



Abstract Book

3rd Scientific Meeting of the Canadian Translational Geroscience Network

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Edwin S.H. Leong Centre for Healthy Aging

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Session 1: Biomedical Geroscience

Keynote: Dr. Alice Kane



Multiomic Markers of Frailty in Mice and Humans

This presentation will give background on measuring heterogeneity in health in aging, particularly focusing on frailty indices in humans and mice. I will discuss recent work using aging mouse models to identify metabolomic and DNA-methylation based biomarkers of frailty, that are both sex-independent and sex specific. I will then present work exploring multi-omic signatures of frailty in large-scale human cohorts, using unsupervised clustering approaches, trajectory analysis and predictive modelling. I will show that frailty is an independent biological state from chronological aging, and present potential frailty biomarkers for follow-up investigations.

Short presentations:

Aura Tamez

Multiple Roads to Longevity: Distinct Aging Strategies Revealed by Opposing Gene Expression Programs in *C. elegans*

Aging is a major risk factor for the development of several chronic diseases, and the population of elderly people is increasing around the world, which means that soon more people will be vulnerable to the onset of age-related disease. Geroscience suggests that by studying the aging mechanisms that contribute to disease, we can identify novel ways to treat and prevent it. To advance our understanding of aging, we used a genomics approach to identify genes regulated by multiple lifespan-extending pathways. We performed RNA sequencing on nine long-lived *Caenorhabditis elegans* mutants representing seven longevity pathways: insulin/IGF-1 signaling, dietary restriction, germline deficiency, impaired chemosensation, reduced translation, elevated mitochondrial ROS, and mild mitochondrial impairment. Comparing gene expression across the entire panel of long-lived mutants revealed three distinct longevity groups that could be clearly distinguished by gene expression. Interestingly, two of these groups showed modulation of specific genetic pathways in opposite directions, suggesting multiple alternative strategies to achieving long life. Upregulated genes in one group were enriched in immunity and metabolism, while many downregulated genes impacted translation and gene expression. To assess the ability of these genes to enhance longevity individually, we knocked down the commonly upregulated genes in long-lived mutants and evaluated the resulting effect on lifespan. Using this approach, we identified several genes that affect lifespan individually. Overall, the shared longevity genes identified in this work offer potential targets to promote healthy aging and decrease age-onset disease.

Dr. Dantong Zhu

Frailty-Based Models Predict Age and Life Expectancy Across Mouse Sex, Strain and Facility

Frailty is a powerful integrative measure of biological aging, but its heterogeneity across genetic backgrounds, environments, and interventions limits its translational utility. To address this challenge, we assembled 29 mouse datasets spanning five commonly used strains—C57BL/6J, C57BL/6N, C57BL/6JNIA, UM-HET3, and Diversity Outbred (DO)—maintained across nine facilities under diverse dietary conditions to develop robust, generalizable frailty-based aging clocks. Using 1,306 naturally aging mice in the discovery cohort, we applied machine learning approaches to build models that predict chronological age and lifespan. We first developed strain-independent random forest models, then constructed subgroup models stratified by biological variables, including strain, sex, and age group. We subsequently retrained models in a transfer cohort comprising DO mice. The resulting models were integrated into two frameworks: the Frailty Item Age Score (FIAS) and the Frailty Item Lifespan Score (FILS). Application of FIAS and FILS to control mice in the validation cohort demonstrated improved predictive performance compared with benchmark linear models and previously published models, FRIGHT and AFRAID. These frameworks also showed superior performance in intervention-treated mice, indicating enhanced generalizability and sensitivity to biological heterogeneity. Collectively, FIAS and FILS provide scalable, strain-aware frailty clocks for quantifying biological age and predicting lifespan across diverse mouse populations.

Christine Gierke

Central, Not Peripheral: A Developmental *Drosophila melanogaster* Model Dissociating Sensory "Hardware" from Behavioral "Software" Under Early Social Stress

Background: Early-life social experience shapes behavioral plasticity across phylogeny, yet whether developmental deprivation disrupts peripheral sensory processing or central behavioral integration remains unclear — a distinction relevant to lifespan models of stress-related vulnerability. *Drosophila melanogaster* larvae, with well-characterized sensorimotor circuitry and conserved stress-response pathways, offer a tractable platform for this dissociation. We tested whether developmental social isolation selectively impairs central behavioral integration ("software") while preserving peripheral sensory function ("hardware"). **Methods:** Canton-S larvae were reared in complete social isolation or in groups from the egg stage. At the L3 stage, larvae were tested in a validated multi-substrate arena (humid, intermediate, dry), with position recorded at 5-minute intervals. Transition-based analyses characterized the temporal structure of substrate use; recurrence was calculated as the proportion of consecutive observations on the same substrate. Locomotor activity was quantified as body contractions and turning events over two minutes on dry or humid substrates. **Results:** Isolated larvae retained the ability to detect and avoid aversive dry substrates, indicating intact peripheral sensory function. In contrast, isolated larvae showed reduced locomotor activity and disrupted transition structure, indicating selectively compromised central behavioral integration; substrate recurrence did not differ between conditions, indicating preserved spatial stability despite reduced activity and complexity. **Conclusion:** These findings support a dissociation between intact peripheral sensory detection and compromised central integration under early-life social stress, indicating that developmental adversity

selectively targets central processing rather than sensory architecture. This hardware/software dissociation establishes *Drosophila* as a tractable platform for isolating neurodevelopmental mechanisms of social deprivation, with relevance to lifespan models in which early central — rather than peripheral — vulnerability may set trajectories toward later-life stress dysregulation and cognitive decline. Note: AI-assisted tools (Claude, Anthropic) were used solely for language editing and grammatical review of this abstract.

Keynote: Dr. James Nelson



Profound Sex Differences and Age-Specificity in Anti-Aging Drug Efficacy: Lessons from 20 Years of the NIA Interventions Testing Program

Over the past 20 years, the National Institute on Aging's Interventions Testing Program (ITP) has revealed striking sex differences in the lifespan benefits of potential anti-aging drugs. Like humans, ITP mice are genetically heterogeneous and exhibit the same male mortality disadvantage. Most successful interventions extend lifespan only or much more in males than females. Moreover, these benefits are often not uniform across the lifespan. In males, mortality reductions occur primarily during the first half of life. In this talk I will describe these patterns and discuss their translational implications. I will also introduce a new analytic tool designed to pinpoint when during the lifespan an intervention reduces mortality, providing information that standard log-rank testing may obscure. This presentation will highlight the importance of asking not just whether a treatment extends lifespan, but in which sex, at what age, and with what implications for translating findings into human therapies.

Workshop: How to Use and Interpret Biological Clocks

Aging clocks are emerging as powerful tools for quantifying different aspects of biological aging, with growing applications in aging research and clinical and translational geroscience. This workshop will begin with a brief introduction to aging clocks, including how they are developed and the different types of clocks currently available. A moderated panel discussion featuring experts in the field will then explore key opportunities and challenges in the use and interpretation of aging clocks, including what different clocks measure, their strengths and limitations, and their potential applications in research and clinical practice.

