



Friday and Saturday
July 18-19, 2025
Virtual

URO-AGING RESEARCH INTEREST GROUP, Day 1

Slides and summary from Day 1, during which groups identified/defined their broader research topic, identified critical knowledge gaps, and listed research barriers.

Group Name & Topic Area

Uro-Aging

Co-leads: Indira Mysorekar and Scott Bauer

- Focused on healthy urologic/urogynecologic aging
- Focused on shared mechanisms of urologic/urogynecologic aging
- Model development for studying urologic/urogynecologic aging

Critical Gaps in Knowledge

Framework for uro-aging model development

- Models across the translational spectrum have different degrees overlap, knowledge leaps will occur at the intersection of models so we need to identify where those overlaps occur

Resilience to age-related declines

- Protective factors the prevent disease, dysfunction, damage
- Relevant to entire translational spectrum, but definitions vary widely depending on level of translation

Heterogeneity in age-related urological syndromes

- Deep phenotyping, heterogeneity in treatment response, overlapping and interacting mechanisms
- Advanced analytics likely required (AI, machine-learning)

Intervention testing

- Anti-aging and pro-resilience interventions already proven in other diseases/systems, need urologic-specific targets
- Leverage advances from other fields, already established target effects and safety

Research Barriers

Lack of investment in conditions affecting older people

- Funding, expertise, inappropriate models, lower visibility science and societal impact, pipeline
- Better treatments for those most affected and in need

Lack of shared language/vocabulary across translational spectrum

- Better cross-disciplinary collaborations and advances
- Faster translation

Lack of engagement from other aging fields

- Missed opportunity to leverage their advances and knowledge
- Multidisciplinary solutions

Sex-specific tools and models

- Different environmental dynamics and susceptibilities, different manifestations, different burden of risk factors
- More personalized interventions and mechanistic understanding

Uro-Aging Breakout Day 1 – Summary from transcription

Broad overview. The discussion focused on integrating sex differences and hormonal effects in uro-aging research, emphasizing the need for comprehensive models from urethra to brain. Key points included:

- Use of diabetic models, voiding assays, and pelvic nerve recordings to understand bladder function.
- Need to explore impact of breastfeeding on nerve and muscle regeneration
- Potential use of tamoxifen post-parturition
- Challenges of mimicking stress incontinence in rodents

The group debated the feasibility of using environmental exposures and predictive models, suggesting the need for large cohort studies and multi-scale approaches to better understand bladder dysfunction and personalize therapy. The group discussed the importance of accessing human and animal tissues, particularly from veterinary patients, to study bladder dysfunction and hormonal influences. They emphasized the potential of using predictive and mechanistic models to understand disease progression and treatment response.

Prioritizing research questions and projects related to uro-aging. Key points included the need to clarify the "complete bladder system" as "from brain to urethra" for better understanding. Specific research questions included the impact of sex hormones on bladder function and the need for a multi-center bio banking approach. The team also considered collaborating with the Aging Dog Project for additional data.

Action Items

- Develop a longitudinal study to follow a cohort of individuals at risk of underactive bladder, with the goal of identifying predictors of disease progression.
- Explore the use of environmental exposures, such as PFAs or Bisphenol A, as potential contributors to lower urinary tract dysfunction.
- Investigate the role of epigenetic changes in mediating the effects of environmental exposures on lower urinary tract function.
- Consider focusing an initial research project on a specific, well-defined clinical condition (e.g., underactive bladder) to build a stronger case for clinical relevance and potential impact.
- Explore the use of predictive modeling approaches, such as machine learning, that combine mechanistic and statistical modeling to better understand the complex factors contributing to lower urinary tract dysfunction.

Outline

Sex Differences and Hormonal Effects

- KS discusses the importance of considering sex as a biological variable and the potential impact of adding estrogen or performing an orchiectomy on basic models.
- Speaker 2 reflects on the various models used in Wisconsin and the lack of comprehensive data on tissue RNA sequencing.
- KS mentions the use of diabetic models and the clustering of different models based on voiding assays.
- Speaker 3 raises a question about the impact of breastfeeding on nerve and muscle regeneration, suggesting a potential clinical study.

