cell GSH biosynthesis yet, a direct relationship remains under described. We sought to understand the role of GSH in the β cell by deleting *Gclc*, an essential gene for GSH biosynthesis. We generated tamoxifen-inducible β cell-specific *Gclc* knockout mice by mating *MIP-Cre/ERT*$^{Tg/-}$;*Gclc*$^{wt/fl}$ mice with *Gclc*$^{fl/fl}$ mice to produce *MIP-Cre/ERT*$^{-/-}$;*Gclc*$^{fl/fl}$ (control) and *MIP-Cre/ERT*$^{Tg/-}$;*Gclc*$^{fl/fl}$ (*βGclc* KO) mice. Male mice aged 2-months were intraperitoneally injected with tamoxifen (100µL, 20mg/mL) for 5 consecutive days. Four-wks post-induction, *βGclc* KO islets had reduced GCLC expression (62% less than control). Islet cell GSH content was unchanged and neither GCLM nor HO-1, markers of oxidative stress, were induced. Glucose tolerance testing showed normal glucose tolerance and mildly elevated plasma insulin ($P = 0.051$) in *βGclc* KO mice (n = 9-10/genotype). Body weight, muscle, and fat mass were unchanged (n = 5-6/genotype). Fasting blood glucose and plasma insulin were assessed at 6-, 8-, 10-, and 13-wks post-induction (n = 5-10/genotype). At 8-wks, *βGclc* KO mice displayed significant hyperglycemia and hypoinsulinemia. Across the time-course, *βGclc* KO mice exhibited a heterogenous diabetes phenotype. Six of 10 *βGclc* KO mice (60%) manifested hyperglycemia (≥ 250 mg/dL) at one timepoint. Half of the hyperglycemic *βGclc* KO mice recovered to ≤ 250 mg/dL at 13-wks; these mice were considered transiently hyperglycemic. Mice that did not recover were considered chronically hyperglycemic. Histologic examination at 13-wks showed transiently hyperglycemic mouse islets were slightly enlarged with granular cytosol while, chronically hyperglycemic mouse islets were smaller with irregular non-circular shape. Our findings demonstrate that β cell GCLC expression is a critical mediator of adult β cell function.

Poster Abstract 10

Quantification of Forearm Adipose Tissue in Patients with Systemic Sclerosis Using Magnetic Resonance Imaging

[1]Agrani Dixit, [1]William Odell, [1] Sophia Kujawski [2]Annie Wang, [2]Xenophon Papademetris, [2]Gigi Galiana, [1]Monique Hinchcliff
Yale School of Medicine [1] Department of Internal Medicine, Section of Rheumatology, Allergy & Immunology, [2] Department of Radiology and Biomedical Imaging

Background
Systemic sclerosis (SSc), an autoimmune rheumatic disorder, causes dermal fibrosis and concomitant intradermal fat atrophy leading to functional impairments, pain, and disability. The modified Rodnan skin score (mRSS) is a pinch test of 17 body areas (0= no fibrosis to 3=hidebound skin) that semi-quantifies skin thickness but is agnostic to intradermal fat atrophy. Limitations include inter and intra-rater variability, confounding edema, and obesity. Previously, we showed that the degree of dorsal forearm fibrosis is a surrogate for mRSS. We propose forearm magnetic resonance imaging (MRI) a non-invasive, objective outcome measure to quantify SSc skin disease (skin fibrosis and fat atrophy).

Methods:
The mRSS was performed and body mass index was determined for SSc patients. Patients with forearm fibrosis scores 0 and 1 were invited to participate in this pilot study. The dominant forearm was imaged using 3T magnet and novel Dixon sequence to isolate adipose tissue. Two trained users annotated and quantified forearm fat (m^3) using BioImage Suite software. Axial adipose thickness and a ratio of ventral fat over dorsal fat were calculated with ImageJ.

Results and Conclusions
Four SSc patients and two age- and sex-matched healthy control (HC) participants underwent MRI. Forearm skin fibrosis scores were 0, 0, 0, 1 with respective mRSS of 2, 6, 7, and 27. The unadjusted median (range) forearm fat volume was 6.62 m^3 (4.06-9.18) in patients and unadjusted mean (SD) 6.20 (5.46-6.94) in HC. Because SSc impacts dorsal versus ventral forearm skin, we measured forearm fat in one axial image midway between the ulnar styloid and the olecranon process. We found a smaller axial adipose ratio with worsened fibrosis (0 mRSS, 0.47 mean) (1 mRSS, 0.38) while HC (0, 0.81). This suggests that increased dermal fibrosis maybe associated with decrease in the ratio of ventral fat over dorsal fat (r^2=0.67). Future steps include recruiting SSc patients with forearm fibrosis scores of 2 and 3 and assessing the validity, reproducibility, and sensitivity of MRI forearm imaging.

Poster Abstract 11

Title: Disparities in health insurance status and use of physical restraints in the emergency department

Authors: *Isaac V. Faustino*[1], Anusha Kumar[1], Ambrose H. Wong[1,2]

Affiliations:

[1]Department of Emergency Medicine, Yale School of Medicine, New Haven, CT, USA

[2]Yale New Haven Health System, New Haven, CT, USA

Abstract

Physical restraint usage are recommended as a “last resort” strategy for agitation because restraint use can lead to patient hesitancy from seeking future emergency care. Racial and ethnic disparities in restraint use have been researched, but the association of insurance status on restraint use is unknown. We aimed to determine the association between insurance status and restraint use, hypothesizing that publicly insured adult patients are restrained more in the emergency department (ED) than those with private insurance.

A cross-sectional study using electronic health records (EHR) across 13 sites within a regional healthcare network in NE United States was conducted. ED visits for adults >= 18 years old from Jan 2013 to Dec 2022 were included. Each visit was mapped to private insurance or public insurance. Physical restraint corresponded to an EHR order. Logistic regression models assessed association between insurance type and physical restraint, potential confounding by age, gender, race and ethnicity, and effect of chief complaint, i.e. behavioral vs non-behavioral. Private insurance was used as reference.

A total of 3,309,220 visits were analyzed. Of these, 42.8% had private insurance and 54.5% had public insurance (2.7% had other insurance). Chief complaint was behavioral in 14.9% of visits and physical restraint was used in 0.6%. Public insurance had statistically higher odds of physical restraint with an odds ratio (OR) of 2.73 (95% CI: 2.63, 2.83). This finding persisted when adjusted for age, gender, and race and ethnicity. Regarding chief complaint, OR with public insurance was 1.81 (1.74, 1.89) when chief complaint was behavioral and 2.42 (2.23, 2.64) when non-behavioral.

Among adult ED visits, restraint use was associated with insurance type and differed by chief complaint, potentially representing structural forces from socioeconomic disparities. Future work includes investigating differences in access to health resources besides hospital care and if this pattern persists nationwide.

Poster Abstract 12

A Comprehensive Rodent Protocol of Blood Flow Restriction Exercise

Andin Fosam, Susana Nakandakari, PhD, Isabella Chavez Miranda, Rachel Perry, Ph.D.
Department of Cellular and Molecular Physiology, Yale School of Medicine, New Haven, CT

Abstract:
Blood flow restriction (BFR)-exercise uses light-weight exercise while partially restricting arterial blood flow to increase muscle mass post-surgically. Animal models of BFR-exercise are not well established. We developed a comprehensive protocol using adult Sprague Dawley rats to investigate BFR-mediated metabolic changes alongside an ongoing clinical trial in post-surgical patients (NCT05012982). Post-surgical muscle loss was modeled in rats via bilateral anterior cruciate ligament (ACL) reconstruction. BFR was achieved by inflating a 1.6cm cuff on the proximal hindlimb above the knee. Rats performed 40 repetitions of knee extensions at 30% bodyweight on a squat apparatus. Quadriceps weight (g) following ACL reconstruction was lower than the non-operative control (2.83, 3.64; p=0.02; n=7). Reduced blood flow (mm/s) was observed via doppler ultrasound over the iliac artery compared to the non-occlusive condition (328.6, 161.6; n=1). This protocol offers a foundation for mechanistic studies of BFR-mediated muscle growth *in vivo*.

Poster Abstract 13

Aortic remodeling following hybrid arch repair with zone 0 to 5 thoracic endovascular aortic repairs for complex arch and descending thoracic aortic pathologies

Irbaz Hameed, MD[1*], Adham Ahmed, BS[1*], Stevan Pupovac, MD[1], Naiem Nassiri, MD[2], Roland Assi, MD, MMS[1], Prashanth Vallabhajosyula, MD, MS[1]

[1]Division of Cardiac Surgery, Department of Surgery, Yale University School of Medicine, New Haven, CT

[2]Division of Vascular Surgery, Department of Surgery, Yale University School of Medicine, New Haven, CT

Objective: For high-risk patients with aortic arch pathology, hybrid aortic arch repair with simultaneous or staged thoracic endovascular repair of the descending aorta may be a viable alternative to open repair. However, data on postintervention aortic remodeling remain limited. We report the short-term outcomes of remodeling of the thoracoabdominal aorta after hybrid arch repair + thoracic endovascular repair.