Moderator:

Dr. Hannah-Ruth Engelbrecht

Postdoctoral Fellow, Simon Fraser University and BC Children's Hospital Research Institute

Panelists:

Dr. Michael Kobor

Edwin S.H. Leong UBC Chair in Healthy Aging – a UBC President’s Excellence Chair

Director, Edwin S.H. Leong Centre for Healthy Aging

Professor and Canada Research Chair in Social Epigenetics, Department of Medical Genetics, University of British Columbia

Fellow, Canadian Institute for Advanced Research (CIFAR)

Dr. Alice Kane

Al and Val Rosenstrauss Fellow at the Charles Perkins Centre, University of Sydney

Assistant Professor at the Institute for Systems Biology

Dr. Jennifer Ailshire

Professor, UPS Foundation Chair in Gerontology, and Associate Dean of Research, Leonard Davis School of Gerontology, University of Southern California

Co-Director, USC/UCLA Center on Biodemography and Population Health

Co-Director, Network on Life Course Health Dynamics & Disparities, University of Southern California

Co-Director, AD/ABRD Resource Center for Minority Aging Research, University of Southern California

Dr. Colin Farrelly

Sir Edward Peacock Professor of Political Theory, Department of Political Studies, Queen’s University

Author, *Aging and the Ethics of Longevity Science* (Oxford University Press, New York 2026)

Session 2: Clinical and Population Geroscience Research

Keynote: Dr. Sara Espinoza



A Translational Geroscience Approach to Frailty: From Concept to Clinical Trial

Frailty is one of the most important clinical manifestations of aging, reflecting a progressive loss of physiological reserve and resilience across multiple systems. In this presentation, Dr. Sara Espinoza will describe a translational geroscience approach to frailty, tracing the path from understanding mechanisms of biological aging to developing and testing interventions designed to preserve function and healthspan. She will discuss how geroscience can inform the identification of individuals most likely to benefit from intervention, the selection of clinically meaningful outcomes, and the design of prevention and treatment trials. Using her clinical studies of metformin and frailty as an example, Dr. Espinoza will highlight both the opportunities and challenges encountered when translating geroscience concepts into clinical trials. She will conclude by considering how precision geroscience may reshape the prevention of frailty and loss of independence.

Short presentations:

Rami Hammad

Serum C-terminal Agrin Fragment as a Biomarker of Age-Related Neuromuscular Decline in Men: Influence of Physical Activity

Background: The C-terminal agrin fragment (CAF), a circulating byproduct of agrin cleavage, has been proposed as a minimally invasive biomarker of NMJ degradation, but its relationships with Age, specific neuromuscular and functional variables, and the potential modulating role of physical activity, remain poorly defined. **Objective:** To examine age- and physical activity-related differences in serum CAF and to test its associations with neuromuscular and functional capacity across the adult male lifespan.

Methods: We studied 136 community-dwelling men aged 20-92 years (active, n=87; inactive, n=49). Serum CAF was measured by ELISA; NCAM-positive fiber proportion was assessed by immunolabeling of vastus lateralis biopsies (n=127). Neuromuscular assessments included maximal voluntary isometric contraction (MVIC), lower-limb muscle power, electromechanical delay (EMD), nerve conduction velocities, H/M ratio, central activation ratio, co-activation, and twitch characteristics. Functional capacity was assessed with the 6-minute walk test, alternating step test, Timed Up and Go, sit-to-stand tests, and fast gait speed. **Results:** Serum CAF increased progressively with age ($\beta = 0.01$, $p = 0.04$) and was positively associated with NCAM-positive fiber proportion ($\beta = 21.51$, $p = 0.0001$). Higher CAF was associated with lower MVIC ($\beta = -0.01$, $p = 0.026$), reduced lower-limb power ($\beta = 0.01$, $p = 0.027$), and poorer performance on the 6MWT, alternating step test, TUG, sit-to-stand, and gait speed ($p < 0.05$). CAF

was associated with longer EMD in the full cohort ($\beta = 0.003$, $p = 0.017$) and inactive men ($\beta = 0.005$, $p = 0.007$), but not active men, and with lower H/M ratio in inactive men only ($\beta = -0.003$, $p = 0.13$). No associations were found with nerve conduction velocities, central activation ratio, co-activation, or twitch amplitude. Active men showed lower CAF than inactive men, particularly after age 70 [$p = 0.023$]. Conclusion: Serum CAF is associated with age-related declines in neuromuscular and functional capacity in men and shows tissue-level concordance with NCAM-positive fiber proportion, supporting its use as an accessible biomarker of NMJ remodeling. Its limited association with most electrophysiological measures indicates it captures a specific component of neuromuscular aging rather than a global index of neuromuscular function. Physical activity was associated with a more favorable CAF profile, particularly among older men, identifying physical activity as a potential modifiable factor in age-related NMJ decline.

Dr. Vincent Marcangeli

Mitochondrial Calcium Handling in Skeletal Muscle Declines with Aging in Women

Introduction: Age-related skeletal muscle atrophy and weakness substantially increase the risk of falls, hospitalization, and mortality. Mitochondrial dysfunction is recognized as a central mechanism underlying muscle aging. The mitochondrial permeability transition pore, a calcium-regulated channel, plays a critical role in mitochondrial homeostasis, and its opening can trigger muscle atrophy programs. Recent evidence in men demonstrates that aging-related alterations in mitochondrial calcium handling resulting from altered mitochondrial permeability transition pore kinetics likely contribute to age-related declines in muscle mass and function. However, whether similar alterations occur in women remains unexplored. Objective: To determine whether mitochondrial calcium handling is impaired during skeletal muscle aging in women. Methods: Thirty-nine healthy women (mean body mass index: 25.7 ± 4.04 kg/m²; age range: 55-84 years) participated in this study. Mitochondrial calcium handling was assessed in permeabilized myofibers obtained from vastus lateralis muscle biopsies. Fibers were subjected to a calcium challenge in a spectrofluorometer cuvette, and mitochondrial calcium uptake was monitored using Calcium Green fluorescent probe. Mitochondrial calcium retention capacity, defined as the amount of calcium required to trigger mitochondrial permeability transition pore opening, and the time to mitochondrial permeability transition pore opening were quantified. We assessed muscle thigh cross sectional area and volume using peripheral quantitative computed tomography (pQCT) and magnetic resonance imaging (MRI) respectively. We complemented our correlation analyses with bootstrap resampling to ensure robustness of the observed associations. Results: Mitochondrial calcium retention capacity declined significantly with age ($r = -0.342$, $p = 0.017$), as did the time to mitochondrial permeability transition pore opening ($r = -0.308$, $p = 0.028$). Mitochondrial calcium retention capacity and time to mPTP opening were significantly associated with thigh muscle area ($r = 0.531$, $p > 0.001$ and $r = 0.432$, $p = 0.004$ respectively). R and p-values obtained after bootstrap resampling indicate that mitochondrial calcium retention capacity and time to mPTP opening correlates with thigh muscle volume assessed by MRI. Conclusions: Mitochondrial calcium retention capacity and mitochondrial permeability transition pore opening kinetics deteriorate with age in women and are correlated with muscle size and volume, mirroring findings previously reported in men. These results suggest that

mitochondrial calcium handling represents a promising therapeutic target for mitigating age-related muscle decline.

