

Funding Opportunity for Basic and Translational Science Studies in the MAPP Research Network

I. Funding Announcement Purpose

The Data Coordinating Core (DCC) for the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network, supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH), invites research grant applications to conduct fundamental basic and translational research focused on urologic chronic pelvic pain syndrome (UCPPS). Successful applicants will become members of a Basic and Translational Science Working Group (BTS WG) of the MAPP Research Network. BTS WG members will work collaboratively with the Network's Steering Committee to develop final protocols to be integrated into the overall aims and objectives of ongoing studies. Between 4 and 8 one-year awards will be made in 2015. This is a one-time competition. Awards will be issued as sub-contracts from the MAPP Network DCC located at the University of Pennsylvania.

II. Overview of the MAPP Research Network

Background

For over two decades the NIDDK has supported research studies of underlying disease mechanisms and clinical trials for UCPPS, a term encompassing interstitial cystitis/bladder pain syndrome (IC/BPS) and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). However, many fundamental questions remain unanswered regarding etiology, natural history, and genetic and other risk factors for development and symptom progression of UCPPS. In addition, no treatments have been found to be generally effective in UCPPS patients.

While many of the past research studies have focused on the bladder and the prostate as the primary source of symptoms of these syndromes, more recent epidemiological studies have shown that conditions sharing chronic pain as a major symptom are often associated with UCPPS. In order to advance the field the NIDDK proposed that the organ-specific focus of UCPPS research should be broadened to assess the interplay between the bladder, lower urinary tract and other physiological systems. As part of this new focus, the NIDDK emphasized that studies of UCPPS should include new and novel methods and approaches involving teams of multi-disciplinary clinical, basic and translational investigators.

MAPP Research Network Scientific Approach

The NIDDK initiated the MAPP Research Network in 2008 as a novel effort to advance our understanding of UCPPS. The MAPP Network's scientific strategy was designed to shift the research focus from the traditional bladder- and prostate-centric views of UCPPS to a systemic perspective, including the potential relationships between UCPPS and other urologic and non-urologic disorders, including fibromyalgia, irritable bowel syndrome, and chronic fatigue syndrome, among others. Additional features of this effort include the emphasis on highly collaborative, multidisciplinary, integrated studies and the inclusion of a wide breath of clinical, epidemiological, and basic research expertise, as well as the involvement of investigators and approaches new to the study of urologic chronic pain. Through this innovative effort the MAPP Network strives to develop new and clinically relevant insights to inform future clinical trials and ultimately advance UCPPS patient care.

Project Period I: During the MAPP Network's first project period (2008-2014), investigators conducted a 12-month longitudinal, observational study of the treated natural history of UCPPS. This included the administration of comprehensive urologic and non-urologic measures and the collection of diverse biological samples. Additional studies, often restricted to one site, were integrated within this central study and added complementary phenotypic data. In addition, the network established a UCPPS Animal Models Working Group that developed validation criteria for UCPPS rodent models and explored diverse mechanistic hypotheses (see **Section IX** for sources of additional information on approach and methods).

Findings to date are revealing new and important insights into UCPPS, including:

- Differing phenotypic characteristics associated with UCPPS patients with pain localized to the pelvis versus those with both pelvic and systemic pain.
- Distinct patterns of symptom change over time (i.e., worsening and improvement) for patient groups based on symptom pain/severity.
- Increased systemic pain sensitivity associated with specific phenotypic sub-groups.
- Symptom flares are much more diverse in terms of severity and frequency than previously described.
- Metabolomic differences between UCPPS patients and controls and between patient sub-groups.
- Inflammatory dysregulation associated with key UCPPS symptoms in females.
- Biomarkers with potential to differentiate UCPPS and provide insights into underlying etiology for some patients.
- Novel neuroanatomical/functional characteristics associated with specific brain white and gray matter regions that distinguish UCPPS patients from controls.
- Inflammatory pathways and microbe-host interactions as potential UCPPS mechanisms in UCPPS animal models.

Additional details on the findings from the first project period can be found in the MAPP Network publications listed later in this announcement.

Project Period II: The second project period of the MAPP Research Network was initiated in July 2014 and will continue through mid-2019. The current organization of the MAPP Research Network includes nine Discovery Sites which recruit study participants and conduct multidisciplinary research studies; a DCC that manages network-wide data collection and performs central data analyses; and a Tissue and Technology Core (TATC) that coordinates biological sample collection, archiving, and distribution.

