

AWARD NUMBER: W81XWH-21-1-0294

TITLE: A Rapid and Simple Blood Test to Identify Gastrointestinal Inflammation in Children with ASD

PRINCIPAL INVESTIGATOR: Stephen J Walker

CONTRACTING ORGANIZATION: Wake Forest University Health Sciences, Winston-Salem, NC

REPORT DATE: May 2023

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release; Distribution Unlimited

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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

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1. REPORT DATE May 2023			2. REPORT TYPE Annual		3. DATES COVERED 01May2022-30Apr2023	
4. TITLE AND SUBTITLE A Rapid and Simple Blood Test to Identify Gastrointestinal Inflammation in Children with ASD					5a. CONTRACT NUMBER W81XWH-21-1-0294	
					5b. GRANT NUMBER AR200124	
					5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Stephen Walker E-Mail: swalker@wakehealth.edu					5d. PROJECT NUMBER	
					5e. TASK NUMBER	
					5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Wake Forest University Health Sciences Medical Center Blvd Winston Salem, NC 27157-0001					8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Development Command Fort Detrick, Maryland 21702-5012					10. SPONSOR/MONITOR'S ACRONYM(S)	
					11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited						
13. SUPPLEMENTARY NOTES						
14. ABSTRACT The primary goal of this proposal is to develop a rapid blood test for ASD ^{EC} by refining and validating the previously published diagnostic biomarker of this ASD phenotype. In SA1 we proposed to refine the putative peripheral blood-base gene expression signature for ASDEC by incorporating whole blood gene expression profile data from both ASD and TD children <i>without</i> GI symptoms. In SA2 we proposed using the validated transcripts from Aim 1 to generate a predictive model in the cohort for Aim 1. We will then test the performance of the predictive model in a new set of 200 ASD GI and 200 ASD no-GI. In Y2, we are largely on target with our progress as we have completed Major Task 1 and Subtasks 1-5, except for Subtask 3 (because collection of blood samples from this cohort {ASD w/o GI symptoms} was only recently completed).						
15. SUBJECT TERMS Autism spectrum disorder, gastrointestinal, microbiota transfer therapy, transcriptomics, microbiome, metabolomics						
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON	
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRDC	
Unclassified	Unclassified	Unclassified	Unclassified	15	19b. TELEPHONE NUMBER (include area code)	

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1. INTRODUCTION

The purpose of this study is to identify a sensitive and specific blood-based biomarker specifically for discrimination and classification of inflammatory bowel disease sub-types in GI-symptomatic children with ASD. In Specific Aim 1 we have proposed to refine our previously identified blood-based biomarker for ASD^{EC} through gene expression profiling of peripheral blood from the original two groups (ASD with GI inflammation & TD with GI symptoms but without GI inflammation) and two additional control groups (ASD & TD without GI symptoms). In Specific Aim 2 we propose to generate the predictive model and validate the putative blood-based biomarker model for ASD^{EC} in an independent cohort. In Specific Aim 3 we will confirm the sensitivity and specificity of the biomarker in blood samples collected retrospectively from ASD^{EC} patients: (a) at the time of diagnosis and prior to the initiation of treatment and then, (b) one year later (i.e., following successful treatment of their GI symptoms).

2. KEYWORDS

Autism spectrum disorder, gastrointestinal, blood-based biomarker, transcriptomics

3. ACCOMPLISHMENTS

- **What were the major goals of this project?**

There are 6 Major Tasks and 17 subtasks detailed on the SOW associated with this project. Each of the 3 Specific Aims is covered in 2 Major Tasks and between 4-8 subtasks. Following procurement of the appropriate IRB and HRPO approvals, Major Tasks 1, 3, and 5 describe sample processing, while Major Tasks 2, 4, and 6 describe acquisition of the molecular (transcriptomic) datasets and data analysis.

- **What was accomplished under these goals?**

Major Task 1, Subtasks 1-5: complete. To date, "Secure IRB and HPRO approvals to receive and use the specimens (human anatomical substances - HAS)" (Major Task 1; subtask 1) has been completed and Major Task 1 (subtasks 2-5) have also been completed. The lone exception is that we are continuing to recruit children with ASD but without GI symptoms, a task that has proven to be more time-consuming due to the paucity of in-clinic visits over the last two years. We have now collected whole blood specimens for >half (N=45, so far) of the N=75 target that was proposed for gene expression analyses. We have decided to proceed without waiting for additional controls and are preparing samples for RNA-Seq, which will commence in June. We are very much *on target* with our progress thus far.