Elaine Xiao

Unpacking Sex and Gender in Age-Related Respiratory Health Outcomes

Objective: Chronic obstructive pulmonary disease (COPD), a common age-related chronic disease and a leading cause of mortality worldwide, is associated with declines in health-related quality of life (HRQoL). While biological sex influences COPD progression, the contribution of gender to HRQoL remains poorly understood. This study examines the effects of gender, independent of sex, on HRQoL over time among older adults with COPD participating in a randomized clinical trial. **Methods:** An observational cross sectional and longitudinal [CA1] study of 223 COPD patients with data on biological sex, gender identity, gender roles (household labour, caregiving, employment, and primary earner status), gender relations (marital status), and institutionalized gender (education, income, occupational social class, and wealth). HRQoL was measured using the EQ-5D-5L and EQ-VAS at baseline, 3- and 6-month follow-up. Multiple imputation by chained equations (20 iterations for [CA2] 30 imputations) addressed missing data. Multivariable linear regression models examined each gender variable associated with baseline EQ-VAS, adjusted for biological sex, age, BMI and smoking. Future mixed models will determine independent associations of gender and change in EQ-VAS. **Results:** Our sample's mean age was 70.5 years (SD 8.3), with 37.2% female and 36.0% self-identified cisgender women. Multivariable-adjusted models showed that COPD patients who reported not working ($\beta = -10.7$ [95% CI: -20.7, -0.7]), not owning a home (-6.0 [95% CI: -11.1, -1.0]), having high school education (-13.5 [95% CI: -21.1, -5.9]), or whose social class was classified as poor (-20.8 [95% CI: -34.9, -6.6]) had significantly lower baseline EQ-VAS scores, compared to respective reference groups. By contrast, COPD patients reporting an equal share of household labour had higher baseline EQ-VAS scores (8.5 [95% CI: 1.3, 15.6]), compared to those reporting no household labour responsibilities. Future analyses will examine longitudinal changes in HRQoL and assess whether the effect of the risk prediction tool in the trial varies by gender. **Conclusions:** Preliminary findings highlight the importance of examining gender independently of biological sex to identify which social gendered factors contribute to healthy aging and quality of life among older adults with COPD.

Raymond Schnuerer

Polyphenol Supplementation and Exercise on Inflammation, Anabolic and Catabolic Signaling, and Cellular Hypertrophy in Skeletal Muscle

Objective: Sarcopenia is associated with a blunted anabolic response of skeletal muscle to dietary protein and contractile activity. Blunted anabolic responses to stimuli are thought to be at least in part due to the age-related development of chronic low-grade inflammation. Polyphenols have potential antioxidant and anti-inflammatory properties, the ingestion of which may alleviate the negative impact of aging on the adaptive response to exercise training. However, the effects of polyphenol intake on inflammatory pathways and protein metabolism in skeletal muscle in older adults undertaking exercise remain unexplored. We recently completed a single-centre, double-blind, two-arm randomized

controlled feasibility trial with a 1:1 allocation ratio, comparing 12 weeks of combined resistance-band and stationary-cycling exercise with either polyphenol supplementation (Phyto-P; 3 g·day⁻¹ n=15) or maltodextrin placebo (3 g·day⁻¹ n=15) in older adults (67 ± 6 y; BMI 28.5 ± 4.6 kg/m²; NCT07441343). The present investigation will probe how polyphenol intake impacted intramuscular and circulating inflammatory markers as well as signaling molecules known to affect protein metabolism from this trial. Methods: Venous blood samples and skeletal muscle biopsies were collected from participants under basal conditions before and after the exercise intervention. Serum concentrations of pro-inflammatory cytokines CRP, IL-6, and TNF-α will be measured using enzyme-linked immunosorbent assays. Protein content of proteins associated with skeletal muscle inflammatory signaling (NF-κB and STAT3), anabolism (mTOR and S6rp), and catabolism (MuRF1 and MAFbx) will be measured using western blotting techniques. Skeletal muscle fiber typing and cross-sectional area will be measured using immunohistochemistry. Significance: Attenuation of basal inflammatory signaling and downstream catabolic pathways through polyphenol supplementation may help restore skeletal muscle anabolic responsiveness to physiological stimuli. If polyphenol supplementation reduces inflammation-mediated anabolic resistance, this effect would be expected to manifest as greater skeletal muscle hypertrophy following resistance exercise training compared with placebo. Such findings would support polyphenol supplementation, alongside resistance exercise, as a potential therapeutic strategy for the prevention or treatment of age-related sarcopenia.

Ayesha Habib

Is Metabolic Health Socially Patterned During the Menopause Transition? A Cross-Sectional Study of Indigenous Mayan Women in Guatemala

Objective: Socioeconomic conditions are established determinants of metabolic health, yet little is known about their relationship with metabolic dysfunction among Indigenous women undergoing the menopausal transition. This study examines whether socioeconomic status (SES) is associated with BMI and trajectories of endogenous insulin secretion among Indigenous Kaqchikel Maya women in Guatemala. Methods: A cross-sectional study using the 2023 wave of the Society, Ecology, and Reproduction Study with repeated urinary C-peptide samples from 71 Indigenous Kaqchikel Maya women aged 39-65 years. SES indicators include women's employment, husbands' employment and occupation, household income sources, land ownership, and sale of surplus food. Anthropometry was collected with the interview data on SES and first-morning urine samples were collected over approximately three months to calculate specific gravity-corrected C-peptide. Data were analysed using descriptive and inferential statistics; future random-coefficient linear regression will examine SES differences in C-peptide trajectories adjusting for confounders identified using a directed acyclic graph. Results: Preliminary descriptive and inferential statistics showed that 52% of women were employed, 85% reported employed husbands, 82% owned land, and households averaged 2.47 (SD 0.89) income sources. Mean BMI was 28.47 kg/m² (SD 4.75), within the overweight range. Median C-peptide was 13.1 (IQR 8.33-23.8). In unadjusted analyses, BMI was significantly higher among women who sold surplus food than among those who did not (30.1 [SD 4.39] vs. 27.4 [SD 4.72] kg/m²; p = 0.016). No significant BMI differences were observed by women's employment, husbands' employment or occupation, land ownership, or number of household income sources. While not statistically significant, median C-peptide

varied across SES groups such as between employed (10.3 [IQR 7.92-12.78]) and unemployed (24.32 [IQR 13.39-35.25]) or land-owner (13.04 [IQR 7.77-23.07]) and no land-ownership (21.28 [9.2-24]).

Conclusions: This study will provide novel evidence on how socioeconomic conditions relate to BMI and trajectories of endogenous insulin secretion among midlife Indigenous women in a country undergoing economic development with the associated nutrition transition. Future findings help advance women's health research and the social epidemiology of aging to enhance the health and wellbeing of aging Indigenous populations.

Workshop: Developing a Clinical Geroscience Protocol

Geroscience clinical trials aim to target the underlying biological processes of aging to improve health and function across multiple age-related conditions and domains. However, important questions remain about what distinguishes a geroscience trial from a conventional disease-specific clinical trial. This interactive workshop will explore the defining characteristics of geroscience trials through discussion of clinical trial protocols, examining their objectives, interventions, and outcomes.

Moderator:

Dr. Alexandra Papaioannou

Professor, Medicine, McMaster University

Professor; Executive Director, Geras Centre for Aging Research at Hamilton Health Sciences

Session 3: Innovations in Geroscience

Keynote: Dr. Emilia Lim



How our Exposures and Age Sculpt our Lung Tissue Towards Cancer

Our lungs bear the cumulative imprint of a lifetime of environmental exposures and biological aging. Yet, how these forces reshape normal lung tissue to create a landscape permissive to cancer remains incompletely understood. In this talk, I will present approaches to understanding how environmental exposures leave their mark on the lung. I will describe our work on anthracosis, the accumulation of particulate pigment in lung tissue, spanning digital pathology to quantify pigment burden and spatial transcriptomics to investigate the cellular neighbourhoods and molecular pathways associated with pigment-laden regions. I will also explore how age, smoking and air pollution shape the clonal expansion of somatic mutations in histologically normal lung, potentially favouring cells carrying cancer-associated alterations. Together, these studies examine how environmental exposures and aging reshape lung tissue across scales, from tissue architecture to cellular ecosystems and somatic evolution, revealing new insights into lung cancer development and opportunities for earlier risk assessment and precision prevention.

