Plan Overview

A Data Management Plan created using DMPTool

Title: Intravesical Gentamycin Coupled with Lactobacillus Rhamnosus for Urinary Health

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Funder: United States Department of Defense (DOD) (defense.gov)

Funding opportunity number: HT9425-23-SCIRP-CTRA

Grant: https://cdmrp.health.mil/funding/pa/HT9425-23-SCIRP-CTRA_GG.pdf

Template: Department of Defense (DOD)

Project abstract:

Background/Readiness: Urinary tract infection (UTI) is the most common outpatient infection world-wide, and for people with spinal cord injury (SCI) with neurogenic lower urinary tract dysfunction (NLUTD) it is not only the most common infection, but also the most common secondary condition, cause for emergency room visits, and infectious cause of hospitalization. Long-standing misconceptions that healthy urine is sterile, and insensitive diagnostics (the standard urine culture preferentially grows E. coli), lead to overtreatment of (presumed) UTI with antibiotics, which contributes to antimicrobial resistance. We propose a transformational approach to UTI treatment with a coupling of instilled intravesical gentamicin plus a live biotherapeutic that disrupts the uropathogenic urobiome, and aims to restore a urobiome that can prevent UTI and lower urinary tract symptoms (LUTS). Our prior work has advanced research in this domain with demonstrated safety and efficacy of intravesical instillation of a live biotherapeutic, Lactobacillus rhamnosus GG (LGG) for bothersome urinary symptoms. Our

readiness for this project is evidenced by our: 1) transforming clinical dogma around healthy urine by demonstrating that a urobiome exists; 2) identifying Lactobacillus as a component lacking in the urobiome of people with NLUTD; and 3) demonstrating the safety and tolerability of intravesical LGG.

Hypothesis or Objective: We focus on people with SCI and NLUTD who manage their bladders with intermittent catheterization (IC). The objectives of the proposed research are to determine the optimal (1) timing and (2) dosing of combined intravesical gentamicin and LGG (gent-LGG) administration in basic and preclinical settings, to inhibit uropathogens and promote re-colonization of the bladder with Lactobacili; and then to (3) carry out a pilot clinical trial of this combination therapy; while (4) collecting input on the lived experience relating to intravesical instillations in people with SCI and disease (SCI/D) who use IC.

Specific Aims and Research Strategy: The specific aims are to:

SA1. Determine requirements for successful instillation of the combination of gent-LGG using enhanced culture techniques and an organoid model: identify species of bacteria most likely to impede LGG colonization; determine antiobiotic susceptibility profiles of LGG and competitors; determine whether the combination requires a time interval or the two interventions can be administered simultaneously.

SA2. Replicate the in vitro results from SA1 in vivo. We will refine a murine model of SCI/D and NLUTD, replicate the results obtained from SA1, and adapt them as needed to optimize information for SA3 as well as future clinical and preclinical work.

SA3. Determine in men and in women with SCI/D and NLUTD: Whether timing (Aims 1 & 2) of coupled gent+LGG will successfully (re-) colonize the human bladder with LGG; whether high (4 doses in 48 hours) vs low (2 doses in 24 hours) is differentially effective for males or females; whether colonization lasts 7, 14, or 28 days; and whether duration of the effect is dependent on dose or sex. This prospective, randomized pilot intervention clinical trial of 2 groups of men and 2 groups of women (N=48) will also collect safety data.

SA4. Early Career Partnering PI Project: Use the FDA patient centering framework to qualitatively determine patient preferences regarding intravesical therapeutics for urinary symptoms and UTI.

Impact: This project responds to the bladder dysfunction priority set forth by the SCIRP by

addressing a critical health priority, improved treatment of UTI and LUTS, with an innovative coupled intravesical gent+LGG intervention. These results will be critical for a pivotal clinical trial in people with SCI/D and NLUTD, as well as for catheter-associated UTI. The basic and preclinical work also serve future research in the domain. Long term, this approach will promote antimicrobial stewardship.

Translation: This work dynamically features translation of work at all stages on the translational continuum.

Military Relevance: A 2018 study revealed that 87% of nearly 400 Veterans had asymptomatic bacteriuria, and of these, 36% “were treated with antibiotics unnecessarily.”1 Successful completion of this work will directly benefit Veterans with SCI impacted by UTI and LUTS, and contribute to antimicrobial stewardship. We “demonstrate a clear path from increased understanding to advancing treatments”; “develop and test an intervention” [gent+LGG]; and we “address the needs of and treatments for individuals across the full lifespan and from acute to chronic injury.”