Major Task 2, Subtasks 1-3: complete. Gene expression analysis was performed on 120 samples (30 individuals from each of the 4 groups) using the 9 previously defined biomarker transcripts. The biomarker did not perform well so the decision was made to analyze the samples generated in Major Task 1 using RNASeq (instead of TaqMan PCR) to derive a more reliable (sensitive/specific) biomarker.

Major Task 3, Subtask 1: complete. RNA isolation and QC of an additional 200 PaxGene blood tubes from ASD^{EC} group is complete and ready for the validation step.

Major Tasks 4-6: incomplete. These remaining tasks are dependent on completing the RNASeq assays and analyzing the data – this work is currently underway.

- **What opportunities for training and professional development has the project provided?**

Nothing to report.

- **How were the results disseminated to communities of interest?**

Nothing to report.

- **What do you plan to do during the next reporting period to accomplish the goals?**

Throughout the course of the next reporting period, we expect to generate and analyze RNA-Seq data from ~350 individual blood samples, identify the predictive biomarker from the bulk Seq data, and perform validation of the biomarker in additional patient samples.

4. IMPACT

- **What was the impact on the development of the principal discipline(s) of the project?**

Nothing to report.

- **What was the impact on other disciplines?**

Nothing to report.

- **What was the impact on technology transfer?**

Nothing to report.

- **What was the impact on society beyond science and technology?**

Nothing to report.

5. CHANGES/PROBLEMS

- **Changes in approach and reasons for change**

The initial plan was to validate a previously described biomarker, consisting of 9 specific transcripts, in samples from ASD (2 groups; with and w/o GI symptoms) and TD (2 groups; with and w/o GI symptoms) children using TaqMan PCR. We discovered (upon performing the tasks outlined in Major Task 2), that the biomarker did not perform well, so the decision was made to identify a more specific and sensitive biomarker through RNASeq of the samples prepared in Major Task 1. This approach has the added benefit of supplying expression data on small RNAs, including microRNAs, in addition to the ~22,000 mRNAs.

- **Actual or anticipated problems or delays and actions or plans to resolve them**

This project is somewhat dependent on getting study samples (whole blood) from clinicians that are not direct study team members and this has proven to take longer than anticipated (mainly due to a steep reduction in in-clinic visits over the last 2 years). Now that most of the relevant restrictions are easing, we anticipate that we can bring this project fully back online and begin assaying samples throughout the first half of this reporting period (May through December 2023).

- **Changes that had a significant impact on expenditures**

Expenditures have aligned well with the completion of Major Tasks 1 & 2, so we are where we expected to be, expenditure-wise, at this point in the project.

- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

Nothing to report.

6. PRODUCTS

- **Publications, conference papers, and presentations**

Nothing to report.

- **Website(s) or other internet site(s)**

Nothing to report.

- **Technologies or techniques**

Nothing to report.

- **Inventions, patent applications, and/or licenses**

Nothing to report.

- **Other products**

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on this project?**

- **Name:** Stephen Walker
- **Project Role:** PI
- **Researcher ID:** 0000-0002-0732-2366
- **Nearest person month worked:** 1.5
- **Contribution to project:** Dr. Walker is responsible for project oversight and management.
- **Funding Support:** this award

- **Name:** Trang Simon
 - **Project Role:** Technician IV
 - **Researcher ID:** n/a
 - **Nearest person month worked:** 2
 - **Contribution to project:** Ms. Simon is responsible for sample handling/processing.
 - **Funding Support:** this award
-
- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**
Yes (please see Other Support Document in Appendices).

 - **What other organizations were involved as partners? N/A**

8. SPECIAL REPORTING REQUIREMENTS

Nothing to report.