Hypoestrogenic State and Clinical Studies

- Speaker 4 mentions the common vaginal issues women face during breastfeeding and the use of vaginal estrogen to alleviate dryness.
- Speaker 2 and Speaker 3 discuss the potential use of tamoxifen post-parturition to prolong the hypoestrogenic state in rodents.
- Speaker 2 questions how to mimic stress incontinence in mice, suggesting the need for engineering solutions to measure intra-abdominal pressure.
- Speaker 3 proposes a project idea involving liquid pressure measurement in rodents, but questions its sellability.

Survivorship of Cancer Patients and Tamoxifen

- Speaker 4 suggests that Tamoxifen, used frequently for breast cancer, could be a relevant model to study hormonal effects on bladder function.
- Speaker 5 mentions other naturally occurring hormonal modulations, such as PCOS, as potential options for research.
- Speaker 2 emphasizes the importance of drilling down to specific aims for grant writing and the common practice of writing in increasing levels of complexity.
- Speaker 6 and Speaker 5 discuss their approaches to organizing aims, with Speaker 6 starting broad and narrowing down and Speaker 5 focusing on in vivo, ex vivo, and mathematical models.

Predictive Models and NIH Interests

- Speaker 5 discusses the potential of predictive models and the historical resistance from NIH, but sees a shift in interest towards these models.
- Speaker 2 and Speaker 5 discuss the importance of having a working document open for collaboration and the need for translational aspects in research.
- Speaker 5 suggests learning from cardiovascular research and applying multi-scale models to bladder research.
- Speaker 7 emphasizes the importance of selling ideas to review panels and stakeholders, and the potential for NIH to be interested in new approaches.

Personalizing Therapy and Prediction Models

- Speaker 8 presents a vision for personalizing therapy through diagnostics, treatment, and outcome collection, and the development of prediction models.
- Speaker 2 questions the feasibility of the approach, while Speaker 8 explains the need to measure a variety of things to understand treatment outcomes.
- Speaker 8 discusses the importance of urethral function and the need for more preclinical exploration to develop better hypotheses.
- Speaker 5 suggests combining statistical models with mechanistic models to create more comprehensive predictive models.

Environmental Exposures and Epigenetic Analysis

- KS discusses the potential of environmental exposures, such as PCBs and PFAs, in contributing to LUTS and the need for large cohort studies.
- Speaker 4 mentions ongoing research in North Carolina on PFAs and the potential for funding in this area.
- KS suggests looking at Bisphenol A as a relevant model for male urology, given the existing literature on its effects.
- Speaker 5 emphasizes the importance of understanding the healthy state before exposure to better understand the impact of environmental factors.

Methodology and Translation in Research

- Speaker 3 discusses the importance of translation in research and the need to envision the end goal to justify the work.
- Speaker 8 suggests starting with tests to see if they are informative and then expanding to larger cohorts.
- Speaker 4 emphasizes the need for a focused model to gain buy-in from clinicians and then expanding to more complex models.

- Speaker 8 proposes a longitudinal study to understand worsening underactive bladder and the feasibility of such a project.

RC2 Mechanism and Core Facilities

- Speaker 8 introduces the RC2 mechanism as a potential funding option for large-scale projects, but acknowledges the challenges in securing funding.
- Speaker 6 suggests using core facilities to support multiple R1 grants and the potential for a U54 grant.
- Speaker 7 discusses the challenges in finding dorsal root ganglia (DRG) for research and the potential benefits of a multi-institutional rapid autopsy DRG collection.
- Speaker 5 proposes writing a white paper to justify the need for a broad approach due to the lack of existing data in the field.

Cross-Fertilization and Finalizing Research Questions

- Speaker 1 explains the opportunity for cross-fertilization during the large group discussion to identify new research questions.
- Speaker 2 suggests using the current ideas to create slides for the large group discussion and prioritizing research questions.
- Speaker 8 questions the need for both proposed and prioritized research questions, suggesting that the prioritized list might suffice.
- The group agrees to finalize the research questions and projects to develop during the large group discussion.

