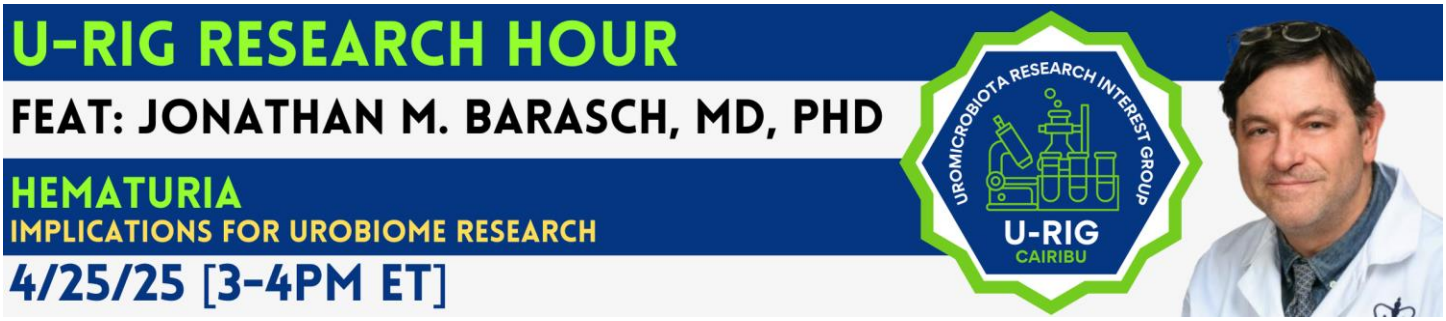
CAIRIBU UROBIOME RESEARCH INTEREST GROUP (U-RIG)

CAIRIBU U-RIG RESEARCH HOURS

EXECUTIVE SUMMARY 4/25/2025 U-RIG RESEARCH HOUR



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

Summary

Dr. Jonathan Barasch's Presentation: The role of heme in urinary tract infection

Iron Metabolism and Its Role in Kidneys and the Urinary System

- Dr. Barasch reviewed the importance of iron in biological systems, such as in DNA replication He described its low availability and the roles of iron in enzyme activity and cell reproduction.
- Iron is bound to various molecules in food, making it unavailable in a free form. **Bacteria compete for iron to support their growth.**
- Dr. Barasch underscored the importance of iron, citing attention it is receiving at multiple upcoming seminars and biology meetings, reflecting its unifying role in science and medicine.

Iron Deficiency

- The process of iron depletion in animals and its impact on bacterial growth is described
- Iron deficiency has deleterious effects during pregnancy, including low birth weight and central nervous system disorders.
- Iron is sparingly available in biological fluids, such as urine**; bacteria have therefore evolved intricate mechanisms to acquire it.**
- Dr. Barasch reviewed how experiments in animals, including those that used iron-deficient diets to induce iron deficiency, demonstrate robust bacterial growth when iron is added, with ferric iron (Fe3+) being less active than ferrous iron (Fe2+).
- The importance of normalizing diets for iron to control for dietary differences was emphasized.

Iron Overload

- Dr. Barasch described how iron overload has been studied in animals. In some studies, a shot of iron sucrose (veneer) was used to induce iron overload.
- The role of excess iron in causing tissue damage and the release of iron from red blood cells by bacteria was reviewed.

N-Gal Protein and Its Role in UTI

- Dr. Barasch introduced N-Gal protein, a mammalian protein released as a defense mechanism in response to bacterial siderophores.
- The role of N-Gal protein in capturing siderophores and its stability in serum proteases was highlighted.
- The structural interaction between enterobactin and N-Gal protein leads to a red color that persists over time.
- Dr. Barasch also noted a correlation between N-Gal protein levels in urine and the presence of bacteria in patients with UTI.

N-Gal Protein Expression in Mouse Models

- The role of N-Gal protein in healing and the structural and functional aspects of N-Gal were discussed.
- Dr. Barasch described a mouse model with a gene for N-Gal protein linked to luciferase to track its expression in UTI. The expression of N-Gal protein in the bladder and kidney during UTI can therefore be observed.
- Findings have revealed higher N-Gal expression in the bladder due to its higher epithelial density. Its expression, however, appears transient, lasting two to twelve hours.