9. APPENDICES

Research Support

Stephen Walker

Previous

Title: Evaluation of Hydrodistension Response as a Clinical Sub-Phenotype in IC/BPS

Time Commitment: 4.8 calendar months (25% effort)

Role: Principal Investigator

Supporting Agency: NIH

NIDDK/MAPP Performance

Period: 07/01/2015 – 06/30/2019

Level of Funding:

Goals: The goals of this proposal are to correlate findings based on current interview scores and clinical measures with molecular information, i.e., gene expression profiles from bladder biopsy tissue, to determine which clinical information is most useful (i.e., sensitive, and specific for IC) diagnostically. The second primary objective is to collect and evaluate quantitative data on how well patients respond to bladder hydrodistention therapy so that, by using this information, a clinician can make an informed decision about who would likely benefit from this therapy and for how long the benefit would likely last.

Overlap: None

Title: Biomarkers for Molecular-Based Decision-Making in Diagnosis and Treatment of Interstitial Cystitis

Time Commitment: 4.2 calendar months (35% effort)

Role: Principal Investigator

Performance Period: 08/01/2015 – 07/31/2018

Level of Funding:

Supporting Agency: NIH R21 DK106554-01

Goals: The goals of this proposal, designed to develop such a tool, are twofold: (1) to correlate anesthetized bladder capacity of IC patients, specifically patients with low (<400 mL) capacity, with gene expression profiles from bladder biopsy tissue, to identify and confirm the underlying pathophysiology and also to identify a clinically useful biomarker and, (2) to determine, from gene expression profiling of peripheral blood from the same IC patients, if there is a sensitive and specific biomarker for IC in blood that can be used to facilitate diagnosis and rational treatment.

Overlap: None

Title: Effects of Microgravity on the Risks of Space Radiation-Induced Leukemogenesis

Time Commitment: 0.72 calendar months (6% effort)

Role: Co-Investigator

Supporting Agency: NASA NNX17AE49G

Name, address of funding agency's procuring Contracting/Grants Officer:

Benjamin Benvenuti; benjamin.s.benvenuti@nasa.gov; Space Life and Physical Sciences Research and Applications Division 300 E ST SW, Washington, D.C. 20546-0001

Performance Period: 02/01/2017 – 07/2019

Level of Funding:

Goals: To investigate this possibility by testing the effects (alone/in combination) of μ G and IR/radiomimetics on the ability of primary human HSC to generate normal numbers of functional immune cells of each lineage, focusing on the formation of DC subsets and appropriate expression of TLR family members

List of Specific Aims:

1. Measure levels of spontaneous and low dose IR/radiomimetic-induced DNA damage and DNA damage response (DDR) kinetics in human HSC exposed to μ G.
2. Perform transcriptomic analyses to define HSC signaling pathways significantly affected by μ G and IR/radiomimetics alone and in combination.
3. Test the ability of HSC to differentiate into functional immune cells in μ G, and express appropriate TLRs.
4. Test the ability of generated NK cells to recognize and lyse leukemic cell lines.

Overlap: None

Title: Autism GI Research

Role: Principal Investigator

Supporting Agency: BHARE Foundation

Performance Period: unrestricted

Level of Funding:

Goals: The goal of this project is to evaluate the metabolomics signature in biospecimens from autism spectrum disorder children who have gastrointestinal inflammation.

Overlap: None

Title: Pilot Studies for the Further Molecular Characterization of Gastrointestinal Co-Morbidity in Autism Spectrum Disorder:

Time Commitment: 7.2 calendar months (15% effort)

Role: Principal Investigator

Supporting Agency:

Anonymous Sponsor

Performance Period:

05/11/2015 – 05/11/2017

Level of Funding:

Goals: Previously demonstrated an ASD-associated ileocolitis that significantly overlaps with, yet is distinct from, classic IBD (e.g., Crohn's disease and ulcerative colitis); validate previous findings and extend them to identify biomarkers in peripheral blood that are shared with those markers obtained from diseased intestinal tissue. **Overlap:** None

Title: Novel Microfluidic Biomarker Detection Platforms to Monitor In Vivo Effects of SPE and GCR Radiation, using Mice with Human Hematopoietic Systems

Time Commitment: 0.96 calendar months (8% effort)

Role: Co-Investigator

Supporting Agency: s/Baylor – NASA Translational Research Institute

Name, address of funding agency's procuring Contracting/Grants Officer: Virginia E. Wotring, Ph.D., Texas Medical Center Innovation Institute, 2450 Holcombe Blvd, Suite X, Houston TX, 77021,

Email: virginia.wotring@bcm.edu

Performance Period: 11/01/2017 – 10/31/2021

Level of Funding:

Goals: Our goal is to identify early and persistent biomarkers of response that may identify susceptibility pathways, genes, and regulatory elements associated with onset and progression of human hematological disease (focusing on leukemia) following exposure to mission-relevant doses of space radiation.

