URO-VOIDING RESEARCH INTEREST GROUP

Connecting investigators and trainees interested in advancing science related to lower urinary tract voiding dysfunctions

Uro-Voiding Breakout Day 1

This research interest group focused on advancing research in urinary dysfunction. Kristin Ebert, MD (pediatric urology, UW-Madison) highlighted the need for better diagnostic tools and personalized medicine, emphasizing the variability in neurogenic bladder phenotypes. Nathan Tykocki, PhD (Michigan State University) discussed the importance of bladder blood flow and urothelial signaling. Jim Hokanson, PhD (Medical College of Wisconsin) emphasized the crossover of symptoms in urological conditions and the need for better diagnostics. Sarah Roccabianca, PhD (Washington University) focused on mechanical biology and sex hormones in bladder dysfunction. Joanna Hannan, PhD (UW-Madison) highlighted the impact of pelvic radiation on bladder function. LaTasha Crawford, VMD, PhD (UW-Madison) discussed the role of sensory innervation in bladder pain. Kim Keil Stietz, PhD (UW-Madison) stressed the impact of environmental toxicants on bladder function. Anneke Verstegen, PhD (BIDMC/Harvard) focused on neural control of continence. Margot Damaser, PhD (Cleveland Clinic) emphasized translational research and device development.

The group focused on improving diagnostics and treatments for bladder dysfunctions. Key themes included multi-modal monitoring, gene therapy, and regenerative treatments. **The group identified four research gaps: bi-directional neural regulation, sex differences in the lower urinary tract, human data mining from brain to bladder, and mechanistic understanding of disease subtypes.** Specific research questions addressed predicting adverse outcomes, understanding disease progression, and identifying physiological fingerprints. The goal is to develop more precise treatments and better characterize bladder diseases.

Action Items

- Reflect on individual knowledge gaps and research interests to share with the group.
- Come prepared on Saturday to discuss specific aims and hypotheses for potential research projects.
- Assign individuals to specific research projects and strategize on grant submission plans.

Kristin Ebert's Introduction and Overview of Urinary Dysfunction Research

- Kristin Ebert introduces herself as a pediatric urologist at the University of Wisconsin.
- She explains the focus of her talk on the clinical perspective of urinary dysfunction research.
- Kristin describes the spectrum of lower urinary tract dysfunction, including overactive bladder, stress incontinence, and underactive bladder.
- She highlights the importance of understanding neurogenic bladder and the need for better diagnostic tools.
- Kristin discusses the challenges of current diagnostics and the need for more precise methods to categorize patients.

Detailed Analysis of Bladder Dysfunction in Spina Bifida Patients

- Kristin presents examples of bladder dysfunction in spina bifida patients using urodynamics tracings.
- She explains the differences between safe and problematic bladders, including bladder diverticula and detrusor sphincter dyssynergia.
- Kristin emphasizes the importance of early intervention to prevent kidney damage.
- She discusses the limitations of current diagnostic methods and the need for better biomarkers and imaging tools.
- Kristin highlights the potential benefits of personalized medicine based on individual patient characteristics.

Research Gaps and Opportunities in Urinary Dysfunction Research

- Kristin identifies key research gaps, including the need for better biomarkers and imaging tools.
- She discusses the challenges of using animal models to study pediatric diseases.
- Kristin emphasizes the importance of integrating urodynamic data with molecular or neurophysiologic data.
- She calls for collaboration between basic scientists and clinicians to develop personalized medicine approaches.
- Kristin challenges the basic scientists to design studies that reflect variability in human disease.

Introduction to the Day's Agenda and Research Roadmaps

- Margot provides an overview of the day's agenda, focusing on developing research roadmaps.
- The goal is to address the public health burden of disease through advanced science.
- The objectives include identifying current knowledge gaps, prioritizing research ideas, and developing specific research questions and hypotheses.