Prioritizing Research Questions and Projects

- Speaker 1 emphasizes the importance of prioritizing tasks and making clear what the priorities are.
- Speaker 2 suggests starting with the prioritized projects and research questions, referencing a Google document.
- Speaker 8 mentions having a different version of a research question and asks for it to be copied.
- Speaker 3 adds molecular phenotyping to the discussion, suggesting the need for biomarkers.

Clarifying the Complete Bladder System

- Speaker 7 asks for clarification on the term "complete bladder system," suggesting "from brain to urethra" might be clearer.
- Speaker 2 agrees, noting the concept stemmed from looking at Benign Prostatic Hyperplasia (BPH) and the prostate.
- Speaker 7 suggests using "from brain to urethra" for both the first and second research questions for clarity.
- Speaker 5 confirms the suggestion, and Speaker 2 acknowledges the mistake in phrasing.

Refining Research Questions and Bullet Points

- Speaker 8 questions the need for all the bullet points, expressing concern about overwhelming the group.
- Speaker 7 asks if the goal is to identify people within the working group or have them sign up for tasks.
- Speaker 1 suggests keeping the "who could be involved" bullet and identifying who will take the lead.
- Speaker 2 emphasizes the need to address feasibility and who could take on specific tasks, mentioning the need for human tissues.

Discussing Human and Animal Tissue Samples

- Speaker 6 suggests a multi-center bio banking approach, including both animal and human tissues.
- Speaker 7 clarifies the need for laboratory animals and mentions the potential of veterinary patient populations.
- Speaker 5 highlights the diversity of veterinary patient models, which can capture a broader range of backgrounds.
- Speaker 7 discusses the feasibility of getting post-mortem samples from veterinary patients and the benefits of their consistent diet.

Exploring Veterinary Bio Banking Opportunities

- Speaker 7 mentions ongoing multi-institutional bio banking efforts, including UC Davis, UW, and UPenn.
- Speaker 7 discusses the ease of getting post-mortem samples from veterinary patients compared to human patients.
- Speaker 2 expresses surprise at the potential learning from veterinary samples, including spay/neuter status.
- Speaker 5 notes the ease of getting lifelong information for veterinary patients compared to human patients.

Investigating the Aging Dog Project

- Speaker 4 suggests tying into the Aging Dog Project for information on incontinence in dogs.
- Speaker 7 mentions a study on PCBs in the urine of dogs with incontinence and the potential for similar studies in cats.
- Speaker 7 discusses the feasibility of multi-institutional bio banking and the benefits of veterinary patient models.
- Speaker 2 and Speaker 5 discuss the potential of using veterinary patient data for research purposes.

Finalizing Research Questions and Lead Assignments

- Speaker 2 asks for input on the final research question, focusing on the impact of sex hormones on bladder function.
- Speaker 7 and Speaker 8 discuss the need for a predictive model to understand disease progression and treatment response.
- Speaker 3 suggests a mechanistic model to identify the data needed for a predictive model.
- Speaker 8 and Speaker 3 discuss the importance of understanding the system's function and the potential disconnect between measurements and nodes.

Assigning Leads and Collaborators for Research Questions

- Speaker 3 nominates Jim to take the lead on the predictive model question.
- Speaker 8 and Speaker 3 discuss the need for a mechanistic model to inform the predictive model.
- Speaker 2 suggests dividing the research questions among the group, with multiple collaborators for each.
- Speaker 4 and Speaker 6 express interest in leading or collaborating on specific research questions.

URO-AGING RESEARCH INTEREST GROUP, Day 2

Slides and summary from Day 2, during which groups identified specific research questions, prioritized them, and identified collaborations and research needs.

Proposed Research Questions

Framework for LUT rejuvenation- The Big Beautiful Pee in P (ease); Pee-s -OUT



Research Questions: Does aging change male and female mucosa-muscle responses?