The major clinical investigation to be conducted during the second project period of the MAPP Network, the Trans-MAPP Symptom Patterns Study (SPS), is a 36-month longitudinal, observational study of the treated natural history of UCPPS. Designed to build upon findings from the first phase (Fig. 1), the Trans-MAPP SPS will characterize symptom change over time and assess underlying biological changes and risk factors associated with urologic and non-urologic symptom patterns. The SPS will also further define clinically relevant UCPPS patient subgroups and phenotypic characteristics associated with response to selected interventions prescribed by treating physicians during their routine clinical management of these patients. Novel phenotypic measures of key symptoms informed from the first phase efforts and expanded biological sample collections will also be obtained. Numerous, complementary studies will be integrated into the central protocol, including expanded analyses of central nervous system structure/function, discovery and targeted biomarker analyses, characterizations of the host microbiome, among others. Further *in vivo* translational studies using UCPPS animal models will also be conducted.

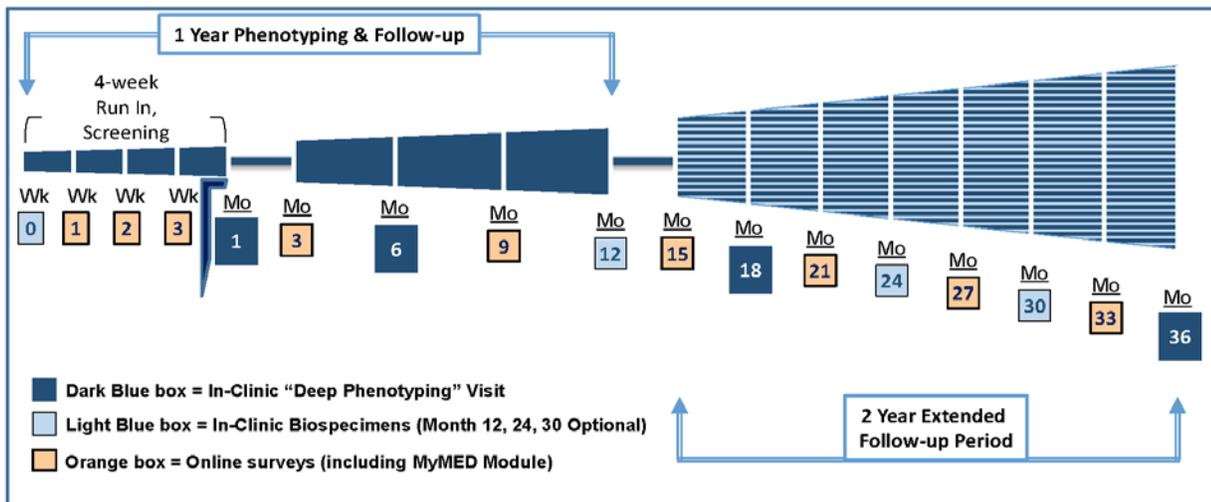


Figure 1. Overview of SPS Phenotyping. A baseline “deep phenotyping” symptom assessment is conducted at week 4 followed by longitudinal internet-based quarterly symptom assessments for a total of 36 months. Each UCPPS participant also returns for in-clinic reduced (“lite”) phenotyping data and bio-specimen collection every 6 months.

III. Expansion of the MAPP Research Network through New Basic and Translational Studies

The purpose of this announcement is to solicit grant applications for integrated basic or translational science studies that use novel analytic tools and methods to provide an improved understanding of clinical features of UCPPS, identify informative subgroups, identify new underlying biological mechanisms that may inform on etiology and/or provide targets for intervention, and describe the pathophysiology of UCPPS. Such studies would provide an additional level of phenotypic data to augment ongoing MAPP Research Network studies.

Applicants are encouraged to propose studies that utilize MAPP Network clinical data and/or biological samples from the first project period, or propose to be integrated into the ongoing SPS Phenotyping study. Studies proposing the use of highly novel and unique methods and technical approaches are encouraged. Studies that propose using available resources developed by other basic, translational, or clinical science studies to address questions relevant to the goals of the MAPP Network (e.g., to validate MAPP Network data) are also encouraged. Appropriate letters of collaboration and/or to authorization for sharing of study data MUST be obtained from relevant study groups or repositories from which data or samples will be obtained and included in the grant application. Studies may propose recruitment of relevant patient/control cohorts at the applicant’s institution with collection of clinical data and biological samples; however, study participants must undergo baseline (and longitudinal, as appropriate) phenotyping that will permit comparison of key measures with SPS participants.

Applications must describe how proposed approaches address the MAPP Network goals of informing future clinical investigations (e.g., designing the next phase of UCPPS trials and follow-on phenotyping efforts) and ultimately improving clinical management of UCPPS patients, and how they are complementary to the broader clinical phenotyping efforts of the MAPP Network. Applicants must provide milestones that should be achieved at the time of the 1 year review.