1. Skelton, F., Grigoryan, L., Holmes, S. A., Poon, I. O. & Trautner, B. Routine Urine Testing at the Spinal Cord Injury Annual Evaluation Leads to Unnecessary Antibiotic Use: A Pilot Study and Future Directions. Arch. Phys. Med. Rehabil. 99, 219–225 (2018).

Start date: 09-30-2024

End date: 09-29-2027

Last modified: 08-21-2023

Copyright information:

Intravesical Gentamycin Coupled with Lactobacillus Rhamnosus for Urinary Health

Types of data produced

The types of data, software, curriculum materials, and other materials to be produced in the course of the project that are publicly releasable.

Sequence data, metadata, and results (ASVs, CFUs) from enhanced culture techniques and organoid model of the urobiome (Aim 1);

Sequence data, metadata, and results (ASVs, CFUs) from the urobiomes of male and female mouse models of SCI/D with NLUTD (Aim 2);

Sequence data, metadata, and results (ASVs, CFUs) from the urobiomes of male and female human participants with SCI/D and NLUTD in the pilot clinical trial, plus demographics and symptom inventories/burden estimates (REDCap-based) and derived outcomes (e.g., definitions of successful recolonization with LGG) (Aim 3);

Qualitative research results summarizing semi-structured interviews reflecting lived experiences of male and female human participants with SCI/D and NLUTD who use instilled intravesical interventions (Aim 4).

Data and metadata standards

The standards to be used for data and metadata format and content.

We will follow FAIR principles (FAIR.org) for all data, and Clinical Trials.gov principles for human subjects data (https://prsinfo.clinicaltrials.gov/definitions.html)

Human response data will be collected via REDCap and shared as de-identified csv files. Data dictionaries will be created for all data sets to include descriptive, administrative, and structural metadata, as appropriate. All scientific data and associated metadata will include relevant information on data formats, data identifiers, definitions, unique identifiers, and other data documentation, including the data dictionary.

Conditions for access and sharing

Conditions for access and sharing including provisions for appropriate protection of

privacy, confidentiality, security, intellectual property, or other rights or requirements.

All data from not-humans will be shared; only de-identified data obtained from humans will be shared. Consistent with the policies of the participating institutions on intellectual property, we will make available any unique research resource produced under this grant for use at other academic or not-for-profit institutions at no cost, except for standard transportation expenses and if applicable the cost of producing the materials/models.

Conditions and provisions for reuse, redistribution, and derivatives

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Conditions and provisions for reuse, redistribution, and the creation of derivative works.

Material transfers will be made with no more restrictive terms than the Simple Letter Agreement (SLA) or the Uniform Biological Materials Transfer Agreement (UBMTA) and without reach-through requirements. Should any intellectual property arise that requires a patent, we will ensure that the technology (materials and data) remains widely available to the research community in accordance with the NIH Principles and Guidelines document.

Sequence data, metadata, and analyses will be immediately made available through NCBI. A BioProject repository, and associated BioSample records, will be created with NCBI to provide metadata regarding the study and individual samples, respectively. All other data submitted to NCBI will be linked to these records. All raw sequence data will be deposited in NCBI's SRA database. Bacterial genome assemblies will be deposited into NCBI's WGS database. Viral genome assemblies will be deposited into the GenBank nucleotide database through NCBI's BankIt submission tool.

Software and R packages developed through this project will be made freely available to the scientific community using the GitHub code repository (github.com). Code will be available through the GNU GPLv3 license

Plans for archiving and preservation

Plans for archiving datasets, or data samples, and other digitally formatted scientific data, and for preservation of access thereto. Explicitly describe how the data that underlies scientific publications will be available for discovery, retrieval, and analysis. In accordance with OSTP Memorandum, digitally formatted scientific data resulting from unclassified, publicly releasable research supported wholly or in part by DoD funding should be stored and publicly accessible to search, retrieve, and analyze to the extent feasible and consistent

with applicable law and policy; agency mission; resource constraints; and U.S. national, homeland, and economic security.

We plan to make the human-specific data available unconditionally through the Open Science Foundation, https://osf.io/kurvd/, DOI 10.17605/OSF.IO/KURVD . Once we have data to share, we will link this page with the other completed projects on lactobacillus for urinary health and the open source peer reviewed publications relevant for work in this area.

Justification for the restriction of data

If, for legitimate reasons, the data cannot be preserved and made available for public access, the plan will include a justification citing such reasons.

NA