Overlap: None

Title: Development of Blood-Based Biomarker for Gastrointestinal Inflammation in GI-Symptomatic Children with ASD

Time Commitment: 0.24 calendar months (2% effort)

Role: Principal Investigator

Supporting Agency: Anonymous

Name, address of funding agency's procuring Contracting/Grants Officer: Not available

Performance Period: 08/21/2018 – 08/20/2021

Level of Funding:

Goals: Refine the putative peripheral blood-base expression signature for ASD through the addition of data from 2 sets of control samples

Overlap: None

Title: ASD-GI Treatment Study

Time Commitment: 0.12 calendar months (1% effort) (no salary support requested)

Role: Co-Investigator

Supporting Agency: The Brain Foundation

Name, address of funding agency's procuring Contracting/Grants Officer: Pramilla Srinivasan, Pleasanton, CA, 94588.

Performance Period: 03/01/2019 – 02/28/2022

Level of Funding:

Goals: The goal of this study is to develop a standard-of-care for children with autism spectrum disorder and co-occurring chronic gastrointestinal symptoms. In this study we will quantify, over one year, GI symptom improvement and behavioral/cognitive changes in 25 ASD children receiving treatment for gastrointestinal symptoms. Patients will be monitored by three validated ASD questionnaires (Vineland Checklist, SARS-2, and ABC Checklist) and two new (not yet validated) GI questionnaires developed by the PI specifically for children with ASD: (1) Gastrointestinal Symptom Scale (GiSS) ASD Bowel Movement Chart and, (2) GiSS-ASD Externalizing GI Behaviors Log.

Overlap: None

Current

Title: 1R01HL135853-01A1 Prenatal Cell and Gene Therapy for Hemophilia A

Time Commitment: 0.36 calendar months (3% effort)

Role: Co-Investigator

Supporting Agency: NIH/NHLBI

Name, address of funding agency's procuring Contracting/Grants Officer: Ryan Lombardi;

Performance Period: 07/14/2017 – 06/30/2023

Level of Funding:

Goals: To prove the safety and efficacy of using cells as a FVIII delivery platform and demonstrate the ability of IUTx to cure or improve HA phenotype and defeat the immune-related hurdles that currently hinder clinical HA treatment.

List of Specific Aims:

1. Determine the ideal cell source to obtain the highest long-term engraftment levels and the in vivo distribution patterns that maximize release of FVIII into the circulation.
2. Use HA sheep to demonstrate that an IUTx approach using the optimal cell source and FVIII transgene construct, can be curative, or at least permanently convert severe HA to a mild phenotype.
3. Test whether receiving IUTx precludes inhibitor induction following postnatal FVIII infusion and/or induces tolerance that persists even after postnatal challenge with FVIII in adjuvant.

Overlap: None

Title: 1R01DK124599-01 Molecular Characterization of a Large Cross-Sectional and Longitudinal Collection of Patients to Investigate Disease Progression in IC/BPS

Time Commitment: 2.28 calendar months (19% effort)

Role: Principal Investigator

Supporting Agency: NIH/NIDDK

Name, address of funding agency's procuring Contracting/Grants Officer: Charlette Kenley,

Performance Period: 05/01/2020 – 04/30/2024

Level of Funding:

Goals: Objectives for this proposal are to use a sophisticated molecular profiling approach, in a broadly heterogeneous group of IC/BPS patients, to: (1) identify patient subgroups that share a similar disease etiology and are therefore likely to respond, as a group, to therapy that targets the underlying mechanism and, (2) identify gene expression modules that are predictive of disease progression in IC/BPS.