Methods: All patients undergoing hybrid arch repair with planned zones 0 to 5 thoracic endovascular repair from January 2020 to March 2022 were retrospectively reviewed. Computed tomography angiography scans preoperatively, after hybrid aortic arch repair, and on long-term follow-up were analyzed for thoracoabdominal aorta remodeling. Mean change in aortic true luminal diameter and full luminal diameter was calculated at every level, and paired-samples *t* test was used to compare means.

Results: Of 39 patients, 38 had follow-up data at a mean duration of 14.9 months. There were a total of 3 (7.7%) deaths, 0 (0.0%) strokes, and 0 (0.0%) paralysis. For the 35 patients undergoing thoracic endovascular repair for aortic dissection, at follow-up, there was a significant increase in the mean true luminal diameter at each level ($P < .05$), except at the aortic bifurcation and common iliac arteries. The largest increase in mean true luminal diameter ($P < .01$) was observed at the level of the left inferior pulmonary vein (mean difference +13.22 mm, 95% CI, 10.38-16.07), tracheal carina (mean difference +13.06 mm, 95% CI, 10.05-16.07), and inferior left atrium (mean difference +11.19 mm, 95% CI, 7.84-14.53).

Conclusions: Hybrid arch repair with zones 0 to 5 leads to improved true lumen augmentation in zones 0 to 8 with complete false lumen thrombosis down to zone 5 at short-term follow-up. Zones 9 to 11, if involved, may require adjunctive treatment strategies for total aortic remodeling and complete false lumen obliteration.

Poster Abstract 14

Identifying Risk Enhancing Factors for Post-Percutaneous Coronary Intervention Acute Kidney Injury from Electronic Health Records

Chenxi Huang, PhD,[1] Karthik Murugiah, MBBS,[1,2] Mitsuaki Sawano, MD, PhD,[1] Amarnath Annapeureddy, MD,[1,2] Harlan M Krumholz[1,2,3]

[1]Center for Outcomes Research and Evaluation, Yale New Haven Hospital, New Haven, Connecticut

[2]Section of Cardiovascular Medicine, Department of Internal Medicine, Yale School of Medicine, New Haven, Connecticut

[3]Department of Health Policy and Management, Yale School of Public Health, New Haven, Connecticut

Background:

Current acute kidney injury (AKI) risk prediction models for patients undergoing percutaneous coronary intervention (PCI) can misclassify up to one-third of the patients who experienced AKI as low risk. We sought to determine potential factors contributing to this misclassification from electronic health record (EHR) data.

Methods:

Among PCI patients at Yale New Haven Hospital between 4/2018-12/2022, we identified those who experienced AKI but were estimated by the National Cardiovascular Data Registry (NCDR) model to be below average risk. Of these 194 patients meeting the criteria, 65 random records were chart reviewed by a cardiologist. Based on available EHR information, we used an inductive approach to identify and develop themes of factors for AKI before the PCI.

Results:

The mean age of patients included in the chart review was 66.7 (SD, 14.0) years; 27.7% were female, and 9.2% were Black people. The mean predicted AKI risk was 4.2%; 21.5% of AKI were stage II or III. We identified three themes of contributing factors to 26 (40.0%) of these patients who were misclassified: (1) Incorrect or ambiguous coding for risk variables was seen in 12 (18.5%) patients, especially in coding cardiac instability; (2) Contrast exposure 72 hours before PCI was noted in 8 (12.3%) patients; (3) Risk-enhancing clinical factors were noted in 13 (20.0%) patients, including late presenting Myocardial Infarction, renal transplant status, nephrectomy, abdominal aneurysm with renal stents, active COVID-19, diabetic ketoacidosis, active metastatic cancer, hip fracture and liver disease.

Conclusions:

Over 1 in 3 patients undergoing PCI have factors noted in the EHR data that may contribute to the underestimation of AKI risk. Addressing or incorporating these factors into AKI risk assessment models could improve the identification of high-risk patients.

Poster Abstract 15

TITLE**: Large-Scale Functional Brain Networks Associated with Disruptive Behavior in Children**

Karim Ibrahim[1], Dustin Scheinost[2], Gregory McCarthy[3], and Denis G. Sukhodolsky[1]

[1]Yale University School of Medicine, Child Study Center; [2]Yale University School of Medicine, [3]Yale University, Department of Psychology

OBJECTIVES: This study investigates if aberrant functional connectivity in large-scale networks involved in the top-down regulation of emotion are associated with disruptive behavior disorders in children. We examined amygdala functional connectivity and brain-wide connectivity in a transdiagnostic sample of children with disruptive behavior using categorical and dimensional approaches.

METHODS: This study included a transdiagnostic sample of 133 children aged 8-16 years: 101 with elevated levels of disruptive behaviors (28 females) and 32 Healthy Controls (13 females). Children received a diagnostic evaluation using the K-SADS. For amygdala connectivity, we conducted a psychophysiological interaction using an amygdala region-of-interest. For brain-wide connectivity, we used connectome-based predictive modelling (CPM) to test associations with disruptive behavior severity. Continuous measures included the parent-rated Child Behavior Checklist Aggressive Behavior Scale and Reactive-Proactive Aggression Questionnaire. Children completed a previosly-validated fMRI task of fearful and calm faces to engage emotion perception circuity.

RESULTS: Categorical analyses revealed reduced connectivity between the amygdala and dorsolateral prefrontal cortex, a key node in emotion regulation circuitry. Dimensional analyses using CPM predicted disruptive behavior severity. Identified networks included connections within and between networks implicated in cognitive control (medial frontal, frontoparietal), social functioning (default mode, salience), and emotion processing (subcortical). A node in the dorsolateral prefrontal cortex emerged as the highest contributing feature in the predictive model. Out-of-sample replication and generalization of findings was demonstrated in an independent sample from the ABCD study.

CONCLUSIONS: Alterations in large-scale neural networks implicated in cognitive control may contribute to increased risk of disruptive behavior in children. The dorsolateral prefrontal cortex—a central hub for cognitive control networks and emotion regulation—emerged as a consistent node, suggesting a potential network target for interventions. These studies served as the foundation of Dr. Karim Ibrahim's independent research program in translational neuroscience, which was developed across the YCCI TL1 and KL2 programs.

This work was supported by NIMH grant R01MH101514 (D.G.S. and K.A.P) and NICHD grant R01HD083881 (D.G.S. and K.A.P). K.I. was a fellow on NCATS grant TL1 TR001864 and KL2 TR001862. K.I. is supported by NIMH grant K23 MH128451.

Poster Abstract 16

Role of Noradrenaline and Macrophage Dynamics in Pulmonary Fibrosis

Genta Ishikawa[1], John McGovern[1], Maor Sauler[1], Xueyan Peng[1], Alexander Ghincea[1], Daisuke Okuno[1], Sam Woo[1], Sheeline Yu[1], Chris J. Lee[1], Tina Saber[1], Huanxing Sun[1], Changwan Ryu[1], and Erica L. Herzog[1,2]

[1]Department of Internal Medicine, Section of Pulmonary, Critical Care, and Sleep Medicine, School of Medicine, Yale University, New Haven, CT, USA

[2]Department of Pathology, School of Medicine, Yale University, New Haven, CT, USA

Rationale: Idiopathic Pulmonary Fibrosis (IPF) is marked by the scarring of lung tissue in adults, with lung transplantation as the only cure. While the pivotal role of lung macrophages in IPF progression is recognized, the influence of noradrenaline (NA), produced by local adrenergic nerves, on macrophages is less understood. This study hypothesizes that NA, via interaction with the α1-adrenoreceptor subtype D (ADRA1D), drives macrophage polarization towards a fibrosis-promoting phenotype. **Methods:** The study initiated by confirming ADRA1D-expressing macrophages in murine and human IPF lungs. A comprehensive approach assessed the NA-ADRA1D interaction's effects, including *in vitro* studies with CRISPR-engineered *ADRA1D-/-* human macrophages, *Adra1d-/-* mouse macrophages, *in vivo* experiments using ADRA1D antagonism, and evaluating α1-adrenoreceptor (α1-AR) antagonists in IPF patients. **Results:** The study identified an accumulation of ADRA1D-expressing macrophages in both murine and human IPF lungs. *In vitro* experiments involving *ADRA1D-/-* human macrophages and primary murine macrophages lacking *Adra1d*, stimulated with recombinant human TGFβ1 and NA, demonstrated an upregulation of pro-inflammatory cytokines including IL-1β, alongside the activation of the TAK1/NF-kB signaling pathway. These findings were supported by *in vivo* results with myeloid-specific *Adra1d KO* mice. Further, single-cell RNA sequencing uncovered pronounced pro-inflammatory polarization in CX3CR1-expressing interstitial macrophages, suggesting a significant interaction with local adrenergic nerves and their derived NA in this specific macrophage population. These pro-inflammatory polarized macrophages inhibited the proliferation of nearby myofibroblasts *in vitro* and reduced bleomycin-induced lung fibrosis *in vivo*. Notably, IPF patients treated with α1-AR antagonists exhibited improved survival and increased plasma IL-1β levels. **Conclusion:** Inhibition of ADRA1D induces a pro-inflammatory polarization in lung macrophages, hindering fibrosis progression. This opens new research avenues into neuroinnate interactions in lung fibrosis, suggesting novel therapeutic approaches.