Keynote: Dr. Jennifer Ailshire



Heat and Biological Aging: Evidence Across Aging Clocks

Could heat exposure accelerate biological aging? This talk draws on research from the U.S. Health and Retirement Study to examine associations between outdoor heat and biological aging among older adults. Evidence spans epigenetic clocks, which capture aging-related changes in DNA methylation, and a clinical biological age measure combining 22 biomarkers across eight physiological systems. The presentation explores how heat intensity and exposure timing relate to accelerated biological aging, highlighting inflammatory and other physiological responses that may precede overt disease. It also examines differences between women and men in heat-associated biological age and biomarker responses. Together, these findings suggest that heat's health burden may extend beyond acute illness and mortality, with implications for understanding unequal vulnerability and protecting healthy aging in a warming world.

Short presentations:

Dr. Alibek Moldakozhayev

Ambient Temperature Shapes Metabolism, Resilience, and Aging Across Species

Ambient temperature is a readily modifiable environmental variable, yet its influence on developmental and aging trajectories remains poorly defined. To address this gap, we exposed nematodes, flies, and

mice to different thermal environments in early life and aged them at various temperatures in adulthood. Across species, we systematically assessed the relationship between ambient temperature, development, and aging by characterizing metabolism, resilience, health, and lifespan. We further investigated the roles of the key interaction parameters in human development and aging, using longitudinal and cross-sectional data from adults and phenotypically rich longitudinal data from premature infants. Across species, we demonstrate that resilience is established during early development and determines aging outcomes in adulthood. We also show that the trajectory and pattern of aging within the same species vary across environments. Finally, we formalize the role of homeostasis in resilience and aging, and show that adjusting environmental signals to reduce the magnitude of metabolic swings prolongs periods near the homeostatic point, and consequently improves health and extends life. Together, these results identify ambient temperature as a powerful, exposure time-dependent determinant of resilience and aging, and highlight early- and late-life thermal conditions as a modifiable factor affecting health and longevity.

Dr. M. Rosie Shrout

Effects of Early and Later Life Adversity on Accelerated Biological Aging

Objective: Abuse in both childhood and adult romantic relationships is linked to age-related health problems. Positive marital dynamics, however, can buffer stress and protect health, particularly as couples grow older. In this longitudinal study, we applied dyadic and life-course stress theories to examine how couples' destructive, abusive conflicts exacerbate biological aging associated with early life adversity, while constructive conflicts temper adversity's biological aging toll. We focused on middle-aged and older couples because, despite their age-related health risks, they remain an understudied group whose relationships are central to health. **Methods:** Married couples ($n=107$ couples, 214 individuals, ages 40-87 years) in mixed-gender relationships completed two visits, two years apart. Partners completed the Childhood Adversities scale, Childhood Trauma Questionnaire, and the Revised Conflict Tactics Scale short form. Blood-based measurements of biological aging included telomere length, T cell p16INK4a expression, and epigenetic age acceleration (EAA; PhenoAgeEAA, GrimAgeEAA, HannumEAA, Horvath2EAA, DunedinPACE). Covariates included sex and comorbidities, with models predicting telomere length and p16INK4a also controlling for chronologic age. **Results:** Linear mixed models showed those with greater childhood family adversities had shorter telomeres ($b=0.001$, $p=0.02$) and faster epigenetic aging (PhenoAgeEAA, GrimAgeEAA, DunedinPACE; $bs=0.01$ to 0.73 , $ps<0.05$). Over two years, childhood family adversities or maltreatment predicted larger rises in (p16INK4a $b=0.16$, $p=0.02$) and accelerated epigenetic aging (Horvath2EAA, PhenoAgeEAA, DunedinPACE; $bs=0.01$ to 0.37 , $ps<0.05$). Couples' destructive conflicts moderated concurrent effects: spouses who experienced adversity or maltreatment in both childhood and the past year of their marriage aged 10 months faster in GrimAgeEAA and DunedinPACE ($bs=0.01$ to 0.12 , $ps<0.01$). Contrary to hypotheses, effects were not significant for constructive conflicts ($ps>0.14$). **Conclusions:** Couples' destructive, abusive conflict tactics exacerbate the harmful effects of early life adversity on the rate of biological aging in mid-to-late life. Constructive conflicts were not related to biological aging nor helped offset adversity's biological aging toll, suggesting that aging biomarkers may be particularly sensitive to couples' hostile interactions. These findings illustrate the combined accelerated aging risks of adverse and abusive relationships in

both early and later life, revealing potential biological pathways to adversity-related increases in morbidity and mortality.

Dr. Annalijn Conklin

Aging Well in The Company We Keep: How Shifts in Social Circles Shape Physiological Determinants of Aging in the CLSA Cohort

Background: Both central obesity and hypertension are important physiological determinants of aging that are influenced by the social environment. Aging brings loss and persistent lack of social interactions but little is known about how shifts in social circles shape these biomarkers of aging in the Canadian population. **Methods:** Two population-based, prospective studies of adults (45+ years) in the Canadian Longitudinal Study on Aging (2011-2021) assessed transitions (Wave 1 to 2) in social isolation (0-1 monthly social activity) and diverse social engagement (5-8 monthly activities). Gender-specific logistic regression models on imputed datasets adjusted for confounders (selected by Directed Acyclic Graphs) to determine which shifts in social circles influenced the new development of central obesity (study one) and hypertension (study two) at Wave 3. **Results:** Compared to women with stable variety of social engagement (5+ monthly activities) between Wave 1 and 2, women reporting persistently low variety of social participation (<5 monthly activities) were 20% more likely to develop central obesity (OR 1.20 [CI95: 1.04, 1.39]) in final models; this result was robust to sex-specific confounders (OR 1.22 [1.05, 1.41]) in sensitivity analyses. In addition, women who remained socially isolated over time (0-1 monthly activities) had 63% higher odds of new-onset hypertension (OR 1.63 [CI95:1.05, 2.53]), compared to women remaining non-isolated from wave 1 to wave 2. This result was robust to adjustment for sex-specific factors and social relationships. In both studies, associations among men were null or in mixed directions. **Conclusions:** Findings from both studies highlight the importance of examining age-related shifts in social connectedness which may be a driver of the biological mechanisms of aging for women in mid to later life. Structural interventions and screening for both social isolation and variety of connectedness could help enhance healthy longevity and improve older women's health outcomes.

Keynote: Dr. Colin Farrelly



The Geroscience Perspective on One Health

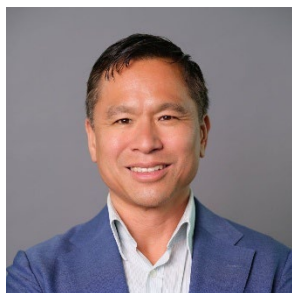
The One Health concept has been invoked to foster collaborations at the intersection of human, animal, and environmental health to address zoonotic disease risk. But the One Health concept is also helpful in framing and addressing the public health imperative to prevent and delay the onset of the chronic diseases of late life, to extend healthy life expectancy in ways that are sustainable and beneficial to animal and environmental health. This is an

urgent global health imperative because healthy life expectancy is not increasing at the same pace as life expectancy, leading to more years being lived in poor health. This talk details the Geroscience Perspective on One Health, a framework that draws attention to the interdependence of healthy human aging and animal and environmental health by emphasizing the importance of pursuing

nonpharmacological (environmental and lifestyle) and potential pharmacological (gerotherapeutics) interventions to increase healthspan.