Can it be reversed/ameliorated using 1) KNOWN agonists and antagonists (e.g. cholinergics, purinergics, muscarinics; hormones, estradiol and testosterone, 2) existing entities identified via integrated analyses; and 3) newly identified modalities (*could be applied iteratively to bladder urethra, prostate) –inclusive of cell types

Anticipated outcomes that can fill knowledge gaps/address barriers

Integrated framework across multiple models and relevance to prioritize measures to improve LUT rejuvenation

- Can this be addressed by someone within the working group-yes
- Does this require collaboration w/ the broader research community-yes

Prioritized Research Questions

- **Research Question**
 - Brief description of approach/strategy to be developed over time
 - Summarize resources, tools, technologies, techniques, models, data that will be used
 - Who will take the lead?
- **Test Known Treatments**
 - i) Mouse models (treatments—Chad/Teresa (...Lori))
 - Test cytometry and other functional aspects in mice, VSA, dose response curves (prelim data with Chad)
 - (try to get prelim data from other animals—monkeys, dogs, cats, eg. Roz Anderson)
 - Hormone treatments and measurement (Teresa) (also Indira)
 - ii) Cell lines (urothelial and muscle cells in vitro)—Pascale
 - iii) organoid/organ on chip models-Indira, Zohreh
 - iv) identify new targets via Glycomics, metabolomics, others... -Indira, Zohreh (Doug, Chad)
- **Human—compare with mice and organ models—bioinformatics and functional tests:** (bioinformatics—colleagues—suggest names)
 - Physiological measures
 - Molecular measures
 - Functional aspects
 - Test cytometry and other functional aspects in mice and compare with humans
 - Barrier function
- **Physiological measurements** (Scott, physiologists?)
 - Treatment response
 - Sensation and physiology (urodynamics , uroflow, retention, —cross connect with UroVoiding group)
 - Efferent activity—voiding dysfunction
 - (biobank) capture urine samples; shed epithelial cells; shed immune cells—cross connect with Uro-Biome group
- **Outcomes data—** (/Allison)
 - Symptoms improvement
 - Prioritize measures
- **Bring in new aging interventions** (ALL)
 - nutraceuticals

Collaborations and Needs

Collaboration

- Highlight any potential or planned collaborations that investigators in your group will pursue

Needs

Prelim data on treatments, outcomes – from urologists and urogynecologists

Develop a systematic prioritization pipeline to identify interventions most likely to benefit LUT/bladder function by integrating multi-omics data from other systems (muscle, cardiovascular, gut, brain) (Including exercise/CR/young blood) – need data

Conduct a Delphi consensus with urology, geroscience, and systems biology experts; rank interventions based on mechanistic overlap, safety profile, and feasibility (need bioinformatics colleagues)

MONEY ! (industry sponsored trials, NIH, foundations, philanthropy?)

General mission statement / goals

Framework for LUT rejuvenation

Uro-Aging Breakout Day 2 – Summary from transcription

Broad overview. The meeting focused on developing deliverables and potential grant applications for the Uro-Aging Breakout. Key tasks included reviewing day one slides, prioritizing research questions, and identifying potential MPI grant applications. The team discussed interventions testing, particularly on hormones, inflammation, senescence, and fibrosis, and the need for systematic analysis across organ systems. They emphasized the importance of multi-omics data, including phenomics, and the development of organ on chip models. The discussion also covered the need for stress tests in both humans and mice to measure resilience and the potential for using non-human models like dogs for specific aging studies. The meeting focused on developing a framework for lower urinary tract rejuvenation, emphasizing the need for integrating multi-omics data and physiological measurements.

Action Items

- Identify and engage a bioinformatics expert to help standardize data analysis and integration across the different models and data types.
- Explore incorporating measures of bladder physiology and neural regulation in human studies, in collaboration with experts in the field.
- Expand existing mouse model studies on bladder muscle responsiveness to known agonists and antagonists across the lifespan.
- Investigate the feasibility of using organ-on-chip models to test bladder mucosa and immune responses to aging.
- Explore integrating multi-omics data (e.g., transcriptomics, proteomics, metabolomics) from human tissue samples and correlating with bladder muscle responsiveness.
- Reach out to other aging research groups to explore collaborations on shared tissue samples and functional readouts.