- Margot emphasizes the importance of team science and the collective intelligence of the participants.
- The deliverables include individual and collaborative grant applications and multiple PI projects.

Round Robin Introductions and Research Focus Areas
SEE SLIDES FOR ROUND ROBIN INTRODUCTIONS

Collaboration and Future Directions
- Participants discuss the importance of collaboration and team science in advancing research.
- The need for better diagnostic tools and personalized medicine is emphasized.
- The potential benefits of integrating urodynamic data with molecular or neurophysiologic data are highlighted.
- The importance of addressing knowledge gaps and developing new research approaches is discussed.

Funding and Research Tools for Improved Diagnostics
- Speaker 3 discusses the funding through 2029 and the use of wireless devices to compare bladder pressures at home with clinical urodynamic testing.
- Emphasis on the need for multi-modal monitoring at home, including bladder measurement, EEG for nocturia, and environmental toxin monitoring.
- Speaker 3 mentions the potential for 21st century treatments like gene therapy and regenerative therapy, using diabetes as an example.

Research Gaps and Barriers
- Speaker 1 outlines the plan to discuss research gaps and barriers and categorize them, with a focus on detailed physiological phenotyping.
- Speaker 3 suggests using the last slide to detail research questions instead of barriers, emphasizing the need for more productive focus.
- Speaker 5 notes the addition of headlines for gaps in a Google Doc and invites participants to move things around to identify four gaps.
- Speaker 1 and Speaker 3 discuss the importance of narrowing down broad areas to fundable aspects for grants.

Identifying Research Questions and Gaps
- Speaker 5 explains the goal of identifying about four themes and generating research questions related to each theme.
- Speaker 1 and Speaker 3 discuss the importance of understanding the normal mechanisms of continence and voiding, and the need for detailed physiological phenotyping.
- Speaker 7 adds the importance of understanding how emptiness is sensed and the need for appropriate braking and loosening mechanisms.
- Speaker 1 emphasizes the need to know the normal mechanisms to influence disease treatment and the potential for basic science grants.

Challenges in Data Collection and Analysis
- Speaker 7 highlights the need for sacral spinal cord and dorsal root ganglia samples for comparative studies between humans and animal models.
- Speaker 8 suggests designing studies to correlate disease states with available biobank tissue.
- Speaker 1 mentions the challenges of getting comprehensive data from living people and the potential for prospective studies.
- Speaker 3 and Speaker 7 discuss the need for phenotyping and clinical data to support research questions.

Breakout Sessions for Research Questions
- Speaker 1 and Speaker 3 discuss the importance of understanding the origin of symptoms and the need for better tools to characterize the disease.
- Speaker 7 emphasizes the need for a physiological fingerprint to predict adverse outcomes and treatment response.
- Speaker 4 and Speaker 1 discuss the importance of understanding sex differences in the lower urinary tract and the need for comprehensive data mining.

Reconvening and Finalizing Research Questions
- Speaker 1 and Speaker 3 discuss the importance of understanding the progression of disease and the need for predictive molecular patterns.
- Speaker 7 highlights the need for a battery of tests to collect comprehensive data and the potential for post-mortem samples.
- Speaker 5 emphasizes the importance of understanding the disease to develop targeted therapies and the need for comprehensive data collection.

Uro-Voiding Breakout Day 2

The discussion focused on integrating sex differences and hormonal effects in uro-voiding models, emphasizing the need for comprehensive data collection and predictive models. Key points included the importance of considering estrogen's role in stress incontinence and breastfeeding, the potential use of tamoxifen in rodents, and the necessity of diverse animal models. The group debated the feasibility of large-scale, longitudinal studies to understand bladder dysfunction, suggesting the use of RNA sequencing and environmental exposure analysis. They also explored the potential of machine learning and predictive models to enhance clinical outcomes, highlighting the need for interdisciplinary collaboration and well-defined research questions. The meeting focused on prioritizing research questions and projects related to uro-voiding. Key points included the need to clarify the "complete bladder system" as "from brain to urethra" for better understanding. 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 urodynamics data to predict disease progression and treatment response, particularly in conditions like spina bifida. The team also considered the development of predictive models to identify necessary data collection and the role of mechanistic models in guiding research.