Overlap: None

Title: W81XWH2010275 - Molecular Studies to Identify Mechanisms that Underlie Symptom Improvement in Microbiota Transfer Therapy Patients

Time Commitment: 2.46 calendar months (20.5% effort)

Role: Principal Investigator

Supporting Agency: USAMRAA

Name, address of funding agency's procuring Contracting/Grants Officer: Ebony S. Simmons

Performance Period: 05/01/2020 – 04/30/2024

Level of Funding:

Goals: Specific Aim #1: Evaluation of gene expression changes that occur following full spectrum microbiota (FSB) treatment in individuals with ASD and chronic gastrointestinal symptoms. Specific Aim #2: Evaluation of metabolite changes that occur following FSB treatment in individuals with ASD and chronic gastrointestinal symptoms. Specific Aim #3: Using a combined molecular profile (gene and metabolite expression) to derive mechanistic

insight regarding symptom improvement following FSB treatment in individuals with ASD and chronic gastrointestinal symptoms.

Overlap: None

Title: Lung Organ Tissue Equivalent Platform for Modeling Chlorine Gas Toxicology and Medical Countermeasure Efficacy

Time Commitment: 0.60 calendar months (5% effort)

Role: Co-Investigator

Supporting Agency: DHHS 75A50119C00058 ASPR-BARDA Office of Assistant Secretary for Preparedness and Response (ASPR)/Biomedical Advanced Research and Development Authority (BARDA)

Name, address of funding agency's procuring Contracting/Grants Officer: Ethan Mueller, US Dept. of Health & Human Services, Office of Assistant Secretary for Preparedness and Response, O'Neill House Office Bldg., Room Number: 21C08, Washington, DC 20515,

Performance Period: 09/26/2019 – 06/30/2024

Level of Funding:

Goals: The overarching goals of the proposed program include validation of the OTE platform for modeling chlorine-mediated pulmonary toxicity, delineating the biochemical toxicity pathways associated with varying levels of chlorine exposure, and screening of compounds, either new or repurposed, as potential countermeasures to pulmonary chlorine injury. Accomplishing these goals would be a significant step towards demonstrating the potential of the OTE platform for the rapid characterization of unknown pulmonary toxins and informing the targeted screening of potential countermeasures.

Overlap: None

Title: Double-Blind, Placebo Controlled Study to Establish the Safety and Efficacy of Super-Concentrated, Freeze-Dried Aloe Vera in the Management of the Symptoms of Interstitial Cystitis

Time Commitment: 0.12 calendar months (1% effort)

Role: Principal Investigator

Supporting Agency: Desert Harvest, Inc.

Name, address of funding agency's procuring Contracting/Grants Officer: Not available

Performance Period: 01/01/2021 – 12/31/2031

Level of Funding:

Goals: The primary objective of this clinical trial is to monitor the safety and efficacy of Desert Harvest's super-concentrated, freeze-dried aloe vera in the management of the symptoms of interstitial cystitis. The symptoms that will be monitored will include urinary frequency, nocturia, dysuria, urinary urgency, and suprapubic pain. Response to therapy will be monitored through questionnaires including the Quality-of-Life Assessment, IC Symptom/Problem Index, MOS Sexual Functioning Guide, University of Wisconsin Symptom Survey, Health Status Questionnaire, Genitourinary Pain Index, and 24-Hour Voiding Diaries.

Overlap: None

Title: W81XWH2110294 A Rapid and Simple Blood Test to Identify Gastrointestinal Inflammation in Children with ASD

Time Commitment: 1.80 calendar months (15% effort)

Role: Principal Investigator

Supporting Agency: Department of Defense

Name, address of funding agency's procuring Contracting/Grants Officer: Asha Phillips
asha.k.phillips.civ@mail.mil

Performance Period: 05/01/2021 – 04/30/2024

Level of Funding:

Goals: Characterize the gene expression profile of the ASDEC phenotype, including: (a) identification of a gene expression based molecular signature in peripheral blood, (b) validation of the blood-based biomarker that is sensitive and specific and can be useful as a minimally-invasive tool for guiding diagnosis and treatment of gastrointestinal inflammation in children with ASD and (c) testing the utility of the biomarker in pre- and post- treatment blood samples from a series of ASDEC patients.