Session 4: Accelerating Geroscience: Industry, Innovation, and Impact

Keynote: Dr. Peng Leong



Building a Therapeutics Company in Aging: Lessons Learned from the Front Lines

BioAge starts drug discovery with human data: longitudinal aging cohorts with decades of follow-up, and serially banked samples coupled with health records and functional measurements. We use these data to identify proteomic changes that track with functional decline, disease risk and survival, then build drugs against those pathways. This talk follows that path from dataset to drug candidates dosed in people, using two programs as case studies: BGE-102, an oral NLRP3 inhibitor now in Phase 2 trials in cardiovascular risk and diabetic macular edema, and our APJ agonist exercise-mimetic program in IND enabling studies. Along the way, we'll discuss how endpoint and biomarker choices constrain what we can even test in people, and what it looks like when a promising hypothesis meets the 'real world' of complex systems biology, regulatory agencies, investor interest and pharma focus.

Keynote: Sarah McCullough



Accelerating Breakthroughs: The Power of Challenge-Based Innovation

What does it take to move bold ideas from discovery to real-world impact? Challenge-based innovation offers a different approach to accelerating breakthroughs by defining ambitious goals, mobilizing diverse expertise, and creating incentives to solve complex global challenges. Drawing on examples from XPRIZE, including the \$101 million XPRIZE Healthspan competition, this talk will explore how incentive prizes and global innovation ecosystems can complement traditional research and commercialization pathways. It will also highlight the role of the XPRIZE Canada Hub in connecting Canadian researchers and innovators with the partnerships, resources, and opportunities needed to advance promising solutions and accelerate their impact.

Keynote: Dr. Gustavo Duque



The World Health Organization's Integrated Care for Older People (ICOPE) framework offers an opportunity to transform how health systems identify, prevent, and address age-related declines in intrinsic capacity. This presentation will explore the implementation of ICOPE in Quebec as a translational geroscience strategy, bridging advances in aging research with practical, person-centred interventions in community settings. The Quebec initiative integrates digital health technologies, artificial intelligence, and geolocalized community resources to support the identification of intrinsic capacity deficits, facilitate

personalized care pathways, and connect older adults with appropriate services. Through collaboration among researchers, clinicians, healthcare decision-makers, and community partners, the initiative aims to move beyond disease-centred approaches toward the early detection and prevention of functional decline. This model illustrates how geroscience principles can be translated into scalable health system interventions that preserve intrinsic capacity, promote resilience, and support healthy aging, independence, and quality of life among older adults.

Keynote: Dr. Ajinkya Ghagre



A Synthetic Thymic Niche for Reversing Age-Related Immune Decline

The thymus is essential for T cell maturation and adaptive immunity, but it naturally shrinks and loses function with age. This age-related thymic involution results from both depletion of T cell progenitors and deterioration of the thymic niche. Together, these changes reduce naïve T cell production and contribute to increased infection, vaccine failure, and autoimmunity in older adults. To address this, we propose a novel regenerative strategy using injectable thymus-like hydrogels designed to recruit endogenous aged hematopoietic stem cells (HSCs) and redirect them toward the lymphoid lineage. By reconstructing the thymic niche while recruiting endogenous progenitors in a single injectable system, this approach provides a potential autologous strategy to counteract immunosenescence. Our goal now is to advance this technology toward preclinical development of a thymus-regenerative therapy, ultimately aiming to improve vaccine responses and immune function in older and immunocompromised populations.

Poster Presenters

#	Presenter
1	Dany Sibai – “Preclinical validation of circulating osteoprogenitor cell infusions as a novel treatment for osteosarcopenia” Osteoporosis affects approximately 18.3% of people worldwide and accounts for over 80% of fractures in individuals aged 50 and older. Many fractures result from falls, often associated with sarcopenia, a condition marked by low muscle mass, strength, and function. Osteoporosis and sarcopenia often coexist as osteosarcopenia, greatly increasing the risk of falls, fractures, and loss of independence in older adults. Despite its high prevalence in both women and men, effective therapies targeting both bone and muscle remain limited. Bone-marrow mesenchymal stromal cells (BM-MSCs) have shown promise in treating frailty, but their clinical use is limited by invasive collection and high cost. Circulating osteoprogenitor (COP) cells, found in peripheral blood, offer a minimally invasive, cost-effective, and scalable alternative. Our team has developed methods to isolate, quantify, and expand COP cells, which share genomic and proteomic similarities with BM-MSCs. We hypothesize that allogeneic human COP (allo-hCOP) cell infusions are safe, well tolerated, and exhibit favorable biodistribution and persistence comparable or superior to allo-hBM-MSCs. To evaluate feasibility, naturally aged 24-month-old C57BL/6 mice, a validated model of osteosarcopenia, will receive systemic cell infusions followed by bioluminescence imaging to assess biodistribution and engraftment. Preliminary cell tracking experiments using allo-hBM-MSC infusions demonstrated successful distribution and persistence across multiple tissues without significant toxicity or severe immune reactions, supporting the feasibility and safety of this approach. Quantitative analyses will examine changes in bone mineral density, muscle mass and muscle strength using appropriate techniques such as histomorphometry, three-point bending, muscle immunohistochemistry, etc. This project will establish the preclinical foundation for the development of allo-hCOP cell therapy as a novel regenerative treatment for osteosarcopenia and age-related musculoskeletal decline.
2	Inna Zaiats – “Linking Senescence to Age-Related Ovarian Cancer” Objective: Ovarian cancer remains one of the deadliest causes of cancer-related deaths in Canadian women, with High Grade Serous Ovarian Cancer (HGSOC) being the most lethal. In HGSOC, older patients show a poorer clinical prognosis and survival compared to younger individuals. The tumor environment of HGSOC is composed of various types of cells that are involved in tumorigenesis. As our tissue architecture changes with age, we experience a depletion of proliferating cells and an increase in the populations of cell cycle-arrested senescent cells. It is unknown how physiologically occurring senescent cells influence both cancerous and non-cancerous components of HGSOC. As the accumulation of senescent cells can have deleterious effects on the neighbouring cellular environment, I hypothesize that senescence accelerates HGSOC development in older individuals. Methods: To test the non-cell autonomous effects of senescent populations on cancer cells, I utilize the approach where I primarily expose ovarian cancer KURAMOCHI cells to media from senescent primary fibroblast IMR90 cells. The effect of senescent conditioned media treatment on cancer cells so far has been studied on their secretome with mass spectrometry and their responsiveness to standard-