Poster Abstract 17

Multi-omic analysis reveals metabolic pathways explaining EGFR inhibition resistance in right-sided colon cancer liver metastasis

Abhishek Jain[b], Montana T. Morris[a], Boshi Sun[a], Vadim Kurbatov[a], Engjel Muca[c] , Zhaoshi Zeng[c] , Ying Jin[a], Jatin Roper[d], Jun Lu[e], Philip B. Paty[c], Caroline H. Johnson[b], Sajid A. Khan[a]

a; Department of Surgery/Surgical Oncology, Yale School of Medicine, 333 Cedar Street, New Haven, CT, 06510, USA, **b;** Department of Environmental Health Sciences, Yale School of Public Health, 60 College Street, New Haven, CT, 06510, USA, **c;** Department of Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY, 10065, USA, **d;** Department of Medicine/Gastroenterology, Duke University School of Medicine, 124 Davison Building, Durham, NC, 27710, USA ,**e;** Department of Genetics, Yale School of Medicine, 333 Cedar Street, New Haven, CT, 06378, USA

There are well demonstrated differences in tumor cell metabolism between right sided (RCC) and left sided (LCC) colon cancer, which could underlie the robust differences observed in their clinical behavior, particularly in metastatic disease. As such, we utilized liquid chromatography-mass spectrometry to perform an untargeted metabolomics analysis comparing frozen liver metastasis (LM) biobank samples derived from patients with RCC (*N = 32*) and LCC (*N = 58*) to further elucidate the unique biology of each. We also performed an untargeted RNA-seq and subsequent network analysis on samples derived from an overlapping subset of patients (RCC: *N = 10*; LCC: *N = 18*). Our biobank demonstrates the inferior survival of patients with RCC-derived LM (*P* = 0.04), a well-established finding. Our metabolomic results demonstrate increased reactive oxygen species (ROS) associated metabolites and bile acids in RCC. Conversely, carnitines, indicators of fatty acid oxidation, are relatively increased in LCC. Integration of transcriptomic and metabolomics analysis implicates increased ROS and *CERCAM gene* activated MEK-ERK, PI3K-AKT, and Transcription Growth Factor Beta (TGF-β) signaling in RCC LM. TGF-β stood out in its ability to unify many of the findings into one mechanism, and its increased abundance together with *CERCAM* in RCC was confirmed by immunohistochemistry. By Integrating all our findings, we unlocked the potential mechanism driving inferior survival and EGFRi resistance in RCC metastatic disease. Our multi-omic analysis reveals several key differences in cellular physiology which taken together may be relevant to clinical differences in tumor behavior between RCC and LCC liver metastasis.

Poster Abstract 18

Association between Hospital-level Socioeconomic Disadvantage and use of Intravenous Benzodiazepines for Sedation During Early Mechanical Ventilation

Snigdha Jain, Aruna Priya, Hayley B. Gershengorn, Allan J. Walkey, Lisa Burry, Harlan M. Krumholz, Hannah Wunsch, Peter K. Lindenauer

Rationale: Critical care guidelines recommend avoidance of benzodiazepines for adults during mechanical ventilation (MV), given their association with greater risk of long-term cognitive impairment and mortality. However, since alternative agents for sedation such as dexmedetomidine and propofol are more expensive than benzodiazepines, resource constraints may influence implementation of evidence-based sedation practices, compromising quality of care. We sought to determine whether hospitals serving a greater proportion of socioeconomically disadvantaged patients use benzodiazepines more frequently for sedation during mechanical ventilation compared to hospitals serving less vulnerable populations.

Methods: We used data from the Premier Healthcare Database (2016-2020) to identify the first episode of mechanical ventilation for 2 or more consecutive days among adults ≥18 years hospitalized with acute respiratory failure (ICD-10-CM codes: J96.00-02) with a stay in the intensive care unit (ICU) as determined by a combination of charge and procedure codes. Our primary outcome was receipt of intravenous benzodiazepine at the hospital level (as a proportion of patients). We ascertained intravenous benzodiazepine use from daily charge codes, excluding administration in doses < 4 mg/day of midazolam equivalents for both of the first 2 days (early) of MV to exclude bolus administration for procedures or intermittent agitation rather than continuous sedation. We excluded patients admitted with benzodiazepine or alcohol intoxication or withdrawal and those with seizures. Our exposure was quartile of hospital-level socioeconomic disadvantage characterized by proportion of patients with Medicaid and uncompensated care (uninsured, charity, and self-pay). We evaluated the association between hospital-level benzodiazepine use and socioeconomic disadvantage using hierarchical logistic regression models including a random intercept for hospital of discharge, adjusting for patient (admission year, age, sex, race, ethnicity, primary payor, organ dysfunction, vasopressor use) and hospital characteristics (rural location, teaching affiliation, bed size, region).

Results: We included 576,656 episodes of mechanical ventilation across 740 hospitals; median age was 65 years (IQR:53,75), 45.1% were female. Intravenous benzodiazepines were used for ≥2 consecutive days in 81,527(14.1%) episodes. Compared with hospitals serving the lowest number of socioeconomically disadvantaged patients (quartile 1,% disadvantaged: 3.9-19.0%), hospitals serving greater volumes of disadvantaged patients (quartile 2: 19.0-26.2%, quartile 3: 26.2-36.8%, quartile 4: 36.8-71.8%) had 10% - 20% greater odds of using benzodiazepines for sedation during early MV [adjusted Odds Ratio (OR) (95% CI): 1.1 (1.0, 1.1) for Quartile 2 vs 1; OR 1.2 (1.1, 1.3) for Quartile 3 vs 1; OR 1.1 (1.0,1.2) for Quartile 4 vs 1].

Conclusion: Hospitals serving a greater proportion of socioeconomically disadvantaged patients are more likely to use intravenous benzodiazepines for adults during early mechanical ventilation compared with those serving fewer disadvantaged patients. Our findings suggest the need to investigate further factors underlying differences in the use of benzodiazepines at the hospital level.

Poster Abstract 19

Nutrient-derived signals regulate eosinophil adaptation to the small intestine

Lisa L. Korn[1], Vassily I. Kutyavin[2], and Ruslan Medzhitov[2,3]

1. Department of Medicine, Section of Rheumatology, Allergy, and Immunology
2. Department of Immunobiology
3. HHMI

Diet plays a fundamental role in human health and disease, in part through influence on immunity. However, much remains to be learned about the ways in which dietary composition controls immune cells. To investigate this question, we fed mice diets containing different macronutrient compositions and found that a high protein diet caused a reduction in small intestine-resident eosinophils. Eosinophils are multifunctional granulocytes which accumulate in helminth infection, allergic inflammation, and hyper-eosinophilic syndromes, where they cause tissue damage through the release of cytotoxic granules and promote inflammation through the release of multiple cytokines. At the same time, in mice as well as humans, the small intestine contains a large population of eosinophils at steady state. The mechanisms by which eosinophils establish residency in the small intestine are not well understood. We found that small intestine eosinophils undergo a process of tissue adaption that involved transit of eosinophils up the crypt-villus axis with time, and changes in eosinophil morphology, surface marker expression, and transcriptional profile. Feeding mice a high protein diet interfered with this tissue adaptation through eosinophil turnover in the small intestine, leading to a depletion of the villus-resident subset. The canonical eosinophil survival factor IL- 5 and the microbiota were largely dispensable for eosinophil adaptation, while the vitamin A metabolite retinoic acid was required through a pathway likely nonredundant with high protein feeding, possibly due to an increased requirement for intracellular retinoic acid in villus eosinophils. Overall, we identified a homeostatic process of eosinophil adaptation to the small intestine that was retinoic acid-dependent and subject to dietary control. These findings highlight a role of nutrient-derived signals in regulating gut immunity.

Poster Abstract 20

Association between patient primary language and use of physical restraints in the emergency department

Anusha Kumar[1], Isaac V. Faustino[1], Andrew Taylor[1], Caitlin Ryus[1], Ambrose Wong[1]

[1]Department of Emergency Medicine, Yale University School of Medicine, New Haven, Connecticut, USA

Language is an important factor for facilitating communication and clinical decision-making within healthcare. Clinicians' comfort with patients' primary language used to communicate their concerns may have significant impact on coercive measures used to manage psychiatric crises. Here, we aim to evaluate associations between language and physical restraints in the emergency department. Research on this topic will allow us to better understand existing patient-centered communicative efforts during symptoms of psychomotor agitation.

This was a retrospective cohort analysis evaluating physical restraint characteristics using electronic medical records from 13 emergency departments (EDs) affiliated with a large regional healthcare network located in the Northeast United States. Data was collected for each ED visit from 2013-2022 for all adult patients ages 18 and older. We performed logistic regression models using the presence of physical restraint orders as the primary outcome. Our models adjusted for gender, language, age, race and ethnicity, chief complaints, and interpreter needed.

In our analysis of 3,406,522 visits, 250,913 included Spanish speakers and 9,057 included Portuguese speakers; 18,546 visits included physical restraint use. Spanish and Portuguese speakers exhibited lower odds of restraint with unadjusted odds ratios of 0.583 and 0.214 (95% CI: (0.543-0.625) and (0.111-0.367)). After adjusting for sex, language, age, race/ethnicity, chief complaints, and need for interpreter, Spanish and Portuguese speakers maintained a reduced likelihood of violent restraint compared to English speakers, with adjusted odds ratios (AORs) of 0.715 and 0.399 and 95% CI of (0.642-0.795) and (0.205-0.694).