Outline

Deliverables and Initial Discussions

- Speaker 1 suggests reviewing deliverables by the end of the session, emphasizing the need for each participant to have at least one potential grant application and each working group to have at least one potential MPI grant application.
- Speaker 2 mentions uploading the final slide presented by Scott to the Google Doc and preliminary ideas for aims, inviting others to join in.
- Speaker 1 clarifies that Speaker 2 is referring to day one slides, while Speaker 2 plans to take notes for day two slides to present later.
- Speaker 3 agrees to share day two slides, and Speaker 4 suggests discussing which research questions from the previous day resonate with participants.

Research Questions and Project Ideas

- Speaker 4 proposes going around the group to discuss which research questions from the previous day are most relevant and to collect ideas for potential projects.
- Speaker 5 discusses intervention testing, focusing on comparing interventions that impact hormones, inflammation, senescence, and fibrosis, and suggests a big grant to pull this out with human data and model systems.
- Speaker 2 agrees with Speaker 5's approach and suggests a systematic analysis of interventions that have worked in other organ systems, including their own work and the amino acid group's work in urinary tract aging.
- Speaker 4 takes notes on the Google Doc and suggests sharing the slides in real-time for better collaboration.

Multi-Scale Omics and Tissue Collection

- Speaker 6 proposes a multi-scale omics project, including phenomics, to find molecular mechanisms and biomarkers for urinary tract aging, focusing on BPH-related tissues.
- Speaker 2 and Speaker 6 discuss the need for biobanks of BPH tissue and the importance of matching tissue, urine, and patient phenotype information.
- Speaker 5 expresses enthusiasm for the idea and suggests expanding on it, while Speaker 4 emphasizes the need to consider both sexes and the limitations of tissue access.
- Speaker 6 highlights the importance of identifying patients close to surgery to match tissue information with urine and patient phenotype data.

Preliminary Analysis and Data Quality

- Speaker 2 asks Chad and Doug about preliminary analysis that could be done as deliverables or grant applications, given the tissue and patient phenotype data they have.
- Speaker 6 explains the challenges of getting quality data without ambient RNA contamination and the use of specific machines and sorting techniques to achieve clean RNA.

- Speaker 4 adds that the idea of using donors to describe overlapping Venn diagrams across the age range of disease donors is valuable, despite the limitations of symptom and physiology data.
- Speaker 6 discusses the importance of tissue tension and muscle dynamics as physiological endpoints and the potential for organ on a chip models to test responsiveness to drugs.

Model Development and Translation

- Speaker 7 suggests establishing new models like organ on chip and organoids to recapitulate healthy tissue and phenotypes, using tissues from deceased donors of various ages.
- Speaker 2 and Speaker 7 discuss the importance of comparing humanized models with established animal models and the need for high-throughput testing in both.
- Speaker 5 proposes testing different people in the same model for healthy versus disease status and comparing back to mouse models.
- Speaker 2 emphasizes the need for humanized models to test interventions and the importance of collaborating with clinical colleagues for proof of concept clinical studies.

Stress Testing and Resilience

- Speaker 4 suggests using stress tests to measure resilience in both human and mouse models, such as bladder filling and overfilling, and the impact of stressors like cyclophosphamide.
- Speaker 2 and Speaker 6 discuss the importance of stress testing in both young and old animals to understand resilience and recovery.
- Speaker 4 proposes using stress tests in humans and mice to align stressors and measure resilience, emphasizing the need for a urologist to help with physiologic measures.
- Speaker 1 mentions a NIH grant focused on stressors in mice that could impact research outcomes, highlighting the importance of controlling for external stressors.

Collaboration and Research Questions

- Speaker 2 suggests focusing on specific research questions to guide the group's efforts and identify potential collaborators and methods.
- Speaker 6 proposes a broad research question: "Does aging change bladder muscle responsiveness to known agonist and antagonist?" to cover both muscle and mucosa.
- Speaker 4 emphasizes the need for a narrow research question to guide the group's efforts and suggests focusing on known aging interventions and their effects on the urinary tract.
- Speaker 2 and Speaker 4 discuss the importance of aligning research questions with existing data and the need for new data collection to validate preclinical models.

