CAIRIBU UROBIOME RESEARCH INTEREST GROUP (U-RIG)

CAIRIBU U-RIG RESEARCH HOURS

EXECUTIVE SUMMARY 1/19/2024 U-RIG RESEARCH HOUR

Goal: Facilitate knowledge exchange and spur collaborations in the urobiome and adjacent fields

DR. ACKERMAN

Urinary Tract Microbiome and Lower Urinary Tract Symptoms

- The urobiome is symbiotic, but there are limited data to support this
- Urobiome dysbiosis can lead to abnormal bladder function and LUTS, including breakdown of the epithelial barrier, immune dysregulation, neuronal dysregulation, increased vascularity, and muscular neuronal dysfunction.
- Many challenges of diagnosing and treating bladder pain
- There is potential to better diagnose and guide microbial-induced treatment for bladder pain, but more research needed

  Analyzing audio transcripts for bladder pain patients
- Lack of distinct microbiome differences for OAB in healthy controls vs. patients, despite next-generation sequencing
- The diagnosis of OAB is subjective due to significant overlap between patients and their heterogeneity
- Researchers used unsupervised clustering analysis on patient questionnaires to identify unique symptoms in bladder pain population, leading to 3 distinct phenotypes: bladder specific pain, non-neurologic pelvic pain, and myofascial pain

Bladder pain phenotypes and microbiome analysis

- Treatment responses vary across subgroups: myofascial pain responds to physical therapy, bladder-specific pain responds to bladder-directed therapies, and non-neurologic pelvic pain doesn't respond to any treatment
- Re: bladder pain – age age influences the urinary microbiome; premenopausal women have a different microbiome than postmenopausal women
  - In a new population of premenopausal patients with bladder pain, 3 distinct groups with different microbiomes were identified, including one with high levels of Lactobacillus and *E. coli*
- Using PCR-based analysis, **thresholds were found that distinguish between patients with bladder-specific pain and those with non-bladder low back pain as well as between responders and non-responders to treatment**
- Strain-level differences in Lactobacillus, particularly in the context of UTI, should be explored. There are limitations of relying solely on diversity measures and principal component analysis
- Status of the gut microbiome related to prior antibiotic exposure; will explore further through mechanistic studies in the lab

Microbiome-pelvic pain connection

- *E. coli* infections associated with urinary tract inflammation in bladder pain while other bacteria are not
- Potential biomarkers for pelvic pain, focusing on microbial changes in the pelvic region, are being studied

Microbiome research and personalized medicine

- *E. coli* in UTI – Genetic diversity and potential for interactions with other microorganisms in the microbiome
- Consider multiple factors when diagnosing and treating OAB, including personalized treatments
- **A convergent approach to understanding OAB is necessary**, focusing on the host response and identifying commonalities across different microbial communities
- Data demonstrate within-person microbiome changes
- Dr. Ackerman presented preliminary data on relationship between symptoms and changes in microbiome
- She proposed three-hit hypothesis for IC involving disturbance to the microbiome, growth of pathogenic strain, and individual differences in response
- Suggests a longitudinal study within an aged cohort, which provide valuable insights into how the microbiome changes over time and how it relates to IC

DR. HALE

The complexities of urinary tract infections and the human microbiome

- Limitations of traditional pathogen-focused approaches to treating infections; important to understand the complex interactions between microbes and their hosts
- Clinicians lack understanding of long-term effects of antibiotic treatments on the microbiome, leading to potential health problems years later

Microbiome research in dogs and its implications for human health

- Microbiome research by Dr. Sarah Fortune (Harvard) demonstrated in translational animal models how environmental compounds affect both host and microbiome (i.e., bladder cancer in dogs and humans)
- Dogs are good model for studying the human microbiome as they share bacteria
  - Many similarities between human and dog urobiomes, despite differences in collection methods and sequencing platforms
- A study found that people in households with dogs shared more similar gut and skin bacterial taxa than households without dogs, suggesting that dogs may act as vectors for sharing bacteria
- Humans and dogs also share UTI-associated *E. coli* strains → potential for interspecies transmission

Urine sample volume and microbial diversity in dogs

- Urine samples >1 mL resulted in more consistent and representative microbial community profiles
- Use of lower volume samples (e.g. 0.5 mL) may lead to loss of rare microbes and inconsistent results
- Fusobacterium was observed in the urine of dogs with bladder cancer but not in healthy dogs, and its abundance increased in dogs with urothelial carcinoma
- *Enterococcus faecalis*, a microbe with functional pathways associated with bladder cancer, was found in both healthy dogs and dogs with bladder cancer, but the dogs with cancer had genes that could degrade polycyclic aromatic hydrocarbons

Using dogs as a model for human urine microbiome

- **Addition of dog urobiomes to human data sets reveals a shared trailing tail of taxa associated with bladder cancer, suggesting dogs as a strong model for the human microbiome**
  - One bladder cancer study in particular demonstrated the importance of host cell removal and urine shotgun metagenomic sequencing as approaches for characterizing the functional potential of urine microbial communities
  - Study showed that some extraction methods bias the community; continued optimization is needed to improve ability to characterize culturable and uncultured microbes in urine