It is anticipated hypothesis testing or hypothesis generating studies supported through this effort may provide a foundation for future research applications (e.g., R01s, R21s, etc.).

Interested applicants are strongly encouraged to contact the NIDDK Project Scientist (see **Section VIII**) and MAPP Network Investigators early in the application process.

Approaches and areas of interest include, but are not limited to:

- New and novel approaches to examine MAPP Network clinical data and biological samples.
- Assessment of novel underlying mechanisms of disease and biological or clinical characteristics that may define clinically meaningful patient sub-groups.
- Basic science studies to examine potential cellular/molecular contributors to UCPPS.
- Genetics/genomics/epigenetics studies, including studies utilizing archived MAPP Network DNA or other biological samples.
- Expanded characterization of UCPPS subjects participating in the Phase II Symptom Patterns Study (SPS), provided any additional patient-burden is judged as minimal and will not interfere with subject recruitment/retention/adherence for MAPP Network studies (see **Section VIII** for review criteria).
- Recruitment of study participants at the applicant institution to perform in-depth characterization (phenotyping) and/or collection and testing of biological samples using relevant patient cohorts or control subjects.

The following topics are considered non-responsive to this solicitation:

- Studies that are duplicative or propose significant overlap with past or ongoing/planned MAPP Research Network studies.
- Biomarker discovery and validation unless a novel assay or approach is proposed that is non-overlapping with MAPP Network efforts.
- Clinical trials.
- Development or study of a rodent model system as the primary aim/goal.
- Survey of the microbiome of the lower urinary tract.

The final study protocols of successful applications will be further developed in collaboration with MAPP Network investigators to ensure feasibility, integration with network studies, translational potential, and added value to the goals of the MAPP Network before implementation. The final data analysis plan will be developed in collaboration with the MAPP Network DCC.

The application must identify a Principal Investigator (PI) (or multiple PIs). Additional personnel should be included that permit formation of a team of investigators with sufficient and complementary expertise. Clinical expertise relevant to the care and treatment of UCPPS patients should be included to ensure a strong focus on clinically significant questions and potential to complement MAPP Research Network clinical phenotyping and goals. Studies may involve collaborative efforts from appropriate individuals from more than one institution, if well justified. All funded investigators will be expected to adhere to all MAPP Network Policies (e.g., data sharing, publications and presentations, etc).

IV. Available Funds and Additional Considerations

The NIDDK plans to allocate up to \$2 million to support 4-8 grant applications through single, one-time awards.

Applicants may request up to \$500,000 Total Costs (Direct Costs plus Indirect Costs, including consortium/contractual costs for establishing sub-award agreements with the DCC at the University of Pennsylvania). These one-time awards may support studies over several years; funded investigators will be responsible for using funds at a rate which allows for sufficient time to completely address the proposed Specific Aims and Goals. Studies should include a proposed plan for utilization of resources over a suitable time period.

Studies will be assessed every 6-12 months by members of the MAPP Network External Experts Panel (EEP) and/or NIDDK Staff. At the 1 year point, studies will undergo a intensive review, and a determination will be made regarding continuation of the study. The NIDDK reserves the right to reduce or withdraw sub-contract funds pending review of progress. Applicants will be encouraged to work with NIDDK Program Staff to explore strategies for continued funding beyond the terms of these sub-contract awards (e.g., through R01 applications). Funding will be provided by the MAPP Research Network DCC through sub-contracts. This is a one-time solicitation.

Studies that propose utilization of MAPP Network data or biological samples must include funds to support the required effort of the MAPP Network DCC or TATC and cost estimates should be developed in consultation with these cores prior to the time of submission.

All data collected and resources generated will be shared by all participating investigators and the MAPP Network during the conduct of the study. The general NIH sharing policy may be found at: http://grants.nih.gov/grants/policy/data_sharing/. Also, see <https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-13-507.html> for MAPP Network sharing policies. MAPP Network policies may be obtained upon request.

V. Eligibility

Individuals with the skills, knowledge, and resources necessary to carry out the proposed research are invited to work with their institution to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH support. Foreign institutions are eligible for this announcement. Current MAPP Research Network grantee institutions are eligible to submit grant applications. However, Principal Investigators (PIs) named on applications in response to this opportunity must have their primary appointment in a Department/Division that is different than the primary affiliation of any current MAPP PIs. Current MAPP Research Network personnel are not eligible to apply as Principal Investigators. However, current MAPP Network PIs may be named as non-paid consultants and cannot receive salary support.

