Develop kidney biomimetic “phantoms” as quality control standards

Kidney Precision Medicine Project (KPMP)

Recent advances in multi-scale interrogation of human tissue and single cells have set the stage for precision medicine to be applied to kidney disease. The objectives of the Kidney Precision Medicine Project are to ethically and safely obtain and evaluate human kidney biopsies from participants with Acute Kidney Injury (AKI) or Chronic Kidney Disease (CKD), create a kidney tissue atlas, define disease subgroups, and identify critical cells, pathways and targets for novel therapies. Specifically, the KPMP aims to develop or facilitate:

1. **Public resource**. Establish a publicly available data hub with clinical, imaging, cellular and molecular data. Anonymized data will be available to the research community upon validation.
2. **Kidney tissue atlas**. Create a set of maps used to classify and locate different cell types and interstitial components. The atlas will help define disease subgroups and identify cells, pathways and targets for novel therapies.
3. **State/transition markers**. Identify a set of cellular and molecular markers that classify cells as healthy, injured, activated, or undergoing recovery via adaptive or maladaptive repair.
4. **Disease subgroups**. Use all available data, including the kidney tissue atlas, to define patient subgroups and allow for clinical stratification into distinct endophenotypes.
5. **Molecular pathways**. Use data to identify and understand healthy and disease pathways that are activated in a particular cell type in a particular subgroup of patients.
6. **Biomarkers**. Discover a set of subgroup and pathway biomarkers. Ideally plasma or urine protein/antibody pairs, but could be urinary exosomes, miRNA, epigenetic marks, etc.

Kidney Tissue Atlas

A major objective of the KPMP is to create a kidney tissue atlas. The atlas is expected to contain a set of 2- and 3-D maps representing health (e.g., healthy living donor, healthy volunteer) and disease (e.g., KPMP AKI and CKD biopsies) across a diverse population (accounting for sex, age, race, and ethnicity). Maps will be used to classify and locate ('paint') different cell types, cell states (healthy, injured, dying, recovering, undergoing adaptive/maladaptive repair, etc.) and interstitial components (collagens, proteoglycans, signaling molecules, etc.). The maps are expected to include specific genes, proteins, RNAs, metabolites, and/or epigenetic landmarks that are visualized by advanced imaging. The maps are expected to facilitate identification of cell, structural, and regional heterogeneity throughout the kidney, and allow for interrogation of compartments that are currently difficult to visualize (interstitium, glomerulus, etc). The atlas will ultimately be used to improve the diagnosis, staging, grading, prognosis, subgroup stratification, and drug effect prediction in AKI and CKD.

KPMP Opportunity Pool

The KPMP recognizes that it must collaborate with the broader research community to fully achieve these objectives. Thus, the KPMP Central Hub will administer an "Opportunity Pool" to facilitate the formation of new partnerships.

Funding Opportunity Announcement

There is a critical need to develop novel biomimetic "phantoms" that can serve as quality control standards to normalize batch effects (ensure traceability, version control, rigor and reproducibility) and to enhance the ability of the research community to compare results from diverse tissue integration methods performed at different sites and at different times. This solicitation aims to form new collaborative partnerships by providing KPMP opportunity pool funds to applicants proposing to design, fabricate, characterize, produce, and distribute novel biomimetic phantoms. Ideally, the phantoms will perform several diverse tasks including, but not limited to:

1. **Tissue processing and Pre-analytic control.** A highly sensitive indicator that can accurately monitor changes (either directly or indirectly) over time to tissue ischemia, hypoxia, analyte degradation, etc. (analogous to a tracking device that can monitor temperature changes of a shipped package).
2. **Analytic control.** A highly stable positive control with reproducible signal integrity over time of appropriate reference transcripts, proteins, metabolites, cells, structures, etc. (analogous to molecular weight markers used for quantitative and qualitative comparisons).

All phantoms need to be fit for purpose (bulk tissue analysis, single cell analysis, immunohistochemistry, proteomics, metabolomics, etc.). Phantoms designed for image-based tissue interrogation methods likely need to have similar mechanical, thermal, electrical, acoustic and optical properties to those of adult human kidney.