ED visits with non-English speaking patients were found to have significantly lower odds of physical restraint. These findings highlight the need for considering language when assessing the use of physical restraint in diverse patient populations. Our findings indicate that patients' verbal dialog may influence clinicians' interpretation of levels of psychomotor agitation. Additionally, understanding de-escalation strategies can assist clinicians with context surrounding language concordance.

Poster Abstract 21

Association Of Autoimmune Disease With Coronary Vasomotor Disorders In Patients With Angina And No Obstructive Coronary Artery Disease

Nida Latif MBBS[1], Natasha Cigarroa MD[2], Margaret Furman MD[1], Attila Feher MD[1], Monique Hinchcliff MD[3], Marah Maayah BS[2], Arshjot Khokhar MD[2]; Steffne Kunnirickal MD[1]; Samit Shah MD[1,4], PhD

[1]Section of Cardiovascular Medicine, Department of Internal Medicine, Yale School of Medicine, New Haven, CT, [2] Yale School of Medicine, New Haven, CT, [3] Section of Rheumatology, Allergy and Immunology, Department of Internal Medicine, Yale School of Medicine, New Haven, CT,[4] VA Connecticut Healthcare System, West Haven, CT

Background

Angina and no obstructive coronary artery disease (ANOCA) is increasingly recognized but predisposing factors are not well characterized. The aim of this study was to assess the incidence of autoimmune disease in patients with ANOCA, and to determine the association with specific coronary vasomotor disorders.

Methods

We conducted a retrospective analysis of patients who underwent clinically indicated invasive coronary angiography and invasive coronary function testing (CFT) at our institution from January 2018 to October 2023. Data regarding autoimmune disease diagnosis, current or prior treatment, and diagnosis of ANOCA endotype were collected and analyzed with multivariable logistic regression.

Results

186 patients were included, 70.4% were female. The median age was 58-years (SD 10.86), and patients were White (66.7%), Black (13.4%), Hispanic/Latino (11.8%), Asian (3.8%), or other (1%). After CFT, patients were found to have CMD (31.2%), vasospastic angina (26.9%), coronary endothelial dysfunction (20.4%), and mixed VA/CMD (8.6%). Autoimmune disease was diagnosed in 16.2% (n= 30) of patients, including systemic lupus erythematosus (23.3%), Sjogren's syndrome (16.7%), rheumatoid arthritis (16.7%), scleroderma (10%), mixed connective tissue disease (10%), systemic vasculitis (10%), antiphospholipid antibody syndrome (6.7%), or other diagnoses (23.3%). The frequency of an organ-specific autoimmune disease was 17.2% (n=32), including autoimmune thyroid disease (53.1%), psoriasis (28.1%), and inflammatory bowel disease (12.5%). Multivariate analysis showed a significant relationship between the presence of systemic autoimmune disease and coronary endothelial dysfunction ($p = 0.024$). There were no other significant associations between coronary vasomotor disorders and any systemic or organ-specific autoimmune disease.

Conclusion

We found that autoimmune disease is common in patients with ANOCA, and there was a significant association between systemic autoimmune disease and coronary endothelial dysfunction. This may be related to the vascular effects of chronic inflammation, which could lead to an increased risk of cardiovascular events.

Poster Abstract 22

User-Centered Evaluation and Adaptation of the Lactation Advice Through Texting Can Help (LATCH) Intervention: A Qualitative Analysis

Josefa L. Martinez-Brockman, PhD, MHS[1,2], Josephine Granner[1,3], Brice Buchanan, MSPH[2], Lisbette Acosta[2], Marilyn Lonczak, MEd, RD, CLC[4], Lori Goeschel, MS, RD, CDN, IBCLC[4], Xiao Xu, PhD[5], Leslie Curry, PhD[6], Marcella Nunez-Smith, MD, MHS[1,2], Rafael Perez-Escamilla, PhD[7]

[1]Yale University School of Medicine, Department of General Internal Medicine
[2] Equity Research and Innovation Center, Yale University School of Medicine, Department of General Internal Medicine
[3] West Haven VA Medical Center, West Haven CT, USA
[4] State of Connecticut, Department of Public Health, Community, Family Health and Prevention Branch, Maternal Child Health and Access to Care Section, Special Supplemental Nutrition Program for Women, Infants and Children
[5] Columbia University Vagelos College of Physicians and Surgeons, Department of Obstetrics and Gynecology
[6] Yale University School of Public Health, Department of Health Policy and Management
[7] Yale University School of Public Health, Department of Social and Behavioral Sciences

Breastfeeding (BF) is vital for maternal and infant health, yet post-hospital discharge support remains a challenge. The Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) provides breastfeeding peer counseling prenatally and up to 1-year post-partum among low-income women in the United States. The Lactation Advice Through Texting Can Help (LATCH) intervention is an evidence-based two-way text messaging intervention that provides breastfeeding education and support in the WIC PC program. The intervention is implemented by peer counselors (PCs) in the WIC program, with the supervision and support of a lactation consultant. This qualitative study's aim was to assess the barriers and facilitators to the implementation of LATCH during the feasibility trial and to investigate strategies for adapting and scaling up the intervention. In-depth interviews with LATCH and PC program key informants aimed to evaluate the intervention and explore its adaptation and scale-up. Interviews were analyzed using line by line inductive thematic analysis. Results showed that LATCH facilitates continued engagement between PCs and WIC mothers; however, implementation feasibility issues remain. Suggested adaptations to LATCH include the use of an integrated comprehensive platform, ensuring continuity of care through an expanded spectrum of communication options, the need to develop a PC support model for “off hours” (or non-business hours), and obtaining local WIC office management’s buy-in for the communications platform and the off-hours PC model. Implementing these changes has the potential to expand access to breastfeeding peer counseling support and work towards breastfeeding equity among low-income women.

Poster Abstract 23

Post-Acute sequelae of COVID-19 in pediatric patients within the United States: A Scoping Review

Christine M Miller[1], Carla Borre[1], Alex Green[1], Melissa Funaro[2], Carlos R Oliveira[1], Akiko Iwasaki[3,4,5]

[1]Department of Pediatrics, Division of Infectious Diseases and Global Health ,Yale University School of Medicine New Haven, CT, USA

[2] Harvey Cushing/John Hay Whitney Medical Library, Yale University, New Haven, CT, USA

[3] Department of Immunobiology, Yale School of Medicine, New Haven, CT, USA; Corresponding author

[4] Howard Hughes Medical Institute, Chevy Chase, Maryland

[5]Center for Infection and Immunity, Yale School of Medicine, New Haven, Connecticut

Abstract:

Background: A subset of children and adolescents experience recurrent or persistent symptoms following SARS-CoV-2 infection, known as post-acute sequelae of COVID-19, (PASC) or Long COVID. The clinical epidemiology of pediatric PASC in the United States (US) is not yet well understood.

Objective: This scoping review aims to synthesize current evidence on the clinical epidemiology of pediatric PASC in the US, describing symptoms, prevalence, duration, and potential mechanisms.

Methods: A comprehensive literature search was conducted using MEDLINE, Embase, CINAHL, Web of Science, and Cochrane databases. Databases were queried using an iterative search strategy from inception until January 29, 2024. Studies including children and adolescents < 21 years of age within the US were considered. A qualitative synthesis was performed, and data from studies were pooled and then narratively synthesized.

Results: From 1028 studies initially identified, 29 met the inclusion criteria. Prevalence of PASC ranged from less than 1% to 27%, with the most compelling evidence suggesting a rate of 3.7%. Risk factors included older age, female sex, asthma, obesity, and severe initial infection. Common symptoms were dyspnea, fatigue, headaches, and chest pain. A multidisciplinary approach for diagnosis and management was common across studies. Most studies had a high risk of bias and were limited by a lack of standardized definitions and short follow-up duration.

Conclusion: Pediatric PASC presents a complex clinical challenge with significant implications for the affected children's futures. Despite some similarities with adult PASC, pediatric cases necessitate distinct considerations due to their developmental stage. This review establishes a foundation for understanding pediatric PASC and highlights the critical need for continued research to optimize prevention and treatment strategies.

Poster Abstract 24

First-line Treatments for Metastatic Pure Large Cell Neuroendocrine Tumors (mLCNEC): Insights from a Clinico-Genomic Global Study

Background:
Therapeutic strategies for LCNEC are not standardized and are derived from protocols for SCLC and NSCLC, which might not be entirely appropriate due to the unique biology of LCNEC.

Methods:
For discovery, we leveraged a multi-institutional retrospective cohort(n=23 centers) of pure mLCNEC. For validation, clinico-genomic profiles of patients with LCNEC were obtained from Caris Life Sciences. Patients received 1st-line systemic therapy and were either treated with chemotherapy(chemo), immunotherapy(IO), or a combination(chemoIO). Clinical outcomes included progression-free survival(PFS), overall survival(OS), and treatment-related adverse events(trAE). Survival comparisons were made by genomic alteration (*TP53/RB1/STK11/KEAP1/KRAS*).

Results:
The discovery cohort had 190 patients with median age at 1st-line systemic therapy of 66 years; 55% (n=105) were males. First-line treatments were chemoIO(n=72), chemo(n=105), or IO(n=13). For the validation cohort(n=158), 47, 99, and 12 received chemo, chemoIO, and IO, respectively.