Other microbiome research in dogs and potential applications

- Differences observed between dog and human vaginal microbiomes
- Potential role for oral cavity microbiota of dogs, including Enterococcus, has interested the veterinary community. The addition of oral microbe studies has potential for further valuable insights

***** BELOW are recent publications from Dr. Ackerman and Dr. Hale *****

Recent publications Dr. Ackerman:

1. Ackerman AL. Penny-wise but pound-foolish: the hidden costs of step therapy for overactive bladder. J Urol 2023;209(6):1045–1047. https://doi.org/10.1097/JU.0000000000003430AI.
2. Dmochowski RR, Newman DK, Rovner ES, Zillioux J, Malik RD, Ackerman AL. Patient and clinician challenges with anticholinergic step therapy in the treatment of overactive bladder: a narrative review. Adv Ther 2023; 40(11):4741–4757. https://doi.org/10.1007/s12325-023-02625-8.
3. Gu C, Ackerman AL. An oldie but a goodie: methenamine as a nonantibiotic solution to the prevention of recurrent urinary tract infections. PLoS Pathogens 2023;19(6), e1011405. https://doi.org/10.1371/journal.ppat.1011405.
4. Ackerman AL, Jackson NJ, Caron AT, Kaufman MR, Routh JC, Lowder JL. Myofascial urinary frequency syndrome is a novel syndrome of bothersome lower urinary tract symptoms associated with myofascial pelvic floor dysfunction. Sci Rep 2023;13(1): 18412. https://doi.org/10.1038/s41598-023-44862-5.
5. Ackerman AL, Torosis M, Jackson NJ, Caron AT, Kaufman MR, Lowder JL, Routh JC. The persistency index: a novel screening tool for identifying myofascial pelvic floor dysfunction in patients seeking care for lower urinary tract symptoms. Am J Obstet Gynecol 2023;229(6):667.e1–667.e11. https://doi.org/10.1016/j.ajog.2023.08.017.
6. Ackerman AL, Jackson NJ, Caron AT, Kaufman MR, Routh JC, Lowder JL. Myofascial frequency syndrome: a novel syndrome of bothersome lower urinary tract symptoms associated with myofascial pelvic floor dysfunction. Sci Rep 2023;13(1):18412. https//doi.org/10.1038/s41598-023-44862-5.
7. Nettey OS, Gu C, Jackson NJ, Ackerman AL. Validation of distinct bladder pain phenotypes utilizing the MAPP Research Network Cohort. Int Urogynecol J 2024; Feb 1, Epub ahead of print. https://doi:10.1007/s00192-024-05735-1.

Recent publications from Dr. Hale:

1. Fan J, Hale VL, Lelieveld LT, Whitworth LJ, Busch-Nentwich EM, Troll M, Edelstein PH, Cox TM, Roca FJ, Aerts JMFG, Ramakrishnan L. Gaucher disease protects against tuberculosis. Proc Nat Acad Sci USA 2023;120(7):e2217673120. https://www.pnas.org/doi/10.1073/pnas.2217673120.
2. Käshammer L, van den Ent F, Jeffery M, Jean NL, Hale VL, Löwe J. Cryo-EM structure of the bacterial divisome core complex and antibiotic target FtsWIQBL. Nat Microbiol 2023;8(6):1149–1159. https://doi.org/10.1038/s41564-023-01368-0.
3. Boley PA, Dennis PM, Faraone JN, Xu J, Liu M, Niu X, Gibson S, Hale V, Wang Q, Liu SL, Saif LJ, Kenney SP. SARS-CoV-2 serological investigation of white-tailed deer in northeastern Ohio. Viruses 2023;15(7):1603. https://doi.org/10.3390/v15071603.
4. Wilde THC, Shukla RK, Madden C, Vodovotz Y, Sharma A, McGraw WS, Hale VL. Simian immunodeficiency virus and storage buffer: field-friendly preservation methods for RNA viral detection in primate feces. mSphere 2023;8(6):e0048423. https://doi.org/10.1128/msphere.00484-23.
5. Moore RM, Hale V, Winston J, Hare T. Harnessing the microbiome to improve the health and well-being of animals and people. Am J Vet Res 2023;84(9):ajvr.23.07.0156. https://doi.org/10.2460/ajvr.23.07.0156.
6. McGlynn A, Mrofchak R, Madan R, Madden C, Jahid MJ, Mollenkopf D, Wittum T, Justice SS, Rudinsky A, Hokamp J, Hale V. Longitudinal examination of urine pH, specific gravity, protein, culture, and antimicrobial resistance profiles in healthy dogs. J Vet Int Med 2023;37(6):2219–2229. https://doi.org/10.1111/jvim.16860.
7. Ehrlich M, Madden C, McBride DS, Nolting JM, Huey D, Kenney S, Wang Q, Saif LJ, Vlasova A, Dennis P, Lombardi D, Gibson S, McLaine A, Lauterbach S, Yaxley P, Winston JA, Diaz-Campos D, Pesapane R, Flint M, Flint J… Hale VL. Lack of SARS-CoV-2 viral RNA detection among a convenience sampling of Ohio wildlife, companion, and agricultural animals, 2020–2021. Animals 2023;13: 2554. https://doi.org/10.3390/ani13162554.