Overlap: None

Title: RPP: #22-01 Using Organ Tissue Equivalents & AI for Predictive Pathologies & Treatment

Time Commitment: 1.20 calendar months (10% effort)

Role: Co-Investigator

Supporting Agency: ATI/MCDC/DTRA

Name, address of funding agency's procuring Contracting/Grants Officer: Not available

Performance Period: 4/01/2022-05/31/2027

Level of Funding:

Goals: The overall objective of this project is to combine the science of machine learning (ML) with the science of 3D organ and tissue culture

Overlap: None

Title: R01DK12833 - Investigation of Non-Invasive Pulsed Electromagnetic Field (PEMF) Therapy for Female

Patients with Interstitial Cystitis / Bladder Pain Syndrome (IC/BPS)

Time Commitment: 2.16 calendar months (18% effort)

Role: Principal Investigator

Supporting Agency: National Institute of Health

Name, address of funding agency's procuring Contracting/Grants Officer: Charlene Kenley NIDDK, kenleyc@extra.niddk.nih.gov,

Performance Period: 04/01/2022 – 03/31/2025

Level of Funding:

Goals: Interstitial cystitis/bladder pain syndrome (IC/BPS) represents a potentially life-long chronic pain disorder that is challenging to diagnose, difficult to treat, and often results in a severely diminished quality-of-life. In this pilot and feasibility clinical trial, we will evaluate the safety and efficacy of a non-invasive therapeutic strategy, pulsed electromagnetic field therapy (PEMF), for pain management in IC/BPS patient subgroups. The goal is to provide preliminary data that will lead to large, hypothesis-driven, multi-center clinical trials.

Overlap: None

Title: Exploring the proposed anti-inflammatory mechanism of action of pulsed

electromagnetic field therapy using urothelial cells from patients with interstitial cystitis/bladder pain syndrome)

Time Commitment: 0.12 calendar months (1% effort)

Role: Principal Investigator

Supporting Agency: International Urogynecological Association

Name, address of funding agency's procuring Contracting/Grants Officer: Not available

Performance Period: 08/01/2022 – 07/31/2023

Level of Funding:

Goals: Interstitial cystitis/bladder pain syndrome (IC/BPS) represents a potentially life-long chronic pain disorder that is challenging to diagnose, difficult to treat, and often results in a severely diminished quality-of-life. In this pilot and feasibility clinical trial, we will evaluate the safety and efficacy of a non-invasive therapeutic strategy, pulsed electromagnetic field therapy (PEMF), for pain management in IC/BPS patient subgroups. The goal is to provide preliminary data that will lead to large, hypothesis-driven, multi-center clinical trials.

Overlap: None

Title: Assessment of Urinary Polymerase Chain Reaction (PCR) and Next Generation Sequencing (NGS) Technology in the Evaluation and Management of Females with Chronic Bladder Pain and Cystitis-Like Symptoms. Protocol 20211649

Time Commitment:

0.06 (.05% effort)

Role: Principal

Investigator

Supporting Agency:

MicroGenDx

Name, address of funding agency's procuring Contracting/Grants Officer: Not available

Performance Period: 10/27/2021 – 10/31/2026

Level of Funding:

Goals: To perform a prospective clinical evaluation of the risks and benefits of PCR/NGS technology in the practical clinical evaluation and management of patients with bladder pain syndrome (BPS) and chronic cystitis-like symptoms (CCS) pursuant to the protocol.

Overlap: None

Title: Using urine derived progenitor stem cells to model bladder urothelium dysfunction in interstitial cystitis/bladder pain syndrome.

Time Commitment: 0.12 (1% effort)

Role: Principal Investigator

Supporting Agency: Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction Foundation (SUFUR).

Name, address of funding agency's procuring Contracting/Grants Officer: Not available

Performance Period: 12/30/2022 – 12/30/2024

Level of Funding:

Goals: Having a relevant and practical disease model that could be used to test urothelial barrier function would enable a multitude of important research applications, e.g., to better understand disease etiology, patient stratification, and disease progression – all supporting the overall objective to develop new and effective therapeutics to treat this highly heterogeneous and

complex disorder.

Overlap: None

Pending

Title: P20 RFA-DK-22-027 Investigation of Fibrosis as an Etiologic Factor for Disease Progression in Interstitial Cystitis / Bladder Pain Syndrome (IC/BPS)

Time Commitment: 2.40 calendar months (20% effort)

Role: Co-Investigator

Supporting Agency: NIH

Name, address of funding agency's procuring Contracting/Grants Officer: Not available

Performance Period: 12/01/2023 – 11/30/2026

Level of Funding:

Goals: Development of an *in vitro* model of bladder urothelium for hypothesis testing.

Overlap: None

Overlap: As additional awards are received commitment will be adjusted appropriately and in accordance with sponsor approval.