Hormonal and Immune Considerations

- Speaker 6 discusses the importance of hormonal factors, such as estradiol and testosterone, in aging and their impact on the urinary tract.
- Speaker 7 suggests including the urobiome in the research, given the availability of data from older women.
- Speaker 4 proposes looking at the effect of age on treatment response and physiology, emphasizing the need for new data collection and collaboration with clinical experts.
- Speaker 2 and Speaker 4 discuss the importance of cross-fertilization with other groups and the need for a comprehensive approach to understanding aging in the urinary tract.

Bioinformatics Integration and Data Standardization

- Speaker 2 emphasizes the need for a bioinformatics person to standardize data across platforms, especially when dealing with core facilities.
- Discussion on the challenges of using semi-processed data from different institutions and the need for raw data analysis.
- Speaker 6 supports the integration of physiology with multi-omics data, particularly ATAC-seq and RNA sequencing.
- Speaker 4 suggests separating outcomes from physiology measurements to better understand the data.

Exploring Brain-Bladder Connections and Aging Interventions

- Speaker 6 discusses the potential of investigating efferent signaling pathways from the brain to tissues using optogenetic models.
- Speaker 4 mentions ongoing work in Pittsburgh on brain and bladder physiology, specifically by Neil Resnick.
- Speaker 2 introduces the idea of nutraceutical interventions and the need for standardized models to test new aging interventions.
- Speaker 4 clarifies that aging interventions should be tested at the end of the descriptive phase to manipulate the aging process.

Developing Translational Models for Aging Interventions

- Speaker 4 outlines the need for a translational model that captures age-related differences in drug response across species.
- Speaker 6 compares the approach to genomics, focusing on physiological changes with age and the response to known drugs.
- Discussion on the importance of identifying drugs that are not affected by aging to better understand drug response differences.
- Speaker 7 emphasizes the need for models that recapitulate clinical responses to treatments, especially those that are not responsive in older populations.

Integrating Multi-Omics Data and Identifying New Targets

- Speaker 6 suggests using organoids for high-throughput screening of potential interventions.
- Speaker 2 proposes using bioinformatics to integrate multi-omics data from other systems to identify new targets.
- Speaker 4 highlights the need for a pipeline that includes testing known treatments and developing new interventions.
- Speaker 7 discusses the importance of showing that models respond similarly to clinical treatments to validate the model.

Challenges in Acquiring Aging Tissues and Collaborations

- Speaker 6 raises the issue of acquiring aging tissues from donors and the importance of freshness for some studies.
- Speaker 7 mentions working with the NDRI to expand tissue collection protocols to include older donors.
- Discussion on the need for collaborations with clinicians and biobank repositories to acquire well-phenotyped tissues.
- Speaker 2 shares the difficulty of obtaining samples from the map network and the success of collaborations with Doug Strand's group.

PEOPLE FOR URO-AGING

Zohreh
Chad
Teresa
Lori
Laura
Indira
Scott
Alison

Jennifer DeBerry
Aria Olumi

Henri Lai ? Urologist
Phillipe Zimmern?

Marianna Alperin (urogynecology)

Physiologists?