In the discovery cohort, there was no significant difference in PFS across the groups on multivariable analysis (p=0.09 and 0.54 for chemo vs. chemoIO; chemo vs. IO comparisons, respectively). Similarly, there was no difference in OS (p=0.77 and 0.23 for chemo vs. chemoIO and chemo vs. IO comparisons, respectively). In the validation cohort, median OS was not significantly different across treatments(*p*=0.38).

In the discovery cohort with genomic data(n=129), those harboring *TP53* mutations in LCNEC exhibited significantly inferior OS and PFS when treated with chemo (Median OS *TP53*-mutant:11mo vs. 24.5mo for *TP53*-WT,*p*=0.04; median PFS *TP53*-mutant 10.4 vs.19.2mo for WT, respectively,*p*=0.008) but not chemoIO.

Any grade trAE occurred in 56(54%), 41(57%), and 6(46%) patients treated with chemo, chemoIO, and IO, respectively. There were significantly less grade≥3 trAEs in the IO-treated group vs. chemo and chemoIO (22%vs.24%vs.0%, respectively,*p*=0.04).

Conclusion:
As first-line therapy for mLCNEC, chemo, chemoIO, and IO show comparable survival outcomes with significantly less toxicities in the IO-treated group. The findings underscore the need for future clinical trials.

A.H. Nassar[1], K. Matteson[1], T. Adeyelu[2], A. Ocejo[3], F. Ardeshir[4], T. Leal[4], S. Ramalingam[4], J.E. Gray[5], K. Hicks[5], D. Kaldas[5], J. Baena[6], M. Zurera Berjaga[6], D.J. Kwiatkowski[7], F. Aboubakar Nana[8], C. Grohe[9], H. Leuders[9], F. Citarella[10], A. Cortellini[10], E.C. Mingo[10], D. Pancirer[11], M. Das[11], T. John Ellis-Caleo[11], J.M. Cheung[12], J.J. Lin[12], A. Watson[13], R. Camidge[13], A. Sridhar[14], K. Parikh[14], F. Crowley[15], T. Marron[15], V. Aggarwal[16], A. Murtaza[17], K. Sankar[17], H. Kawtharany[18], J. Zhang[18], D. Owen[19], M. Li[19], M. Nagasaka[20], D. Pinato[21], K. Alhamad[22], S. Puri[22], N. Awosika[21], U. Zaman[23], M. Evans[24], A. Vanderwalde[24], G. Lopez[3], h. borghaei[25], C. Kim[26], A.R. Naqash[23], A. Chiang[1]

[1]Yale Cancer Center, New Haven/CT/USA ,[2]CARIS, Irving/TX/USA ,[3]Jackson Memorial Hospital, Miami/FL/USA ,[4]Emory Winship, Atlanta/GA/USA ,[5]Moffitt Cancer Center, Tampa/FL/USA ,[6]Hospital 12 de Octubre, Madrid/ES ,[7]Brigham and Women's Hospital, Boston/MA/USA ,[8]UC Louvain, Louvain-la-Neuve/BE ,[9]Klinik für Pneumologie-Evangelische Lungenklinik, Berlin Buch, Berlin/DE ,[10]Università Campus Bio-Medico di Roma, Roma/IT ,[11]Stanford, California/CA/USA ,[12]MGH, Boston/MA/USA ,[13]University of Colorado Cancer Center, Denver/CO/USA ,[14]Mayo Clinic, Rochester/MN/USA ,[15]Mount Sinai Icahn School of Medicine, New York/NY/USA ,[16]Georgetown, Washington/DE/USA ,[17]Cedars Sinai Medical Center, Los Angeles/CA/USA ,[18]University of Kansas Medical Center, Andover/KS/USA ,[19]The Ohio State University Comprehensive Cancer Center, Ohio/OH/USA ,[20]UC Irvine, Irvine/CA/USA ,[21]Imperial College, London/GB ,[22]Huntsman Cancer Institute, Utah/UT/USA ,[23]Stephensen Cancer Center, Oklahoma City/OK/USA ,[24]Caris Life Sciences, Irving/TX/USA ,[25]Fox Chase Cancer Center, Philadelphia/PA/USA ,[26]MedStar Georgetown Cancer Institute, Washington/DC/USA

Poster Abstract 25

Title: Utilization of Ambulatory Blood Pressure Monitoring in Children and Adolescents with Hypertension

Authors: James T. Nugent, MD MPH[1]; David C. Kaelber, MD PhD MPH[2]

Affiliations: [1]Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut; [2]Departments of Pediatrics, Internal Medicine, Population and Quantitative Health Sciences, Center for Clinical Informatics Research and Education, Case Western Reserve University and MetroHealth System, Cleveland, Ohio.

Background: Pediatric guidelines recommend that children with high blood pressure (BP) in clinic undergo ambulatory blood pressure monitoring (ABPM) outside clinic to diagnose hypertension. However, ABPM may not be feasible for the growing pediatric population with hypertension.

Objective: (1) To determine the frequency of ABPM in children with hypertension and children with conditions associated with masked hypertension; (2) to compare characteristics of children with hypertension that had ABPM with those that did not have ABPM.

Methods: We performed a retrospective cohort study using electronic health records in the TriNetX US Research Network, a repository of >74 million patients from 43 health systems. We identified children in whom ABPM is indicated if they were 6-18 years old and had an ambulatory visit between 2018-2022 with a new ICD-10 code for hypertension or an ICD-10 code for a condition associated with masked hypertension based on the 2017 guideline (chronic kidney disease, solid organ transplant, obesity, obstructive sleep apnea, neurofibromatosis, Turner syndrome, Williams syndrome, coarctation, prematurity, diabetes mellitus). Completion of ABPM was determined by CPT code.

Results: Of 42,474 children diagnosed with hypertension in 2018-2022 (mean 13.7 years [SD, 3.4], 58% male, 55% White, 19% Black, 18% Hispanic), 3365 (7.9%) had ever completed ABPM. The proportion of children that completed ABPM within 1 year of their hypertension diagnosis increased from 4.8% in 2018 to 8.8% in 2022. In the analysis of specific conditions in which ABPM is recommended, ABPM utilization ranged from 12.7% in solid organ transplant to 0.7% in prematurity. Compared with patients without ABPM, patients with ABPM had higher clinic BP, were more likely to have secondary hypertension, and were more likely to be prescribed antihypertensive medications after diagnosis.

Conclusions: Utilization of ABPM in children is low. Future work is needed to expand access to ABPM and explore alternative strategies to measure BP outside clinic.

Poster Abstract 26

Title: “It’s all connected:” A mixed methods study of insomnia, stigma, and discrimination among individuals on medication for opioid use disorder

Authors: Uzoji Nwanaji-Enwerem RN, FNP-BC, Lois S. Sadler PhD, RN, FAAN, Meghan O’Connell MPH, Declan Barry PhD, Tish M. Knobf PhD, RN, FAAN, Sangchoon Jeon PhD, Dustin Scheinost PhD, BS, Klar Yaggi MD, MPH, BA, Nancy S. Redeker PhD, RN, FAHA, FAAN

Abstract:

Objectives: Insomnia is one of the most common sleep disorders among those with opioid use disorder (OUD), including those on medication for OUD. There is a dearth of literature exploring the role of social stressors on sleep outcomes among this group. The purpose of this study was to explore the association between OUD-related stigma and intersectional discrimination with insomnia among individuals on medication for OUD.

Methods: Participants were recruited from treatment clinics in the Northeast United States. Using a convergent mixed-methods research design, we explored associations with stigma (The Brief Opioid Stigma Scale), intersectional discrimination (Intersectional Discrimination Index), and insomnia (Insomnia Severity Index) through quantitative survey data and qualitative data from interviews for participant experiences. Data from the quantitative (n = 120) and qualitative (n = 25) components of the study were integrated for interpretation.

Results: Quantitative analysis indicated weak to moderate positive correlations between intersectional discrimination, and exploratory variables including pain, perceived stress, and psychological distress with insomnia severity. The qualitative analysis generated 4 main themes, which highlighted negative emotions and ruminations as factors that participants connected experiences with stigma and discrimination to poor sleep outcomes. Integration of data identified concordant and discordant findings.

Conclusions: Stigma, discrimination, physical symptoms, and psychological distress appear to contribute to poor sleep outcomes among those with OUD. Future research should target maladaptive outcomes of rumination and negative emotions to improve sleep outcomes among those with OUD.