Action Items

- Discuss the possibility of incorporating more mechanistic, computational, and predictive modeling approaches into the research plan, while considering the challenges of obtaining buy-in from clinicians and reviewers.
- Explore the feasibility of a longitudinal study to monitor the progression of underactive bladder in a cohort of at-risk individuals and identify factors associated with worsening symptoms.
- Investigate the potential role of environmental exposures, such as PFAs or Bisphenol A, in the development of lower urinary tract dysfunction, potentially leveraging existing cohorts with relevant data.

Sex Differences and Hormonal Effects on Uro-Voiding

- KS discusses the importance of considering sex differences and hormonal effects in uro-voiding models.
- KS suggests adding estrogen manipulation to basic models to study its effects on the urethra to brain pathway.
- Speaker 2 mentions various models used in Wisconsin, including those for prostate hyperplasia, and the lack of RNA sequencing data on bladder tissue.
- KS highlights the clustering of different models (obstruction, diabetic, inflammation) based on voiding assays and the need for new data collection methods like pelvic nerve recordings and calcium imaging.

Animal Models and Hormonal Regeneration

- Speaker 3 raises a question about the regenerative effects of estrogen on nerves and muscles during breastfeeding.
- Speaker 4 mentions vaginal estrogen prescriptions for women in a hypoestrogenic state due to vaginal atrophy.
- Speaker 2 and Speaker 3 discuss the potential use of tamoxifen post-parturition to prolong hypoestrogenic states in rodents.
- Speaker 2 inquires about methods to mimic stress incontinence in mice and the need for engineering solutions to measure intra-abdominal pressure.

Clinical Studies and Tamoxifen Side Effects

- Speaker 4 discusses the use of tamoxifen in breast cancer patients and its negative effects on sexual and bladder function.
- Speaker 5 suggests exploring other naturally occurring hormonal modulations like PCOS for their dysfunctional effects.
- Speaker 2 emphasizes the importance of writing specific aims for grants and the common practice of writing in increasing levels of complexity.
- Speaker 6 and Speaker 5 share their approaches to organizing aims, with Speaker 6 starting broad and focusing in and Speaker 5 starting with in vivo characterization and ending with a mathematical model.

Predictive Models and NIH Interests

- Speaker 5 discusses the potential of predictive models and the historical resistance from NIH to numerical models.
- Speaker 2 mentions the NIDDK/NIH FDA meeting and the various acronyms for animal models and novel approaches.
- Speaker 5 suggests that predictive models can be a useful tool for hypothesis generation and moving away from animal models.
- Speaker 7 highlights the importance of selling ideas to review panels and the potential for NIH to be interested in new approaches.

Multi-Site Efforts and Prediction Modeling

- Speaker 8 presents a vision for personalized therapy through diagnostics, treatment, and outcome collection, with a focus on prediction modeling.
- Speaker 8 suggests measuring a variety of factors simultaneously to understand treatment outcomes better.
- Speaker 2 and Speaker 8 discuss the challenges of using questionnaire data and the need for more effective measures.

- Speaker 8 emphasizes the importance of a multi-site effort to gather large numbers of data points and optimize for time, cost, and setting.

Environmental Exposures and Predictive Modeling
- KS discusses the potential of using environmental exposures to predict LUTS risk, mentioning ongoing investigations with PCB chemicals.
- Speaker 4 highlights the work being done in North Carolina on PFAs exposure and its impact on bladder disorders.
- Speaker 5 suggests exploring the use of machine learning to combine statistical models with mechanistic models for better predictions.
- Speaker 3 emphasizes the need for a clinical parallel to mechanistic models and the potential for machine learning to guide research.