Bioinformaticians in urology space

IDENTIFY RESEARCH GAPS & BARRIERS

KNOWLEDGE GAPS & RESEARCH NEEDS	BARRIERS & CHALLENGES
1. Scalable tools to study mechanisms and interventions 2. Understanding of impact of bladder immunity and epigenetics on disease susceptibility 3. Necessary/causative vs resiliency factors for urinary symptoms or LUTD in older adults 4. Prioritize anti-aging interventions to test in humans (which affect the LUT aging processes and physiology the strongest?) 5. Non-invasive LUT physiologic measures 6. Can we prevent BPH/LUTS 7. How to personalize treatment (right target, right treatment, right patient) 8. Systems approach? 9. Understanding normal accumulation of dysfunction through aging 10. How longevity interventions impact the lower urinary tract 11. Multidimensional impact of the aging lower urinary tract 12. A hands-on training across non-cancer urology disease research approaches (clinical/translational to foundational science) 13. Understanding how organ parts (cells) contribute to function of whole (organ + multiorgan systems) 14. Roles of the urethra in urinary disease 15. Exact mechanisms and factors that drive health and aging related diseases in the urogenital organs. 16. Teasing out the complex dynamic interaction of sex-specific microenvironmental factors (e.g., microbiome, hormone, age, multicellular/organ-interactions, local and systemic immunity, etc) 17. Time-dependent factors influencing progression and flares of symptoms in the everyday lives of older adults 18. Lack of standardization of defining mechanism relevance across translational spectrum (molecular, cellular, tissue, organ, physiology, complex humans) - how do you test whether X molecular process affects physiology? When is a molecular process that doesn't affect physiology still worth investigating and when is it not? Which risk factors identified in humans and are worth recapitulating and testing as causal mechanisms in animal models and which are not? 19. Method to rigorously and systematically prioritize/screen candidate mechanisms for studying in humans 20. Distinguishing age-related changes that do or do not cause disease, dysfunction, symptoms	1. Investment in understanding and treating LUTD in older women and men 2. Sharing of samples/data across institutions/groups 3. Lack of precision and shared language (e.g., for patient selection) 4. Lack of representation across the lifespan (esp the oldest older, who experience the greatest burden of LUTD) 5. Lack of shared understanding of study designs across the translational spectrum - what is needed to translate an animal model to humans? Or to test a causal mechanism in a pre-clinical/animal model? 6. Ageism - less societal emphasis on solving problems that predominantly affect older people 7. Older adults are highly heterogenous (which makes it harder to identify a single mechanism) 8. Lack of physiologically relevant human in vitro models of LUT mucosa and aging LUT 9. Absence of relevant female, male and age-specific cell sources for modeling diseases that have disparity across sex- and age-specific groups 10. Longitudinal human aging studies with LUT function measures 11. Lack of interest/awareness of age-related LUTD among aging researchers in other fields 12. Contrasting priorities, frameworks, and vocabularies for basic, translational, and clinical outcomes researchers in uro-aging 13. Lack of feasible tools for assessing dynamic changes in physiologic, microbial, and other mechanistic contributors to LUTS in older adults' everyday lives 14. LUTS is a syndrome - need accurate phenotyping and biomarkers or other methods of clinically identifying patients who are more likely to respond to an intervention targeting a specific mechanism

CATEGORIZE RESEARCH GAPS & BARRIERS

Mechanistic Understanding of Clinical Aging in the Lower Urinary Tract

Testing resilience? At human level, organ level, cellular level

- Form (Molecular, Cellular, organ system) & Function (Physiology) & Clinical Manifestations (Symptoms)
- Understanding normal accumulation of changes vs dysfunction
- Need method of prioritizing in both directions (mechanisms $\leftarrow \rightarrow$ disease/symptoms risk factors)

Imaging data (cystoscopy); urines, tissue samples;

Systems and multiscale integration—connect with HUBMap?

Causative (= if present then will develop disease/dysfunction) vs. protective (= if present then will NOT develop disease/dysfunction) factors:

Causal mechanisms across species and models?

Prioritizing and testing interventions

collaborations with engineers and more

Scalable tools, assembloids,

Prioritizing mechanisms -

Heterogeneity in syndromes

Framework for moving fluidly across the translational spectrum (model development with aging focus)

- Requires very specific definitions at every stage: symptoms (humans only), behavioral (humans, animal), complex physiologic responses (humans, animal), humanized animal models, xenografts (humans, animal, in vitro), high resolution mechanism (in vitro)

Some thoughts on aims:

#4 (interventions)

Prioritize candidate anti-aging and pro-resilience interventions for bladder aging.

Develop a systematic prioritization pipeline to identify interventions most likely to benefit LUT/bladder function by integrating multi-omics data from other systems (muscle, cardiovascular, gut) and what we know about bladder aging to map shared mechanistic nodes; conduct a Delphi consensus with urology, geroscience, and systems biology experts; rank interventions based on mechanistic overlap, safety profile, and feasibility.

Test high-priority interventions in preclinical urologic aging models

E.g., organoids, organ on chip models; maybe mouse—evaluate molecular outcomes and functional outcomes (if mice); and assess sex specific effects

Collaborators: Scott, Chad, Zohreh, Teresa/Laura, maybe a systems biology person?