Poster Abstract 27

Characterizing the role of ultra-rare *de novo* variants in attention-deficit/hyperactivity disorder

Authors: Emily Olfson[1,2], Luis C. Farhat[1,3], Wenzhong Liu[1], Lawrence A. Vitulano[1], Gwyneth Zai[4,5], Monicke O. Lima[3], Justin Parent[6,7,8], Guilherme V. Polanczyk[3], Carolina Cappi[9], James L. Kennedy[4,5], Thomas V. Fernandez[1,10]
[1] Child Study Center, Yale University, New Haven, CT, USA
[2] Wu Tsai Institute, Yale University, New Haven, CT, USA
[3] Division of Child & Adolescent Psychiatry, Department of Psychiatry, Faculdade de Medicina FMUSP, Universidade de São Paulo, São Paulo, Brazil
[4] Tanenbaum Centre, Molecular Brain Sciences Department, Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, Ontario, Canada
[5] Institute of Medical Science and Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada
[6] University of Rhode Island, Kingston, RI, USA
[7] Bradley/Hasbro Children's Research Center, E.P. Bradley Hospital, Providence, RI, USA
[8] Alpert Medical School of Brown University, Providence, RI, USA
[9] Department of Psychiatry at Icahn School of Medicine at Mount Sinai Hospital, New York, NY, USA
[10] Department of Psychiatry, Yale University, New Haven, CT, USA

Introduction: Attention-deficit/hyperactivity disorder (ADHD) affects 3-5% of children worldwide and is highly heritable (~70-80%). DNA sequencing of families is a powerful approach for risk gene discovery in childhood neurodevelopmental conditions, but has yet to be extensively leveraged for studying ADHD.

Methods: High-coverage (80x) whole-exome DNA sequencing was conducted in 152 parent-child trios, comprised of a child with ADHD and both biological parents. We compared this data to 788 previously sequenced unaffected control trios. Based on studies of related conditions, we hypothesized an increased burden of rare *de novo* protein-truncating variants (including stop codons, frameshift and splice site variants) and missense variants predicted to be damaging in the ADHD probands compared to controls. To identify ADHD risk genes, we applied the Transmission And De Novo Association test (extTADA), combining our *de novo* findings with gene-damaging variants from a large independent ADHD case-control dataset (3,206 ADHD cases and 5,002 controls). Finally, using our list of genes harboring *de novo* gene-damaging variants, we explored overlap with previously reported risk genes and conducted pathway analyses.

Results: Our findings show an enrichment of rare and ultra-rare *de novo* gene-damaging variants in ADHD cases compared to controls (rare gene-damaging *de novo* rate ratio 1.67, p=.03; ultra-rare rate ratio 1.93, p=.007). Among the 147 parent-child trios, we identify 24 ultra-rare *de novo* damaging variants. One gene, lysine demethylase 5B (*KDM5B*), had ultra-rare *de novo* gene-damaging variants in two unrelated individuals and was found to be a risk gene for ADHD in the combined extTADA analysis (FDR=.04). Genes harboring *de novo* gene-damaging variants in the ADHD cases overlap with previously identified neuropsychiatric risk genes highlight canonical pathways.

Conclusion: Our results demonstrate the contribution of rare *de novo* gene-damaging variants in ADHD and highlight *KDM5B* as a risk gene, providing new insight into the biological underpinnings of ADHD.

Poster Abstract 28

Identification of novel variants in the malaria transmission Blocking vaccine candidate Pfs25

Alessandra Orfano[1], Awa Cisse[1], Leeah Han[1], Laty G. Thiam[2], Khadidiatou Mangou[2], Adam J. Moore[1,3,] Aboubacar Ba[2], Rebecca Li[1], Mariama N. Pouye[2], Fatoumata Diallo[2], Seynabou D. Sene[2], Elhadji Malick Ngom[2], Bacary D. Sadio[4], Alassane Mbengue[2], Christopher Membi[5], Zul Premji[5], Thomas Bazie[6], Anyirékun Fabrice Some[6], Sunil Parikh[1], Roch Dabire[6], Brian Foy[7], Jean-Bosco Ouedraogo[6], Natalie Olson[1], Michael Cappello[1], Amy K. Bei[1]

[1]Department of Epidemiology of Microbial Diseases, Yale School of Public Health, New Haven, CT, USA. [2]G4-Malaria Experimental Genetic Approaches & Vaccines, Pôle Immunophysiopathologie et Maladies Infectieuses, Institut Pasteur de Dakar, Dakar, Senegal. [3]Department of Pathology, Microbiology, and Immunology, School of Veterinary Medicine, University of California Davis, Davis, CA, USA. [4]Pôle Virologie, Institut Pasteur de Dakar, Dakar, Senegal. [5]Department of Parasitology and Medical Entomology, Muhimbili University College of Health Sciences, Dar-es-Salaam, Tanzania.[6] Institute of Health Science Research, Bobo-Dioulasso, Burkina Faso. [7] Arthropod-borne and Infectious Diseases Laboratory, Department of Microbiology, Immunology and Pathology, Colorado State University, Fort Collins, CO USA.

Malaria remains a significant global health challenge, causing 249 million cases and over 600 thousand deaths worldwide in 2022. With the rise of antimalarial drugs and insecticide resistance, there is an urgent need for effective vaccines and treatments targeting multiple stages of the parasite's life cycle. Thus, transmission-blocking vaccines (TBVs) offer promise for malaria elimination by reducing transmission within communities. However, the genetic diversity of the parasite presents a significant obstacle to vaccine development. We employed next-generation amplicon deep sequencing to identify non-synonymous single nucleotide polymorphisms (SNPs) in 209 *Plasmodium falciparum* samples from four endemic African countries: Senegal, Tanzania, Ghana, and Burkina Faso. We identified 26 SNPs including 25 novel variants and assessed their population prevalence and frequency. Notably, five variants were detected in multiple samples (L63V, V143I, S39G, L63P, and E59G), while the remaining 21 were rare variants found in individual samples. Analysis of country-specific prevalence revealed varying proportions of mutant alleles, with Ghana exhibiting the highest prevalence (58.62%), followed by Senegal (27.59%), Tanzania (6.9%), and Burkina Faso (6.9%). Furthermore, we categorized SNPs based on their frequency, identifying dominant variants with frequencies exceeding 25%, as well as rare variants with frequencies below 2%. The threading analysis of the Pfs25 protein structure revealed SNPs in two distinct categories: A) SNPs that have the potential to influence the binding between Pfs25 and antibodies and potentially lead to immune evasion, and B) SNPs that can potentially modify the structure of Pfs25 protein. Our results demonstrate that despite Pfs25 being considered a conserved gene, there are additional SNPs beyond the nine previously reported. However, it is noteworthy that the majority of these newly discovered SNPs display low population frequency and prevalence. Further research exploring the functional implications of these variations is crucial in elucidating their role in malaria transmission and informing control measures.

Poster Abstract 29

Antiviral CMPK2 protein modulates mitochondria morphodynamics

Joanna B. Pawlak[1,2], Jack Chun-Chieh Hsu[1], Peter Cresswell[1,3] and Maudry Laurent-Rolle[2,4*].
[1]Department of Immunobiology, Yale University School of Medicine, New Haven, CT 06520, USA
[2]Department of Internal Medicine, Section of Infectious Diseases, Yale University School of Medicine, New Haven, CT 06520, USA
[3]Department of Cell Biology, Yale University School of Medicine, New Haven, CT 06520, USA
[4]Department of Microbial Pathogenesis, Yale University School of Medicine, New Haven, CT 06520, USA

Cytidine/Uridine Monophosphate Kinase 2 (CMPK2) is an antiviral interferon induced protein and potential anti-flavivirus drug candidate. CMPK2 has a mitochondrial localization sequence that targets it to the mitochondria. We showed that human CMPK2 exhibits antiviral activity against flaviviruses when localized in the mitochondria. The mitochondria serve as a critical platform for RIG-I-MAVS-dependent activation of the innate immune responses to viral infection. RIG-I pathway activation is known to promote mitochondrial elongation increasing endoplasmic reticulum-mitochondria contacts and consequently enhancing innate immune signaling. However, flaviviruses like dengue and Zika virus, usurp mitochondrial processes to evade the immune response and enhance viral replication. Dengue and Zika virus infections result in mitochondrial elongation and dampening of the RIG-I dependent activation of the interferon response. To probe the molecular role of CMPK2 in the mitochondria, we used deep machine learning processes to analyze electron microscopy images of wild type and CMPK2 knockout HFF cells, mock, or IFN-I treated, and found that the mitochondria of CMPK2 knock out cells are significantly less elongated compared to wild type cells. This phenotype is reversed by type I interferon treatment. We employed immunoprecipitation-mass spectrometry (IP-MS) studies to identify cellular proteins that interact with human CMPK2. We found a promising target hit, the mitochondrial protein TUFM, which inhibits RIG-I and MAVS signaling. We will examine the molecular function of CMPK2 in mitochondrial morphodynamics and its role in the innate immune response.

Poster Abstract 30

Enhancing immune responses to melanoma with the RIG-I antiviral pathway agonist SLR14

Perry C.[*], Frey A.[*], Fei, Y., Tong W., Mackie M., He M., Clulo K., Ouerghi F., Wei J., Cordero-Dumit T., Ding M., Guo W., Clune J., Olino K., Ishizuka J.

*these authors contributed equally to the work

Background:

Despite the transformational impact of immune checkpoint blockade (ICB) in melanoma, only approximately half of patients derive long-term survival benefit. T cells with antiviral signatures have the capacity to secrete inflammatory cytokines/chemokines and deliver potent cytotoxic signals ideal for tumor immunity. A promising therapeutic target is agonism of the double-stranded RNA (dsRNA) antiviral sensor RIG-I. The novel RIG-I agonist Stem Loop RNA (SLR)14 enhanced inflammatory cytokine release and improved the control of murine tumors by TILs and other immune cell types. We tested the hypothesis that SLR14 transforms T cells to a cytotoxic antiviral state in immunologically “cold” human tumor specimens via type-1 interferon.