Heme and Its Role in UTI

- As heme in urine is a source of iron for bacteria, Dr. Barasch noted the historical context of iron deficiency anemia as a protective factor against infections.
- He explained how the presence of urine iron during infection can be measured by atomic absorption; studies have shown increased levels for four hours post-infection.
- The structural and functional aspects of enterobactin and other iron chelators was discussed, including their interactions with bacteria and mammalian proteins.
- Dr. Barasch described the use of organic molecules by bacteria with high affinity for capturing iron.

Heme's Impact on Urothelial Damage

- In newer findings, Dr. Barasch has found:
    - Heme reduces urothelial damage during UTI, resulting in a reduction in shedding and the preservation of urothelial cells
    - An increase in intercellular bridges (ICBs) in the presence of heme
    - Heme suppresses inflammation and neutrophil activation
    - Downregulation of inflammatory pathways, identified with the use of RNA sequencing to compare gene expression in UTI and UTI plus

TLR4 and Its Role in Heme's Protective Effect

- Dr. Barasch hypothesized that heme's protective effect is extracellular via inhibition of cytokine expression and neutrophil activation.
- He introduced TLR4 as a critical molecule in the protective effect of heme on urothelial cells.
- The role of TLR4 in endocytosis and its interaction with CD14 was discussed.
- The impact of TLR4 mutation on urothelial damage and the rescue effect of heme was discussed.

Future Directions and Collaborative Efforts

- The need for further experiments to confirm the role of TLR4 in the protective effect of heme was stated.
- In particular, Dr. Barasch emphasized **the need for collaborative efforts to create the necessary mouse models that will allow continued research.**
- The importance of understanding the role of ICBs in the protective effect of heme was highlighted.

Jonathan Barasch, MD, PhD, *is a Professor in the Department of Pathology and Cell Biology in the Division of Nephrology at Columbia University. His research focuses on kidney organogenesis and the mechanisms that produce the epithelial phenotype during the conversion of mesenchymal cells. Additionally, his lab investigates how iron delivery influences kidney development and injury response suggesting a potential connection between iron metabolism, microbial byproducts in the urobiome, and epithelial signaling.*

A few of Dr. Barasch's recent relevant publications follow:

1. Steers NJ, **Barasch J**. Their last will and testament: dying immune cells protect the urinary system with extracellular DNA traps. ***Kidney Int***. 2023;104(2):236-238. doi: 10.1016/j.kint.2023.05.021. PMCID: PMC10950419. PMID: 37479384.
2. Munoz JA, Uhlemann AC, **Barasch J**. Innate bacteriostatic mechanisms defend the urinary tract. ***Annu Rev Physiol***. 2022;84:533-558. doi:10.1146/annurev-physiol-052521-121810. Epub 2021 Nov 15. PMCID: PMC9185666. PMID: 34780258.
3. Forster CS, Johnson K, Patel V, Wax R, Rodig N, **Barasch J**. Urinary NGAL deficiency in recurrent urinary tract infections. ***Pediatr Nephrol***. 2017;32(6):1077-1080. doi: 10.1007/s00467-017-3607-6. Epub 2017 Feb 16. PMCID: PMC5417074. PMID: 28210838.
4. Paragas N, Kulkarni R, Werth M, Schmidt-Ott KM, Forster C, Deng R, Zhang Q, Singer E, Klose AD, Shen TH, Francis KP, Ray S, Vijayakumar S, Seward S, Bovino ME, Xu K, Takabe Y, Amaral FE, Mohan S, Wax R, Corbin K, Sanna-Cherchi S, Mori K, Johnson L, Nickolas T, D'Agati V, Lin CS, Qiu A, Al-Awqati Q, Ratner AJ, **Barasch J**. α-Intercalated cells defend the urinary system from bacterial infection. ***J Clin Invest***. 2014;124(7):2963-76. doi: 10.1172/JCI71630. Epub 2014 Jun 17. PMCID: PMC4071397. PMID: 24937428.
5. Paragas N, Qiu A, Zhang Q, Samstein B, Deng SX, Schmidt-Ott KM, Viltard M, Yu W, Forster CS, Gong G, Liu Y, Kulkarni R, Mori K, Kalandadze A, Ratner AJ, Devarajan P, Landry DW, D'Agati V, Lin CS, **Barasch J**. The Ngal reporter mouse detects the response of the kidney to injury in real time. ***Nat Med***. 2011;17(2):216-22. doi: 10.1038/nm.2290. Epub 2011 Jan 16. PMCID: PMC3059503. PMID: 21240264.