performance corresponded to an age-related atrophy of type IIx/IIb muscle fibers. We conclude that force generation and endurance of the DIAm required for breathing motor function is preserved in old age, while DIAm sarcopenia does impair more forceful expulsive airway clearance and voiding behaviors.

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Assessing the preclinical potential of the antidepressant agomelatine for Alzheimer's disease

Grace Terry[1], Lei Xie[2], Peter Serrano[3], Patricia Rockwell[4] and Maria Figueiredo-Pereira[4]
[1]Weill Cornell Graduate School of Medical Sciences, Hunter College, CUNY Graduate Center; [2]Hunter College Dept. of Comp. Sci, CUNY Graduate Center; [3]Hunter College Dept of Psychology, CUNY Graduate Center and [4]Hunter College Dept of Biological Sciences, CUNY Graduate Center

OBJECTIVES/GOALS: Alzheimer's disease (AD) has limited treatments and an extremely high rate of clinical trial failure. Through a collaborative effort, Agomelatine (AGO) was identified as having repurposing potential for AD. This study sets out to evaluate the preclinical potential of AGO for the treatment of AD. METHODS/STUDY POPULATION: The TgF344-AD rat model (expresses human mutant "Swedish" amyloid-precursor protein and a Δ exon 9 presenilin 1) was used to test AGO's potential to reduce cognitive deficits and neuropathology. The model was chosen due to its age-dependent progressive AD pathology and cognitive decline. Treatment with AGO at ~10 mg/kg body weight/day began at 5 months of age (pre-pathology) and continued until 11 months of age when cognitive testing (active place avoidance task) and tissue collection occurred. Immunohistochemistry was used to evaluate amyloid beta plaque burden and microglial response in the hippocampus. RESULTS/ANTICIPATED RESULTS: AGO-treated female TgF344-AD rats showed reduced cognitive deficits with an increased latency to first entrance in aPAT testing compared to nontreated transgenic littermates. There were no differences between the cognitive performance of AGO treated and untreated male TgF344-AD rats. Interestingly, this reduced cognitive deficit did not correlate with decreased amyloid beta pathology in female AGO-treated rats yet male transgenic treated rats did have decreased amyloid burden in the dentate gyrus (DG) of the hippocampus. AGO modulated microglial activation in the DG of female transgenic rats. DISCUSSION/SIGNIFICANCE OF IMPACT: AGO reduced cognitive deficits in females, but did not change their amyloid burden. This suggests that AGO could increase resilience to amyloid deposition in female rats. With the recent development of amyloid targeting drugs, novel non-amyloidogenic treatments have a large translational potential.

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Quantitative air trapping analysis in lung transplant recipients

Raul Villacreses, Ashten Sherman, Josalyn Cho, Tahuanty Pena and Julia Klesney-Tait
University of Iowa

OBJECTIVES/GOALS: Bronchiolitis obliterans syndrome (BOS), a form of chronic lung allograft dysfunction (CLAD) that primarily affects the small airways, is often diagnosed too late using standard pulmonary function tests. This project aims to evaluate whether quantitative air trapping analysis can serve as an early diagnostic tool for BOS. METHODS/STUDY POPULATION: We performed a retrospective analysis of 134 computed tomography scans with inspiratory and expiratory protocols from 73 lung transplant recipients (48 male, 25 female). Quantitative air trapping analysis was performed by VIDA Diagnostics using a supervised machine learning technique called disease probability measure (DPM). RESULTS/ANTICIPATED RESULTS: We found that lung transplant recipients exhibit significantly more air trapping compared to healthy controls and other small airway diseases, such as long COVID and cystic fibrosis. Notably, lung transplant recipients showed increased air trapping in the upper lobes. However, when separating participants into CLAD and non-CLAD groups, those meeting criteria for CLAD had significantly more air trapping in the left lower lobe. Additionally, only 2 out of 16 participants meeting CLAD criteria had less than 20% air trapping in their lungs, suggesting early involvement of the small airways. DISCUSSION/SIGNIFICANCE OF IMPACT: Quantitative air trapping analysis seems to be an important diagnostic modality in the early detection of lung transplant-related small airway disease. Prospective longitudinal studies are needed to evaluate the spatial pathophysiology in these patients and to determine whether early air trapping can predict the development of CLAD.