Young blood injections /serum/immune cells or whole blood –diluted–

Test urines

Compare the effect of aging interventions on impact LUT (hormones, senescence, and fibrosis)

- Human, animal, and cell line

#3 (heterogeneity) Assuming there are multiple molecular mechanisms, deeply phenotype across all the levels of -omics,

tissue, physiology, and symptoms

#2 (resilience)--AGING-LURN type thing/SEN NET

Normal and case controlled LUT age-related conditions—

Measurement of resilience in tissues that are akin to those in humans

Types of stressors—e.g. Fear; bladder distention;

- Preliminary data available from Doug/Chad collaboration

Functional output-

Preliminary data from mouse models, young vs. aged, male and female—integrated multi-omics and urothelial organoids

Human organ-on-chip models (1st model 'healthy aging'--then condition specific

#1 model development

Test known working entities (anti-muscarinics, Botox, beta3 -agonists) in models such as urothelial organoids/assembloids with muscles, neurons, immune cells, smoothmuscle -on chip co-cultures (lessons learned from brain, intestine)

Parabiosis models

Young blood injections

Caloric restriction

Cellular reprogramming (e.g. AAV from Altos)

Key Question:

Does aging change male and female bladder-muscle responses to KNOWN agonists and antagonists (e.g. cholinergics, purinergics, muscarinics) *could be applied iteratively to urethra/prostate) -- add hormones, estradiol and testosterone

- Get some prelim data from urologists and urogynecologists –*suggest names:*)
- Develop a systematic prioritization pipeline to identify interventions most likely to benefit LUT/bladder function by integrating multi-omics data from other systems (muscle, cardiovascular, gut) (Including exercise/CR/young blood) and what we know about bladder aging to map shared mechanistic nodes; conduct a Delphi consensus with urology, geroscience, and systems biology experts; rank interventions based on mechanistic overlap, safety profile, and feasibility.

Test Known Treatments

Mouse models (treatments, Chad)

1. **Test cytometry and other functional aspects in mice, VSA, dose response curves** (prelim data with Chad)
 - a. Try to get prelim data from other animals—monkeys, dogs, cats, eg. Roz Anderson)
 - b. Hormone treatments and measurement (**Teresa**) (also **Indira**)
2. **Cell lines (urothelial and muscle cells in vitro) - Pascale**
 - a. Organoid/organ on chip models - **Indira, Zohreh**
 - b. Identify new targets via glycomics, metabolomics, others...
3. **Human—compare with mice and organ models-bioinformatics and functional tests: (bioinformatics-colleagues-suggest names)**
 - a. Physiological measures
 - b. Molecular measures
 - c. Functional aspects
 - d. Test cytometry and other functional aspects in mice and compare with humans
 - e. Barrier function, (industry sponsored trials or NIH?

4. Physiological measurements (Scott)

- a. Treatment response
- b. Sensation and physiology (urodynamics, uroflow, retention – ***cross connect w/UroVoiding group***)
- c. Efferent activity – voiding dysfunction
(biobank) capture urine samples; shed epithelial cells; shed immune cells

5. Outcomes data– (Allison)

- Symptoms improvement
- Prioritize measures

6. Bring in new aging interventions

- nutraceuticals,

FROM NIA:

- A-1: Identify genetic, molecular and cellular factors that determine the rate of aging processes.
- A-2: Determine how cellular and molecular changes associated with aging contribute to decreased resilience and increased morbidity and influence response to treatment of age-associated physical conditions.
- A-3: Determine how cellular and molecular bases of changes associated with aging contribute to the development and course of age-related dementia and treatment response.
- A-4: Identify factors associated with successful aging and resilience against disease and dysfunction.
- A-5: Understand the sensory and motor changes associated with aging and how they lead to decreased function and increased risk of morbidity.
- A-6: Identify and characterize interventions that hold the promise of increasing healthy lifespan.
- A-7: Develop and/or identify biomarkers (including genetic, epigenetic, molecular, cellular, immunological, metabolic, and microbiome-related) that are applicable to aging and geroscience research.