Methods:

We obtained 9 surgical resections from primary melanoma tumors and lymph node metastases and made single-cell suspension replicates of tumor and infiltrating immune cell co-cultures. We stimulated with IFNβ, SLR14, αPD-1, αCD3/CD28+αPD-1 or αCD3/CD28 for 42-48 hours. We Flourescently Activated Cell Sorted (FACS) live cells and then barcoded for multiplexed single cell sequencing using 10x scRNAseq. To visualize the transcriptional response and assign differentiation trajectories following stimulation, we applied PHATE (potential of heat diffusion for affinity-based transition embedding), which facilitates visualization of state transitions, and Slingshot, which defines lineage relationships.

Results:

Following SLR14 stimulation, this approach revealed shifts in tumor co-culture cell-type transcriptional phenotypes of stem-like progenitor and terminally differentiated T cell populations. RIG-I agonism induced new CD4+ and CD8+ populations not observed in positive or negative control conditions. In tumor cells, NK cells and T cells, SLR14 stimulation induced expression of canonical IFN-stimulated genes. In CD8+ T cells, however, we observed specific programs of activation and survival including *CD69* (p=0.00003), and *IL2RG* (p=0.000006). Similarly, SLR14-induced antiviral CD4+ T cells without any significant increase in Foxp3+ Tregs.

Conclusion:

RIG-I agonist SLR14 stimulates tumor-infiltrating T cells into antiviral states in tumor-immune co-cultures.

Poster Abstract 31

Loss of PDCD4 augments antitumor immune activity in melanoma

Olivia K. Provance[1], Thuy T. Tran[1], Harriet M. Kluger[1], Lucia B. Jilaveanu[1]

[1]Department of Medicine, Section of Medical Oncology, Yale University School of Medicine, 333 Cedar Street, SHM234E, New Haven, CT 06520, USA

While a significant improvement has been made in the treatment of melanoma through development of systemic therapies, including immunotherapy, many patients will have resistance or disease recurrence, generating a barrier to these otherwise effective treatments. Identification and characterization of new molecules contributing to melanoma progression is needed for enhanced treatment strategies. Our novel preclinical investigations identified that programmed cell death 4 (PDCD4) is expressed by melanoma cells and in the melanoma tumor microenvironment, and that high expression is associated with improved survival and elevated immune infiltration. Given the importance of tumor cell intrinsic and extrinsic changes that orchestrate melanoma growth and response to therapy, we hypothesized that PDCD4 may have a central role in mediating immune cell activity thus regulating melanoma growth. We conducted mechanistic investigations *in vitro* using human T-cell and melanoma cell lines. We identified that loss of PDCD4 in CD4+ T cells decreases granzyme-b, IFN-gamma production, and subsequent cell killing of a subset of melanoma cells. For *in vivo* studies, YUMMER1.7 melanoma cells were injected subcutaneously into PDCD4$^{-/-}$ and wildtype (WT) C57BL/6 mice. Tumors grown in PDCD4$^{-/-}$ mice were larger than tumors grown in WT mice and presented a decreased population of infiltrating cytotoxic CD8+ T-cells and an elevated population of M2-macrophages as analyzed by flow cytometry. Lastly, in a tumor microarray of 67 pre-treatment melanoma tumors collected from patients who attained disease control to immunotherapy, we found that high PDCD4 in CD3+ T-cells is associated with improved treatment-related survival. These results demonstrate unique characteristics of PDCD4 in the melanoma immune compartment and begin to pave the way for future investigations of the therapeutic application of PDCD4.

Poster Abstract 32

High Ambient Temperature in Pregnancy and Risk of Childhood Acute Lymphoblastic Leukemia

Tormod Rogne, MD PhD[1,2], Rong Wang, PhD[1], Pin Wang, PhD[3], Nicole C. Deziel, PhD[3], Catherine Metayer, MD, PhD[4], Joseph L. Wiemels, PhD[5], Kai Chen, PhD[3], Joshua L. Warren, PhD[6], Xiaomei Ma, PhD[1]

Affiliations:

1) Department of Chronic Disease Epidemiology, Yale School of Public Health, New Haven, CT, USA
2) Center for Perinatal, Pediatric and Environmental Epidemiology, Yale School of Public Health, New Haven, CT, USA
3) Department of Environmental Health Sciences, Yale School of Public Health, New Haven, CT, USA
4) School of Public Health, University of California, Berkeley, CA, USA.
5) Center for Genetic Epidemiology, Department of Population and Public Health Sciences, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA.
6) Department of Biostatistics, Yale School of Public Health, New Haven, CT, USA

Corresponding author:
Tormod Rogne
Department of Chronic Disease Epidemiology,
Yale School of Public Health,
One Church Street, 6th Floor,
New Haven, CT 06510, USA
Email: tormod.rogne@yale.edu
Phone: +1 (203)-737-7977
ORCiD: https://orcid.org/0000-0002-9581-7384

Conflict of interest: The authors report no conflict of interest.

Funding/Support: This work was supported by the Yale Center on Climate Change and Health. T. Rogne was funded by CTSA Grant Number UL1 TR001863 from the National Center for Advancing Translational Science (NCATS), a component of the National Institutes of Health (NIH). J. Warren was supported by the National Institutes of Health grants R01 ES028346 and P30 CA016359. The contents of this manuscript are solely the responsibility of the authors and do not necessarily represent the official views of NIH.

Role of funding: The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Contributors: TR was involved in the conceptualizing of the study, funding acquisition, literature search, figure creation, study design, data collection, data analysis, data interpretation, writing and revising the manuscript. RW was involved in the data analysis, figure creation, revising the manuscript, data collection and data interpretation. PW was involved in the data collection and revising the manuscript. NCD was involved in the funding acquisition, literature search, revising the manuscript, and data interpretation. CM was involved in the data collection, literature search and revising the manuscript. JLW was involved in the data collection, literature search and revising the manuscript. KC was involved in the funding acquisition, data collection, data interpretation, and revising the manuscript. JLW was involved in the funding acquisition, data analysis, data interpretation, writing and revising the manuscript. XM was involved in the conceptualizing of the study, funding acquisition, literature search, study design, data collection, data interpretation, and revising the manuscript.

ABSTRACT

Background: High ambient temperature is increasingly common due to climate change and is associated with risk of adverse pregnancy outcomes. Acute lymphoblastic leukemia (ALL) is the most common malignancy in children, the incidence is increasing, and in the United States it disproportionately affects Latino children. We aimed to investigate the potential association between high ambient temperature in pregnancy and risk of childhood ALL.

Methods: We used data from California birth records (1982-2015) and California Cancer Registry (1988-2015) to identify ALL cases diagnosed <14 years and 50 times as many controls matched by sex, race, ethnicity, and date of last menstrual period. Ambient temperatures were estimated on a 1-km grid. Association between ambient temperature and ALL was evaluated per gestational week, restricted to May-September, adjusting for confounders. Bayesian meta-regression was applied to identify critical exposure windows. For sensitivity analyses, we evaluated a 90-day pre-pregnancy period (assuming no direct effect before pregnancy), adjusted for relative humidity and particulate matter less than 2.5 microns in aerodynamic diameter, and constructed an alternatively matched dataset for exposure contrast by seasonality.

Findings: Our study included 6,258 ALL cases and 307,579 controls. The peak association between ambient temperature and risk of ALL was observed in gestational week 8, where a 5 °C increase was associated with an odds ratio of 1.09 (95% confidence interval 1.04-1.14) and 1.05 (95% confidence interval 1.00-1.11) among Latino and non-Latino White children, respectively. The sensitivity analyses supported this.

Interpretation: Our findings suggest an association between high ambient temperature in early pregnancy and risk of childhood ALL. Further replication and investigation of mechanistic pathways may inform mitigation strategies.

Poster Abstract 33

Patient-Level Social Determinants of Health Risk Factors and Short-Term Outcomes After Major Thoracic and Abdominal Surgery Across a Statewide Academic Healthcare System

Kurt Schultz, MD[1], Emily Park, BA[1], Julianna Mastrorilli, BS[2], Ira Leeds, MD, MBA, ScM[1]

[1]Division of Colon & Rectal Surgery, Department of Surgery, Yale School of Medicine
[2]Department of Chronic Disease Epidemiology, Yale School of Public Health

ABSTRACT

Background: Early evidence supports an association between social determinants of health (SDOH) and surgical outcomes. Historically though, these studies have lacked patient-level SDOH granularity and diversity of surgical disease. The aim of this study was to use routine, bedside questionnaires to assess the association of patient-level SDOH risk factors with postoperative complications after major thoracic and abdominal surgery.

Methods: This was a retrospective study of patients who underwent major thoracic or abdominal surgery at a single institution from January 2022 to June 2023. SDOH risk factors were collected by bedside nursing staff. The explanatory variable was “any SDOH risk factor,” defined as having ≥ one SDOH risk factor. The primary outcome was any 30-day complications. Distributions of categorical variables were compared by Chi-squared tests and continuous variables by Wilcoxon rank-sum tests.