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The epithelial–mesenchymal transition protects heterogeneous breast tumors against immune attack in multiple species

Kimaya Bakhle[1], Shiney Chandraganti[2], Brian Feng[2], Brenda Ramos-Villanueva[2] and Andrew Miller[2]
[1]Anushka Cornell University and [2]Dongre Cornell University College of Veterinary Medicine

OBJECTIVES/GOALS: Our aim was to identify how the epithelial–mesenchymal transition shields heterogeneous breast tumors against immune attack. Additionally, we endeavored to understand whether our findings were conserved in canine mammary tumors as a translational model for human breast tumors. METHODS/STUDY POPULATION: To understand interactions between quasi-mesenchymal (qM) tumor cells, epithelial (E) tumor cells, and immune cells within heterogeneous breast tumors, we utilized a preclinical mouse model established in our lab. In this system, we can precisely control the proportions of E and qM tumor cells within tumors and study what immune cells infiltrate these tumors in response, using flow cytometry and immunofluorescent staining. Using this model, we have also established cell lines to study E and qM tumor cells in vitro. Finally, we used immunohistochemistry to label immune cells in canine mammary tumors and quantified the presence of these cells in relation to the expression of epithelial and mesenchymal cellular markers. RESULTS/ANTICIPATED RESULTS: We observed that immune suppression within heterogeneous mammary tumors is driven by local, rather than systemic, effects of quasi-mesenchymal (qM) tumor cells. The presence of systemic qM-derived factors does not alter immune cell infiltration nor sensitivity to immunotherapy of epithelial (E) tumors. Furthermore, I found that the local activity of qM-derived factors within heterogeneous tumors induces

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immune-suppressive changes in surrounding E cells, which protects them against immune attack. Finally, I found that canine mammary tumors with higher proportions of qM tumor cells assemble an immune-suppressive tumor microenvironment, highlighting the translational potential of our findings. DISCUSSION/SIGNIFICANCE OF IMPACT: We identified that the epithelial–mesenchymal transition induces immune-suppressive changes in heterogeneous tumors. These findings may reveal novel therapeutic targets for treatment of refractory tumors. Our findings in canine tumors suggest that these mechanisms are conserved across species.

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Buffering the impact of violence exposure: The role of caregiver and peer support on adolescent brain connectivity*

Emma Jagasia[1], Mary Nebel Beth[2], Nancy Perrin[2], Jaquelyn Campbell[2] and Sara Johnson[3]
[1]Johns Hopkins; [2]Johns Hopkins School of Nursing and [3]Kennedy Krieger Institute

OBJECTIVES/GOALS: Adolescence is a critical period where brain networks are thought to be influenced by environmental factors. This presentation examines violence exposure's impact on brain connectivity and identifies potential protective factors. METHODS/STUDY POPULATION: A secondary data analysis was conducted using data from a subsample of the Adolescent Brain Cognitive Development Study (release 5.1). Youth who completed victimization questionnaires at two time points were eligible for inclusion, resulting in 2016 participants. Linear regression was utilized to analyze associations between violence exposure measured by the juvenile victimization questionnaire and functional connectivity of specified regions of interests using the Gordon functional parcellation for cortical regions and the Freesurfer parcellation for subcortical regions. Moderation analysis will be utilized to assess the effects of peer and caregiver support on the associations between violence exposure and functional connectivity, currently ongoing. RESULTS/ANTICIPATED RESULTS: Between 18 and 59% of the sample reported experiencing at least one form of violence exposure, with racial differences noted in missing versus complete data. Multiple domains of violence and cumulative exposure were associated with both increased and decreased functional connectivity across within-network, between-network, and network-subcortical regions. At baseline, internet violence was linked to lower within-network connectivity, while peer victimization was associated with higher connectivity at both baseline and follow-up. Between network analysis showed lower connectivity with witnessing violence at baseline and higher connectivity with internet victimization at follow-up. DISCUSSION/SIGNIFICANCE OF IMPACT: These findings emphasize the need for further exploration of the underlying mechanisms that link violence exposure to developmental trajectories and identification of protective factors such as caregiver and peer support, to inform interventions and promote resilience in affected youth.