	of-care drugs Carboplatin and Paclitaxel. Results/Findings: The mass spectrometry analysis identified SFRP1 and MROH1 as candidates whose significance will be determined in ongoing experiments. I also demonstrated that exposure of KURAMOCHI cells to senescent conditioned media resulted in an increase in their chemoresistance to Carboplatin and showed no change in response to Paclitaxel. Conclusions: My current findings suggest that the senescent secretome affects the phenotype of cancer cells by changing their chemoresistance to Carboplatin. My future directions involve testing the response of senescent conditioned media pre-treated ovarian cancer cells to other standard-of-care chemotherapeutic agents and investigating the mechanism of senescence-associated chemoresistance. Studying the role of physiological senescence in HGSOC could expand our understanding of how the specifics of senescent and cancer cells interaction can be utilized to improve health outcomes for older individuals with ovarian cancer.
3	Claire Bokang Ko – “Trade-off between lifespan and stress resistance under mild mitoUPR activation” The mitochondrial unfolded protein response (mitoUPR) is a stress response pathway that responds to mitochondrial insults by altering gene expression to recover mitochondrial homeostasis. The mitoUPR is mediated by the stress-activated transcription factor ATFS-1 (activating transcription factor associated with stress 1). Constitutive activation of ATFS-1 increases resistance to exogenous stressors but paradoxically decreases lifespan. In this work, we determined the optimal levels of expression of activated ATFS-1 with respect to lifespan and resistance to stress by treating constitutively active atfs-1(et17) worms with different concentrations of RNA interference (RNAi) bacteria targeting atfs-1. We observed the maximum lifespan of atfs-1(et17) worms at full-strength atfs-1 RNAi, which was significantly longer than wild-type lifespan. Under the conditions of maximum lifespan, atfs-1(et17) worms did not show enhanced resistance to stress, suggesting a trade-off between stress resistance and longevity. The maximum resistance to stress in atfs-1(et17) worms occurred on empty vector. Under these conditions, atfs-1(et17) worms are short-lived. This indicates that constitutive activation of ATFS-1 can increase lifespan or enhance resistance to stress but not both, at the same time. Overall, these results demonstrate that constitutively active ATFS-1 can extend lifespan when expressed at low levels and that this lifespan extension is not dependent on the ability of ATFS-1 to enhance resistance to stress.
4	Kenneth Ofori-Amanfo – “mONTage: A Long-Read Sequencing Workflow for Joint Genomic and Epigenetic Age Analysis” Objective As the Canadian population ages, there are more efforts to promote healthy aging. Profiling DNA methylation via array-based epigenetic clocks is a well-studied approach for estimating biological age. However, array-based methods offer limited genome coverage and require separate procedures to profile genomic features. Long-read sequencing fills in these gaps by simultaneously profiling genome-wide DNA methylation and DNA sequence over complex and repetitive regions of the genome. Our objectives are to (1) develop mONTage, a workflow for joint genomic and epigenetic age analysis using long-read data, and (2) apply this workflow to the Personalized Oncogenomics (POG) cohort (n = 162) to identify traits associated with epigenetic age. Methods For our first aim, we created mONTage, a deployable Nextflow workflow that conducts genetic analysis and biological age estimates. We then compared epigenetic age estimates of cell lines (n = 4) that have been profiled with both methylation

	microarrays and Oxford Nanopore Technologies (ONT) data to see if they produce similar results. For our second aim, we ran mONTage on ONT-profiled blood samples from the POG cohort, grouping individuals by sex, chemotherapy exposure, and genotype at loci of interest. In this workflow we will use clocks included in the ‘methylock’ package in R (Horvath, Hannum, BLUP, and EN) and wf-human-variation for variant calling. Results/Findings: Array-based epigenetic clock estimates using long-read sequencing data correlated with chronological age in the POG cohort. Further analyses in the POG cohort are ongoing, benchmarking the pipeline and preliminary age acceleration comparisons across sex, chemotherapy exposure, and genotype groups. When comparing cell lines profiled with both platforms, long-read-derived age estimates were lower than those from array data. The difference between these estimates was smaller in clocks comprised of more CpGs, though this comparison was limited to four paired samples. Conclusions: If long-read sequencing produces epigenetic age estimates comparable to array-derived data, this would allow researchers to apply well-studied geroscience tools to a new technology while building on previous knowledge. This workflow enables researchers to jointly assess genomic and epigenetic contributions to epigenetic aging through approaches not currently available with array-based methods.
5	Noah Gittens – “Polyphenol Supplementation and Exercise on Physical Performance in Older Adults: A Randomized Controlled Pilot Feasibility Trial” Objective: Regular exercise supports healthy aging by preserving physical function and independence and reducing the risk of chronic diseases and all-cause mortality. However, older adults face barriers to sustained participation in structured exercise, including transportation, cost, limited accessibility, health limitations, and low exercise self-efficacy. This pilot trial evaluated the feasibility of recruiting and retaining community-dwelling older adults in a 12-week combined resistance-band and stationery-cycling intervention. Preliminary changes in strength, aerobic capacity, physical function, frailty, and well-being, and the potential additive effects of daily polyphenol supplementation, were also explored. Methods: Forty adults aged ≥ 60 years were randomized in a double-blind design to receive either a Lactuca sativa-derived polyphenol supplement (Phyto-P; 3 g·day⁻¹) or maltodextrin placebo. Participants completed two progressive full-body resistance-band sessions and two steady-state cycling sessions at 60% of peak work rate weekly for 12 weeks. Feasibility, outcomes included recruitment, retention, exercise attendance, supplement adherence, adverse events, and assessment completion. Exploratory outcomes included knee-extensor maximal voluntary contraction (MVC), isotonic power, handgrip strength, peak cycling work rate, Short Physical Performance Battery (SPPB), 30-second sit-to-stand, stair-climb performance, functional reach, CLSA Frailty Index, and WHO-5 well-being. Statistical significance was set at $P < 0.05$. Results: The recruitment target of 40 participants was achieved within 12 months, and 34 completed the trial (85% retention). Among completers, exercise attendance was 90$\pm$5%, including 92$\pm$5.% for resistance training and 87$\pm$8% for aerobic training. Supplement adherence was 93.9$\pm$5.3%, and all prespecified feasibility targets were met. Exploratory analyses showed improvements in MVC ($P=0.005$), SPPB ($P < 0.001$), isotonic peak power, peak cycling work rate, 30-second sit-to-stand, stair-climb performance, functional reach, and WHO-5 well-being. Handgrip strength and frailty index score did not change significantly. No additional effects of polyphenol supplementation were identified. Conclusions: This combined resistance-band and stationery-cycling intervention was feasible and achieved high retention and adherence. Preliminary improvements across several domains of physical capacity support further evaluation of this accessible exercise model in a larger, adequately powered trial.

6	Tisha Haukongo – “LINE-1 Retrotransposon Expression in People Living with and without HIV” Objectives: Long Interspersed Nuclear Element-1 (LINE-1) is the only autonomous retrotransposon family currently active in the human genome. Dysregulated LINE-1 expression has been associated with biological aging, chronic inflammation, and age-associated diseases. People living with HIV experience persistent immune activation and chronic inflammation despite effective antiretroviral therapy (ART), contributing to accelerated biological aging. Persistent virus infections may influence endogenous LINE-1 regulation, while HIV nucleoside reverse transcriptase inhibitors (NRTIs) may inhibit reverse transcription of LINE-1 RNA. Despite growing interest in endogenous retroelements in inflammation and aging, relatively little is known about LINE-1 regulation in people living with HIV. Our objective is to characterize LINE-1 mRNA expression and examine its association with HIV-associated and aging-related factors. We hypothesize that LINE-1 mRNA expression is associated with HIV status, older age, higher burden of persistent viruses, sex, and ART exposure. Methods and Expected results: This cross-sectional nested case-control observational study will use existing biological samples and socio-demographic/clinical data from over 300 female and male participants (≥16y) enrolled in two studies: BCC3 and REDOSE. Serology on several persistent viruses will be performed using ELISA. LINE-1 mRNA expression will be measured in peripheral blood using RT-qPCR targeting LINE-1 ORF2 transcripts and normalized to β-actin expression. Descriptive statistics will summarize demographic, clinical, and biological characteristics. Comparisons of LINE-1 expression between participant groups will be performed using parametric or non-parametric statistics, as appropriate. Multivariable regression analyses will evaluate associations between LINE-1 mRNA expression and HIV status, age, sex, persistent virus burden, and NRTI exposure while adjusting for potential confounding variables. Exploratory analyses will examine associations with inflammatory marker profiles, where available. Conclusion/Significance: This study aims to improve understanding of factors associated with endogenous LINE-1 expression in people living with and without HIV. The insight gained will advance our understanding of the potential mechanisms underlying chronic inflammation and accelerated biological aging, thereby contributing to the field of geroscience.
7	Ana Paola Cano Morris – “Systematic Characterization of the Genetic Determinants of the SASP Response” Cellular senescence is a hallmark of aging triggered by stressors such as telomere attrition, genomic instability, and chemotherapy. Senescent cells undergo a stable cell-cycle arrest but remain metabolically active and influence surrounding cells through their senescence-associated secretory phenotype (SASP). This altered intercellular communication can disrupt tissue homeostasis and propagate age-associated dysfunction, yet the genetic factors that determine how recipient cells respond to SASP remain poorly understood. We hypothesize that there are specific genetic dependencies that dictate cellular sensitivity or resistance to the SASP and that these dependencies can be therapeutically targeted in aging and cancer. To address this hypothesis, we generated conditioned media from proliferating, replicatively-induced senescent, and etoposide-induced senescent human fibroblasts and assessed their effects on recipient-cell proliferation and transcriptional responses. These distinct secretomes produced context-dependent effects on recipient cells. Quantitative proteomic analysis of the conditioned media identified, relative to proliferating conditioned media, 155 differentially abundant proteins in replicatively-induced senescent conditioned media and 185 in etoposide-induced