Methodology and Translational Approaches
- Speaker 3 discusses the importance of translational research and the long-term goals of improving clinical outcomes.
- Speaker 8 suggests starting with intermediate steps to develop tests and understand their informative value.
- Speaker 4 emphasizes the need for focused models to gain clinical buy-in and the potential for expanding research later.
- Speaker 8 highlights the importance of understanding the progression of bladder disorders and the need for longitudinal studies.

Research Questions and Project Development
- Speaker 2 suggests focusing on specific research questions to develop hypotheses and inform grant proposals.
- Speaker 6 proposes a more general approach to include the whole translational part and testing the completeness of models.
- Speaker 2 and Speaker 6 discuss the potential for using core facilities to support multiple R1 grants.
- Speaker 8 mentions the possibility of applying for an RC2 grant to support the development of a human-mouse model.

Collaborative Efforts and Data Collection
- Speaker 7 discusses the challenges of finding dorsal root ganglia (DRG) for research and the potential benefits of a multi-institutional collaboration.
- Speaker 5 suggests writing a white paper to justify the need for a broad data collection approach due to the lack of existing data.
- Speaker 2 and Speaker 7 discuss the importance of full-thickness biopsies for understanding bladder and urethra disorders.
- Speaker 5 emphasizes the need for a comprehensive approach to collect data from various levels of biological organization.

Final Thoughts and Next Steps
- Speaker 2 and Speaker 1 discuss the importance of prioritizing research questions and developing focused projects.
- Speaker 8 emphasizes the need for a multi-site effort to gather large numbers of data points and optimize for time, cost, and setting.

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 the third research question and asks for it to be copied.
- Speaker 3 proposes adding molecular phenotyping to the research questions, highlighting the need for explanation in presentations.

Clarifying the Complete Bladder System
- Speaker 7 asks for clarification on the term "complete bladder system," suggesting "from brain to urethra" for better understanding.
- Speaker 2 agrees, noting the concept stemmed from looking at BPH and the prostate.
- Speaker 5 confirms the clarity of the phrasing, and Speaker 2 acknowledges the mistake in the initial wording.
- Speaker 8 questions the need for all the bullet points, expressing concern about overwhelming the group.

Identifying Research Leads and Collaborators
- Speaker 1 suggests keeping one bullet from the initial page to identify who could be involved and who will take the lead.
- Speaker 2 proposes keeping the prioritized research questions as an overview and addressing the need for access to human tissues.
- Speaker 6 suggests a multi-center bio banking approach, including both animal and human tissues.

- Speaker 7 highlights the feasibility of veterinary patient populations for hormonal and environmental influences studies.

Exploring Veterinary Models and Data

- Speaker 7 discusses the benefits of veterinary patient populations for studying hormonal and environmental influences.
- Speaker 4 mentions the aging dog project and its potential relevance to the discussion.
- Speaker 7 shares insights from a cat study on neurodegenerative disease, noting the feasibility of getting post-mortem samples.
- Speaker 2 expresses interest in the potential for learning from veterinary models and the importance of lifelong information for veterinary patients.

Developing Predictive Models

- Speaker 2 asks for another research question, focusing on the impact of sex hormones on bladder function and dysfunction.
- Speaker 8 suggests using urodynamics data to understand the progression of neurogenic bladder in spina bifida.
- Speaker 3 proposes a question about the data needed to create a predictive model, emphasizing the importance of preclinical work.
- Speakers 8 and 3 discuss the need for a mechanistic model to identify the information needed for a predictive model.

Assigning Leads and Collaborators

- Speaker 3 nominates Jim to take the lead on the predictive model question.
- Speakers 8 and 3 discuss the importance of a mechanistic model in developing a predictive model.
- Speaker 2 suggests assigning leads and collaborators for each research question to ensure coverage and expertise.
- Speakers 4 and 6 express interest in collaborating on specific research questions, highlighting their relevant expertise.