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The diffusion of vaginal bacterial extracellular vesicles through cervicovaginal mucus facilitates inflammation in female reproductive tract cells

Darby Steinman[1], Alyssa Petersen[2], Ethan Bolinger[2], Hannah C. Zierden[3] and Robert E[4]
[1]University of Maryland, College Park; [2]Department of Chemistry and Biochemistry, University of Maryland; [3]Fischell Department of Bioengineering, Department of Chemistry and Biochemistry and [4]Fischell Institute for Biomedical Devices,Department of Obstetrics, Gynecology and Reproductive Sciences

OBJECTIVES/GOALS: To probe microbe and bacterial extracellular vesicle (bEV) mobility through biological barriers, we use novel multiple-particle tracking technology. The goal is to evaluate changes caused by extracellular vesicles relevant to placental function and neonatal development. METHODS/STUDY POPULATION: We conducted multiple particle tracking to assess whole bacterial and bEV mobility in cervicovaginal mucus. To accomplish this, cervicovaginal mucus was self-collected from 10 women. Mucus samples were characterized via wet mount, Nugent score, and pH measurements. In parallel, we cultured commercially available vaginal bacteria strains in anaerobic conditions. We isolated bEVs via ultracentrifugation, and subsequently characterized them via nanoparticle tracking analysis to measure size, ζ-potential, and concentration. We investigated reproductive tract tissues response to bEVs. We dosed vaginal, endometrial, myometrial, and placental cells lines with bEVs over a 24 h period and determined uptake, viability, and cytokine production. One-way analysis of variance was used for statistical analysis. RESULTS/ANTICIPATED RESULTS: Based on our previous work, size and ζ-potential greatly affect particle mobility in mucus. *G. vaginalis* and *M. mulieris* were smaller than *L. crispatus* and *L. iners*. *G. vaginalis* had a more net-neutral ζ-potential compared to other bEVs. During multiple-particle tracking analysis, whole bacteria were unable to diffuse through vaginal mucus, while bEVs showed increased mobility. Through fluorescence levels, we determined *M. mulieris* bEVs reach >90% uptake at 24 h. Uptake was verified via microscopy. Across all strains, bEVs were not detrimental to placental viability. When investigating cytokine production in placental cells, an increase in IL-6 was seen after treatment with *L. iners* bEVs, while TNFα was increased after treatment with *G. vaginalis* bEVs. DISCUSSION/SIGNIFICANCE OF IMPACT: Vaginal microbiome dysbiosis increases adverse obstetric indications. We demonstrate that bacteria are unable to ascend to reproductive tissues. We propose that bEVs travel through vaginal mucus, facilitating microbe–host communication. This impacts obstetric disease pathology and is relevant for diagnostic criteria during pregnancy.

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CD8+ T-cell transfer induces adverse alterations to the post-myocardial infarction scar*

Shaoni Dasgupta[1], Maya Learnmonth[2], Alexa Corker[3], Miguel Troncoso[4], Ralph H. Johnson Veterans[5], Philip Broughton[5], Catalin F. Baicu[6], D. Bradshaw[6] and Carolina Kristine Y. DeLeon-Pennell[6]
[1]Medical University of South Carolina; [2]Medical University of South Carolina and Mayo Clinic College of Medicine and Science; [3]Medical University of South Carolina Affairs Medical Center; [4]Medical University of South Carolina and University of South Carolina School of Medicine Greenville; [5]Medical University of South Carolina Amy and [6]Medical University of South Medical University of South Carolina

OBJECTIVES/GOALS: Cardiovascular disease, particularly myocardial infarction (MI), is a leading cause of death in the USA. Previous studies have identified CD8+ T-cells as adverse regulators post-MI. We hypothesized that CD8+ T-cells impair cardiac function by altering scar composition. METHODS/STUDY POPULATION: MI was

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