	senescent conditioned media. Furthermore, direct comparison of the two senescent conditions identified 86 differentially abundant proteins, highlighting the heterogeneity of senescent-cell signalling. Building on these findings, we performed a genome-wide CRISPR-Cas9 knockout screen in NALM-6 pre-B acute lymphoblastic leukemia cells exposed to conditioned media from proliferating, replicatively-induced senescent, or etoposide-induced senescent fibroblasts. By tracking guide abundance over time and comparing each exposure with time-matched medium controls, we identified candidate genes whose loss alters cellular sensitivity or resistance to senescent signals. We will present the latest prioritized hits and pathways, including both shared responses and effects specific to distinct senescent secretomes. Together, this work identifies recipient-cell genotype as an important determinant of the response to senescent-cell signalling. Defining these response pathways may shed light on the contribution of the paracrine signalling response to systemic dysfunction during aging and reveal therapeutic opportunities that modify cellular susceptibility to SASP.
8	Jennifer Wilkinson – “Mitochondrial respiration increases with exercise, but not polyphenols, in community-dwelling older females and males” Objective: Advanced aging is associated with low-grade systemic inflammation that is linked to frailty, reductions in skeletal muscle size and strength, and increases in all-cause mortality. Systemic inflammation is associated with mitochondrial dysfunction via increased reactive oxygen species production and is exacerbated during exercise. Polyphenol supplementation may mitigate this exacerbation via antioxidant properties. To-date, the effect of a combination resistance band exercise and moderate intensity cardiovascular exercise training programme with polyphenol supplementation on mitochondrial respiration has not been measured in older adults. The objective of this study was to determine the effect of polyphenol supplementation on mitochondrial respiration in older adults undergoing 12 weeks of exercise training. We hypothesized that polyphenol supplementation would augment adaptive increases in mitochondrial respiration with exercise. Methods: Forty community-dwelling older adults were randomized and stratified by sex. Thirty-four community-dwelling older adults (67±6y/o; n=21 F, n=13 M; BMI 28.5±4.6) completed 12 weeks of a combination progressive resistance band (2x/week) and cardiovascular (2x/week; 45mins @60% work rate peak) exercise training with or without polyphenol supplementation. Participants were provided a Lacutca sativa-derived polyphenol supplement (Phyto-P: 3g/day, n=18) or a maltodextrin placebo (3g/day; n=16) in a randomized, double-blinded manner. Fasted skeletal muscle biopsies were taken from the vastus lateralis prior and post intervention to measure maximal carbohydrate-supported mitochondrial respiration using high resolution respirometry. Results: The 12-week combination resistance band and cardiovascular exercise training increased leak (+0.65pmol/s/mgww; p=0.03) and maximal complex I supported (+6.0pmol/s/mgww; p=0.04) mitochondrial respiration, irrespective of supplementation. Maximal complex I and II supported mitochondrial respiration was similar between the groups pre- and post-exercise intervention, irrespective of supplementation. Conclusion: Our results are in line with previous research that shows that combined resistance band and cardiovascular exercise over 12 weeks increases mitochondrial respiration. Additionally, in line with previous research, we have identified that polyphenols do not alter older adult responses to exercise programmes. Therefore, exercise interventions that include progressive resistance training and cardiovascular exercise, but not polyphenol supplementation, may improve mitochondrial function in older adults.
9	Emma Lo – “Characterization of Markers of Lung Aging Using Spatial Transcriptomics”

	Aging is a major risk factor for chronic lung diseases and increased susceptibility to environmental exposures, yet spatial markers of healthy lung aging remain poorly characterized. Identifying aging markers is essential for distinguishing healthy trajectories from disease-associated changes, enabling earlier disease detection and prevention. This study aims to identify spatial markers and niches associated with lung aging using spatial transcriptomics, which preserves tissue architecture and enables investigation of age-related changes in cellular organization that cannot be resolved using alternative approaches. We hypothesized that aging is associated with distinct spatial gene expression and cellular neighbourhood patterns in healthy human lung tissues reflecting physiological aging and increased vulnerability to age-related diseases. Publicly available 10x Genomics human lung datasets were analyzed from donors aged 29-78. To identify age-associated molecular changes, differential gene expression and cell-type abundance analyses were performed. Spatial neighbourhoods were constructed to characterize age-related shifts in cellular organization and neighbourhood enrichment. Ligand-receptor predictions were integrated with spatial enrichment scores to identify transcriptionally and spatially supported cell-cell communication networks. Lineage-specific trajectory analyses were performed, comparing cellular progression and transcriptional dynamics across age groups. Candidate markers were evaluated for relevance to aging-related processes, providing insight into how aging may be associated with increased risks for certain conditions. Analyses confirmed single-cell findings of age-associated regenerative capacity reduction, immune remodelling, and extracellular matrix reorganization. Differential expression and cell-type abundance shifts demonstrated reduced alveolar identity, including downregulation of alveolar markers, and increased expression of extracellular matrix regulators like CCN2. Spatial neighbourhood analysis revealed age-related reorganization of cellular niches, including increased fibroblast-immune cell neighbourhood frequencies with age. Integrating ligand-receptor predictions with spatial enrichment identified age-dependent differences in cell-cell communication networks concentrated in stromal-immune and epithelial-stromal pairs, like enriched fibroblast-T-cell interactions in older samples. Trajectory analyses indicated age-associated alterations in endothelial cellular state progression, suggesting aging may influence both organization and progression of cellular states. These findings advance understanding of human lung aging by identifying spatial markers unresolvable by non-spatial transcriptomic approaches. This establishes a framework for distinguishing physiological aging from disease-associated remodelling and provides markers that support detection, interventions, and future geroscience research to promote healthy aging.
10	Raphaëlle Koerber – “The Effects of Pitch Lowering on Audibility in Age-Related Hearing Loss” Objective: Patients with presbycusis are less sensitive to high-frequency sounds. As a result, care providers have been counselled to speak in a lower pitch with older adults. We tested whether this recommendation increases speech audibility in presbycusis. Methods: Thirty-one women provided standardized recordings of baseline and deepened-pitch speech. For each recording we calculated the Speech Intelligibility Index - the proportion of speech sounds exceeding standardized presbycusis thresholds. We also compared the speech rate, fundamental frequency, and long-term averaged speech spectra (LTASS) of the two recording types. Results/Findings: There was no difference in Speech Intelligibility Indices between the pitch conditions, $t(31) = 0.55$, $p = 0.40$. Visual inspection of the LTASS showed no apparent shift of vocal energy from high to mid or low frequency bands with pitch deepening. Rather, participants lowered their fundamental frequency (i.e., rate of vocal cord vibration) from 183.4