Results: There were 1,196 patients who met inclusion criteria. For the four SDOH risk factors, 1.8% (n=22) of patients had medium- or high-risk housing situations, 0.9% (n=11) had unmet transportation needs, 3.2% (n=38) had food insecurity, and 3.4% (n=41) had medium or high financial resource strain. 6.1% (n=73) of patients had any SDOH risk factor. For major thoracic surgery, there were no differences in short-term outcomes between patients with and without any SDOH risk. For major abdominal surgery, patients with any SDOH risk factor had approximately two times the odds of having any 30-day complication compared to patients with no SDOH risk factors (OR, 2.10; 95% CI, 1.03-4.29; p=0.042).

Conclusions: Patients who screen positive for at least one SDOH risk factor have a higher likelihood of worse short-term outcomes after abdominal surgery, but not after thoracic surgery, compared to those with no SDOH risk factors. Future studies should investigate if more comprehensive screening modalities improve the quality of data collection and enhance identification of vulnerable populations undergoing major surgery.

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Poster Abstract 34

Applying Dual Energy Post-processing to Postmortem Coronary Computed Tomographic Angiography: A Feasibility Study

Nadia Solomon[1], Billy C Vermillion[2], Sun-Joo Jang[2], Harold Sanchez[3], Matthew Hoerner[1], Babina Gosangi[1], Stephanie L Thorn[2], Chi Liu[1], Albert J Sinusas[4]

[1] Radiology and Biomedical Imaging, Yale University, United States

[2] Yale Translational Research Imaging Center, Yale University, United States

[3] Pathology, Yale University, United States

[4] Internal Medicine - Cardiology, Yale University, United States

Objectives

Research suggests almost two-thirds of autopsies may be forgone by using postmortem CT angiography. While dual energy (DE) post-processing has been applied in both ante- and postmortem settings, research on its application to postmortem coronary computed tomographic angiography (PMCCTA) is limited.

Methods

Phantoms were created using combinations of iodinated (nonaqueous Angiofil®, aqueous OmnipaqueTM) and gadolinium (Dotarem®) contrast, with water dilutions. Phantoms were imaged using DE single-source CT (Definition Edge, Siemens; Dual Energy, 80/140 kV). Ex-vivo PMCCTA of a porcine heart was then performed using a cone beam fluoroscopy system (Allura Xper FD20, Philips) before and serially after injection of gadolinium 0.25 mmol/mL, followed by 6% Angiofil®. The heart was then imaged using DE single-source CT. DE post-processing was performed with SyngoVia software (Siemens).

Results

DE analysis successfully discriminated between iodine and gadolinium in the first phantom. In the second phantom, 6% Angiofil® layered on top of aqueous gadolinium, facilitating differentiation. In the heart, Angiofil® opacified the epicardial vessels while gadolinium diffused into the myocardium.

Conclusions

DE post-processing may be useful for isolating iodinated from gadolinium contrast in ex vivo PMCCTA. Serial injection of gadolinium and Angiofil® may allow for simultaneous characterization of vascular patency and changes in myocardial perfusion associated with either infarction or reperfusion injury.

Poster Abstract 35

Impact of inflammation on endometrial-placental communication via extracellular vesicles

Semilore Babawale, Jacy Scott, Mancy Tong
Yale School of Medicine, New Haven, CT, United States

Viral infections increase the risk for miscarriage and adverse pregnancy outcomes; yet the mechanisms remain unclear. We previously reported that viral double-stranded RNA (dsRNA) can induce inflammation in human endometrial stromal cells (EnSC) and reduce their decidualization. This is a key process that prepares EnSCs for implantation by increasing their release of soluble factors and extracellular vesicles (EVs). Here, we examined the downstream effects of early viral dsRNA exposure on endometrial EV production, placental function and pregnancy outcome.

C57BL/6 mice were administered viral dsRNA or saline on the morning of copulatory plug identification (GD0.5). On GD15.5, fetuses were weighed and placentas were collected for staining and RT-qPCR. *In vitro*, human EnSCs were treated with dsRNA before being exposed to base (NT) or decidualization (Dec) media. After 96hr, EVs were isolated from cell-free conditioned media and added to human trophoblasts. Trophoblast secretion of IL-8 and TIMP-1 were quantified by ELISA. Trophoblast migration in response to EVs were determined using transwell assays.

Preimplantation exposure to viral dsRNA significantly reduced litter size and fetal weight compared to control mice. Early viral dsRNA exposure also decreased the placental junctional zone: labyrinth zone ratio and expression of nutrient transporters. *In vitro*, while viral dsRNA did not affect the number or size of EVs released by EnSCs, these EVs increased trophoblast IL-8 and TIMP-1 secretion and decreased trophoblast migration compared to those treated with EVs from control Dec EnSCs.

Preimplantation exposure to viral dsRNA reduced fetal growth *in vivo*, which was associated with altered placentation and placental nutrient transporter expression. *In vitro*, we observed that viral dsRNA induced endometrial production of EVs that increase trophoblast inflammation and decrease migration. This work highlights a potential pathway by which early viral infection can lead to adverse pregnancy outcome through altered endometrial decidualization and EV-mediated trophoblast dysfunction.

Poster Abstract 36

UPREGULATED PLA2G10 IN CANCER IMPAIRS T CELL INFILTRATION TO DAMPEN IMMUNITY

Tianxiang Zhang[1], Weiwei Yu[1], Xiaoxiao Cheng[1], Jacky Yeung[1, 2], Viviana Ahumada[3], Paul C. Norris[4], Kurt A. Schalper[3], Miguel F. Sanmamed[1,5] and Lieping Chen[1, *]

[1]Department of Immunobiology, Yale University School of Medicine, New Haven, CT, USA
[2]Department of Neurosurgery, Yale University School of Medicine, New Haven, CT, USA
[3]Department of Pathology, Yale University School of Medicine, New Haven, CT, USA
[4]Sciex Demo Lab, Framingham, MA, USA
[5]Program of Immunology and Immunotherapy, Center for Applied Medical Research, University of Navarra, Pamplona, Spain

T cells are often absent from human cancer tissues during both spontaneously-raised immunity and therapeutic immunotherapy, even in the presence of a functional T cell-recruiting chemokine system, suggesting the existence of T cell exclusion mechanisms that impair infiltration. Using a genome-wide *in vitro* screening platform, we identified a role for phospholipase A2 group 10 (PLA2G10) protein in T cell exclusion. PLA2G10 upregulation is widespread in human cancers and is associated with poor T cell infiltration in tumor tissues. PLA2G10 overexpression in immunogenic mouse tumors excluded T cells from infiltration, resulting in resistance to anti-PD- 1 immunotherapy. PLA2G10 can hydrolyze phospholipids into small lipid metabolites thus inhibiting chemokine-mediated T cell mobility. Ablation of PLA2G10's enzymatic activity enhanced T cell infiltration and sensitized PLA2G10-overexpressing tumors to immunotherapies. Our study implicates a role for PLA2G10 in T cell exclusion from tumors and suggests a potential target for cancer immunotherapy.

Poster Abstract 37

The Crosstalk between Pain/Stress, Mitochondrial Dysfunction and Neurodevelopmental Outcomes in Preterm Infants in the NICU

Tingting Zhao, Yale School of Nursing

Abstract

Objective/Goals: Early life pain/stress impacts infants' neurodevelopmental outcomes. Mitochondrial dysfunction may interface between infants' stress and neurodevelopment. The study aims to investigate the associations between pain/stress, proteins associated with mitochondrial dysfunction, and neurobehavioral responses in preterm infants.

Methods/Study Population: A prospective cohort study was conducted with 33 preterm infants enrolled between September, 2017, to July, 2022, at two affiliated NICUs in Hartford and Farmington CT. Daily pain/stress experienced during NICU was documented. At 36-38 weeks post-menstrual age (PMA), neurobehavioral outcomes were evaluated using the NICU Network Neurobehavioral Scale (NNNS) and buccal swabs for Mass spectrometry-based proteomics analysis. Lasso statistical methods were conducted to study the association between protein abundance and infants' NNNS summary scores. Multiple linear regression and Gene Ontology (GO) enrichment analyses were performed to examine how clinical characteristics and neurodevelopmental outcomes may be associated with protein levels and underlying molecular pathways.

Results: **During NICU hospitalization, preterm premature rupture of membrane (PPROM) were negatively associated with neurobehavioral outcomes. The protein functions including leptin receptor binding activity, glutathione disulfide oxidoreductase** activity and response to oxidative stress, lipid metabolism, phosphate and proton transmembrane transporter activity were negatively associated with neurobehavioral outcomes, in the contrast, cytoskeletal regulation, epithelial barrier and protection function were found to be positively associated with the neurodevelopmental outcomes. In addition, mitochondrial dysfunction-related proteins (SPRR2A, PAIP1, S100A3, MT-CO2, PiC, GLRX, PHB2, and BNIPL-2, ABLIM1, UNC45A, Keratins, MUC1, and CYB5B) were found to be associated with neurobehavioral outcomes.

Discussion/Significance of Impact: Mitochondrial dysfunction-related proteins were observed to be associated with early life pain/stress and neurodevelopmental outcomes in infants. Large-scale studies with longitudinal datasets are warranted. Buccal proteins could be used to predict potential neurobehavioral outcomes. In addition, individualized skin integrity protection should be provided to preterm infants during their NICU stay.

Keywords: Preterm infants, Mitochondrial dysfunction, Pain/stress, Neurodevelopmental outcomes.