VI. Application Format

Applications submitted in response to this announcement should follow the guidelines for a NIH R01 application using standard SF424 forms. All page limitations described in the SF424 Application Guide and the NIH Table of Page Limits (http://www.grants.nih.gov/grants/forms_page_limits.htm) must be followed with the following exception: The **Research Strategy** section of the application may not exceed 6 pages.

For information on the SF424 application see: <http://grants.nih.gov/grants/funding/424/index.htm>.

Counter signatures from Institutional Grants Offices are required at the time of submission.

Applicants are encouraged to consider below described review criteria in the development of their proposals (see **Section VIII**).

VII. Key Dates and Application Submission

Key Dates

Release date: January 28, 2015

Application Receipt date: June 15, 2015

Review: July-August, 2015
Sub-contract Award: August-September, 2015

Where to Send Applications

An electronic version (e.g., PDF) of the application should be sent to the MAPP Network DCC Project Manager with a cc to the NIDDK Project Scientist (see **Section IX** for contact information) on or before the above receipt date. Late, non-responsive, or incomplete applications will not be considered. Do not submit applications electronically through Grants.gov.

VIII. Application Review

Review Process and Criteria

The MAPP Research Network's External Experts Panel (EEP) will conduct the review of responding applications. Additional ad hoc reviewers may be added, as needed, to ensure adequate expertise. The application review group will be led by a member of the EEP and coordinated by the NIDDK Project Scientist.

The EEP will initially assess the below points. The EEP may consult on the below with the MAPP Network Executive Committee on a case-by-case basis.

- Relevance of the proposed study to the goals of the MAPP Network.
- Potential overlap with completed or planned MAPP Network studies.
- Burden on study participants and impact on non-renewable samples or other resources.
- Appropriateness of funds to support collaborative MAPP Network Core activities, if needed.

For applications that are acceptable for the above, reviewers will be asked to judge the overall scientific merit of the application, including the likelihood of the proposal for success and the potential contribution to the overall goals of the MAPP Network, as well as the practicality of the efforts to be completed with the resources requested.

Review criteria will include:

- Merit and feasibility of research study design and methods to address the MAPP Network's goals in understanding the pathophysiology of UCPPS, informing future clinical studies, and ultimate potential to enhance clinical care.
- Innovation of approaches.
- Potential for productive integration and collaboration with the MAPP Network.
- Qualification and experience of the Principal Investigator and assembled team and potential to bring new insights and expertise to the existing Network.
- Appropriateness of proposed timeline and budget, including support of MAPP Network Cores, if needed.
- Demonstrated willingness to collaborate within the Network and adhere to MAPP Network Policies (e.g., sharing, publication), as outlined in the original MAPP Network solicitations (see **Section IX**).

No numerical scores will be assigned; however, a brief critique will be provided to applicants. The NIDDK will use EEP comments in award selection.

Funding Decisions

Funding decisions will be made by the NIDDK and will be based on (i) an assessment of scientific merit and other review criteria and recommendations from the MAPP Research Network EEP, and (ii) availability of funds. All awards are subject to possible EEP-recommended and/or administrative reductions in requested funds. The NIDDK retains all rights and responsibilities outlined in the original MAPP Research Network Funding Opportunity Announcement (RFA-DK-07-003) and subsequent

announcements (RFA-DK-13-501, RFA-DK-13-507, RFA-DK-025). Funded investigators will be required to adhere to all MAPP Network policies (e.g., sharing, publication).

For those applications selected to receive awards, the final level of funding and sub-contract terms will be determined by NIDDK following discussions between the Principal Investigator (and respective institutional Grants Office) and the MAPP Network DCC.

Resubmissions and Appeals

This is a one-time Funding Announcement. Revised applications will be not be accepted. No Appeals to the Scientific Review will be considered.

IX. For Additional Information and Questions

The following will provide additional background on the MAPP Research Network:

Key MAPP Network Reviews and Methods Articles:

- Clemens JQ, Mullins C, Kusek JW, Kirkali Z, et al. The MAPP research network: a novel study of urologic chronic pelvic pain syndromes. *BMC Urology* 2014, 14:57
Available at: <http://www.biomedcentral.com/1471-2490/14/57>
- Landis JR, Williams DA, Lucia MS, Clauw DJ, et al. The MAPP research network: design, patient characterization and operations. *BMC Urology* 2014, 14:58.
Available at: <http://www.biomedcentral.com/1471-2490/14/58>

Selected MAPP Network Publications:

- Kilpatrick LA, Kutch JJ, Tillisch K, Naliboff, B et al. Alterations in resting state oscillations and connectivity in sensory and motor networks in women with interstitial cystitis/painful bladder syndrome. *J Urol*. Vol. 192, 947-955, September 2014
- Schrepf A, O'Donnell MA, Luo Y, Bradley CS et al. Inflammation and inflammatory control in interstitial cystitis/bladder pain syndrome: Associations with painful symptoms. *Pain*. 2014 Sep; 155(9): 1755-61.
- Stemler KM, Crock LW, Lai HH, Mills JC, Gereau RW 4th and Mysorekar IU: Protamine sulfate-induced bladder injury is protective from distention-induced bladder pain. *J Urol* 189(1): 343-51, 2013. PMID 23174261.
- Sutcliffe S, Colditz GA, Pakpahan R, Bradley CS, et al. Changes in symptoms during urologic chronic pelvic pain syndrome symptom flares: Findings from one site of the MAPP Research Network. *Neurourol Urodyn*. 2013 Nov 23.
- Lai HH, North CS, Andriole GL, Sayuk GS, Hong BA. Polysymptomatic, Polysyndromic Presentation of Patients With Urological Chronic Pelvic Pain Syndrome. *J Urol* 187(6):2106-12, 2012.
- Lai H, Hong B, North C, Andriole G, Song D, Cupps L, Ness T, Sayuk G, Alpers D, Hong B. Characterization of a subset of urologic chronic pelvic pain syndrome (UCPPS) patients with a poly-symptomatic, poly-syndromic pattern of presentation. *J Urol* 191 (6): 1802-1807.
- Sutcliffe S, Colditz GA, Goodman MS, Pakpahan R, Vetter J, Ness TJ, Andriole GL, Lai HH. Urologic Chronic Pelvic Pain Syndrome Symptom Flares: Characterization of the Full Spectrum of Flares at Two Sites of the Mapp Research Network. *BJU Int*. 2014 Apr 15.
- Crock LW, Kolber BJ, Morgan CD, Sadler KE, Vogt SK, Bruchas MR, Gereau RW 4th. Central amygdala mGluR5 in the modulation of visceral pain. *J Neurosci* 10;32(41):14217-26, 2012.
- Chaturvedi KS, Hung CS, Crowley JR, Stapleton AE, Henderson JP. The siderophore yersiniabactin protects uropathogenic *Escherichia coli* from copper toxicity in vivo. *Nat Chem Biol* 8(8):731-6, 2012.
- Rudick CN, Jiang M, Yaggie RE, Pavlov VI, Done J, Heckman CJ, Whitfield C, Schaeffer AJ, Klumpp DJ. O-Antigen Modulates Infection-Induced Pain States. *PLoS One* 7(8):e41273, 2012.
- Lai HH, Qiu CS, Crock LW, Morales ME, Ness TJ, Gereau RW 4th. Activation of spinal extracellular signal-regulated kinases (ERK) 1/2 is associated with the development of visceral hyperalgesia of the bladder. *Pain* 152(9):2117-24, 2011.
- Kim R, Liu W, Chen X, Kreder KJ, Luo Y. Intravesical Dimethyl Sulfoxide Inhibits Acute and Chronic Bladder Inflammation in Transgenic Experimental Autoimmune Cystitis Models. *J Biomed Biotechnol* 2011:937061, 2011
- Lv H, Hung CS, Chaturvedi KS, Hooton TM, Henderson JP. Development of an Integrated Metabolomic Profiling Approach for Infectious Diseases Research. *Analyst* 136(22):4752-63, 2011.
- Lv H, Henderson JP: Yersinia high pathogenicity island genes modify the *Escherichia coli* primary metabolome independently of siderophore production. *J Proteome Res*. 2011 Dec 2;10(12):5547-54.

- Rodríguez MÁ, Afari N, Buchwald DS; National Institute of Diabetes and Digestive and Kidney Diseases Working Group on Urological Chronic Pelvic Pain. Evidence for Overlap Between Urological and Nonurological. J Urol 182(5):2123-31, 2009.

MAPP Research Network website:

<http://www.mappnetwork.org/>

Link to past MAPP Research Network Funding Initiatives (RFAs):

MAPP Network First Project Period:

<http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-07-003.html>

<https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-13-501.html>

MAPP Network Second Project Period:

<https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-13-507.html>

<https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-13-025.html>

Additional details and information regarding MAPP Network studies and resources are available upon request. Direct questions to either the NIDDK Project Scientist and/or the MAPP Network Data Coordinating Core (DCC) Project Manager:

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