	Hz (SD 23.1) to 167.6 Hz (SD 23.8), $t(30) = -5.03$, $p < 0.001$. Speech rate was slower in the deep-pitch recordings, $t(31) = 6.40$, $p < 0.001$; Cohen's $d = 0.69$. Conclusion: Our findings suggest lowering vocal pitch does not meaningfully shift high-frequency speech sounds into an audible range for age-induced hearing loss. These higher sounds are made by the lips, teeth, and tongue and so their frequency is not directly lowered by relaxing the vocal cords to deepen perceived vocal pitch. However, pitch lowering was associated with spontaneously slower speech, and further research might explore whether it cues other features of clear speech.
11	Sanarya Al-Jaf – “Sex-specific Effects of mGluR5 Signaling on Cerebrovascular Dysfunction in Alzheimer’s Disease” Objective: Alzheimer’s disease (AD) is characterized by progressive cognitive decline and is associated with early cerebrovascular dysfunction. Astrocytes are critical regulators of cerebral blood flow (CBF) through neurovascular coupling (NVC), and aberrant activation of astrocytic metabotropic glutamate receptor 5 (mGluR5) by amyloid-beta ($A\beta$) may contribute to this dysfunction. This study aims to determine whether disrupted astrocytic mGluR5 signaling contributes to impaired CBF and cognitive dysfunction in AD, and whether these mechanisms differ between sexes. We hypothesize that $A\beta$-induced dysregulation of mGluR5 signaling impairs NVC and CBF in a sex-specific manner. Methods: Male and female 5xFAD mice, a mouse model of amyloidosis, will be used to assess the relationship between mGluR5 signaling, cerebrovascular function, and cognition. CBF and cognitive function will be assessed at defined stages of disease progression, with molecular analyses used to characterize downstream mGluR5 signaling. The therapeutic potential of mGluR5 inhibition will be examined using the selective negative allosteric modulator CTEP. Results/Findings: Preliminary data demonstrate that CBF deficits emerge approximately four months before detectable cognitive impairment in male 5xFAD mice, suggesting that cerebrovascular dysfunction may be an early feature of AD pathology. Chronic CTEP treatment rescues both CBF deficits and cognitive impairments in male 5xFAD mice. Ongoing studies will determine whether comparable deficits occur in female mice, whether CTEP produces similar effects across sexes. Conclusions: This work will establish whether astrocytic mGluR5 is a mechanistic link between $A\beta$ pathology and cerebrovascular dysfunction in AD and determine how this relationship varies by sex. Identifying astrocytic mGluR5 as a mediator of early CBF dysfunction could reveal a novel, cell-specific therapeutic target for preserving vascular and cognitive function in AD and advance understanding of sex-specific mechanisms underlying disease progression.
12	Emily Ye – “Sex-dependent effects of mGluR5 and M1 mAChR allosteric modulators on receptor localization and signaling in Alzheimer’s disease models” Background: Alzheimer’s disease (AD) is a neurodegenerative disorder characterized by progressive memory loss and cognitive decline. Women account for over 60% of AD cases, highlighting the need to understand sex-specific mechanisms of disease. AD is characterized by beta-amyloid and hyperphosphorylated tau accumulation, which disrupt neuronal signalling and alter G protein-coupled receptors, including metabotropic glutamate receptor 5 (mGluR5) and M1 muscarinic acetylcholine receptor (M1 mAChR), which are critical for learning and memory. Because receptor function depends on proper subcellular localization, AD-related disruptions in receptor trafficking may contribute to altered signalling and disease progression. Objective: The goal of this study is to investigate sex-specific differences in mGluR5 and M1 mAChR expression, localization, and signalling upon interaction with beta-amyloid or hyperphosphorylated tau

	protein in mouse models of Alzheimer’s disease, aiming to provide sex-tailored therapies for management of the disease. Methods: Using male and female wild-type, 5xFAD (with beta-amyloid pathology), and P301S (with tau pathology) mouse models, brain cortical tissue will be isolated, sliced, and treated ex-vivo with selective modulators of mGluR5 and M1 mAChR. Subcellular fractionation and immunoblotting will be used to determine receptor localization across cellular compartments and assess downstream signalling pathways. This approach enables us to examine how AD pathology and biological sex influence receptor trafficking and signalling, which are critical for neuronal function. Findings: Preliminary data reveal sex-dependent differences in receptor localization. Following mGluR5 inhibition, female wild-type mice exhibited reduced plasma membrane mGluR5, whereas males showed no change. M1 mAChR activation increased intracellular receptor expression in males but not females. Beta-amyloid pathology promoted intracellular redistribution of M1 mAChR, while tau pathology reduced plasma membrane mGluR5 following receptor inhibition. These findings suggest that AD pathology and biological sex differentially regulate receptor localization, which may contribute to altered neuronal signalling during disease progression. Significance: This work addresses a critical gap in understanding how receptor localization contributes to sex-specific mechanisms of AD. By identifying how beta-amyloid and hyperphosphorylated tau alter mGluR5 and M1 mAChR trafficking and signalling in males and females, this research will provide mechanistic insight into disease progression, and ultimately inform the development of more precise, sex-tailored therapeutic strategies for AD.
13	A Palumbo – “Longitudinal Multi-Omic Profiling During the Initiation of Masculinizing Gender-Affirming Hormone Therapy: A Two-Year Case Study” Objectives: Gender-affirming hormone therapy (GAHT) is a central component of care for many transgender and gender diverse people, however, the longitudinal molecular effects remain understudied, with most studies relying on cross-sectional sampling and limited biomarker analysis. This study leverages long-term, systems level approaches, such as multi-omic studies, can better capture the dynamic biological changes associated with GAHT. Key objectives are: (1) To generate a longitudinal multi-omic resource characterizing molecular dynamics over the first two years of hormonal treatment, (2) To characterize the time-based patterns of molecular variation across proteomic, lipidomic, and metabolomic layers using an integrative systems biology framework, and (3) To explore how longitudinal molecular data can inform personalized approaches to GAHT over the lifetime. Methods: We conducted a longitudinal case study of a transmasculine individual initiating testosterone-based GAHT over a two-year period. Serial samples of plasma, peripheral mononuclear blood cells (PMBCs), and urine were collected at 46 timepoints following initiation of GAHT. Multi-omic analyses, including proteomics, lipidomics, and metabolomics, were performed to assess temporal changes across biological systems. Results: Preliminary findings demonstrate the feasibility of multi-omic analysis in transgender health research. Early analyses suggest temporal changes in lipid metabolism, proteomic landscape, and endocrine signalling, indicating system-wide responses to GAHT. Ongoing analyses are focused on identifying consistent patterns associated with physiological adaptation to GAHT. Conclusion: This study highlights the potential of longitudinal multi-omic approaches to capture individual responses to GAHT while focusing on high-throughput data to gather mechanistic insight relevant to clinical outcomes. These findings are relevant to clinical outcomes, suggesting that GAHT may influence immune tolerance and metabolic adaptation across the lifespan.

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