Upon development and validation, it is anticipated that phantoms will be included alongside (not "spiked-into") every KPMP biopsy obtained from patient participants (to monitor changes that occur in tissue integrity during procurement, shipping, handling, etc.) and used as positive controls for each tissue interrogation platform (to assess experimental variability over time). As described above, it's unlikely that a single phantom will be able to accomplish all tasks. Thus, it is acknowledged that a panel or suite of phantoms – each optimized for a subset of tasks – will be required to accomplish all of these diverse tasks. Strong applications will fully consider the current tissue processing protocols and analytic pipelines used by the KPMP.

If the use of human tissue is proposed, applicants are encouraged to provide a written commitment from their local IRB to obtain consent for people to participate in the KPMP and for the collection, use, and sharing of human samples and appropriate affiliated metadata for research purposes. Award will be contingent on IRB approval.

Awardees will become full members of the KPMP and have the same responsibilities and access to data and results as other KPMP awardees. As such, all awardees must adhere to the KPMP Publications and Presentations (P&P) language and the participating **Institution(s)** must sign the KPMP Confidential Disclosure Agreement (CDA) and Material Transfer Agreement (MTA) documents.

Foreign Institutions are eligible to apply.

Application

Five (5) page applications requesting up to **$100,000 total costs per year for three years** are due **June 28, 2019**.

- The application is the standard PHS 398 form including face, abstract, detailed budget, biosketches (up to 5 pages each), and research plan. The research plan is limited to 5 pages and should include proposed plans for the design, fabrication, characterization, production and distribution of novel biomimetic phantoms for the KPMP and broader research community.
- All applications must propose appropriate quality control measures to show that the phantom reproducibly does what it's designed to do.
- All applications should carefully consider the current KPMP tissue processing protocols and analytic pipelines and discuss feasible approaches to develop and validate a phantom.
- Outstanding applications will provide preliminary data on the ability of developmental phantoms to (1) monitor changes over time in variables like tissue ischemia, hypoxia, redox, etc. and/or (2) maintain signal stability over time of appropriate reference transcripts, proteins, metabolites, etc. Relevant thermal, electrical, acoustic, and optical properties of the proposed phantoms must be discussed in detail, including predicted benefits and potential shortcomings.
- All applications must be milestone-driven and include a detailed list of expected deliverables and a well-defined timeline.
- Applicants must state a willingness to travel key personnel two times a year to the Bethesda, MD area for KPMP meetings.
- All applications must be submitted via the KPMP website (PDF format only please).

Budget

- Applications of 5 pages may request up to $100,000 (direct + indirect costs) total costs per year for three years. These costs must include travel of travel key personnel two times a year to the Bethesda area for KPMP meetings.
- A written summary of progress is due annually and following the completion of the funding period. Outyear funding is contingent on prior year progress.
- Awards will be made as subcontracts from the KPMP Central Hub (CH) at the University of Washington and not directly by the NIH.
- The number of awards will depend upon the number, quality, duration, and cost of the applications received.
- Funded awards are not allowed to submit a competitive renewal application and unfunded applications are not allowed to revise and resubmit an amended application.

Peer Review

- Each application will receive a primary review by multiple external referees and be given scores for Significance, Investigator, Innovation, Approach, and Environment and an Overall Score

based on the NIH Scoring System. Scores will range from 1 to 9, where a score of 1-3 indicates an application addressing a problem of high importance/interest in the field and may have some or no weaknesses. A score of 4-6 may be addressing a problem of high importance in the field, but weaknesses in the criteria bring down the overall impact to medium. A score of 7-9 may be addressing a problem of moderate/high importance in the field, but weaknesses in the criteria bring down the overall impact to low. A score of 5 is considered an average score. Please note that the Overall Score is NOT an average of the other scores.

- Reviewers will also strongly consider the following review criteria:
    - Does the application propose to form a new partnership that will add significant value to the KPMP?
    - Does the application propose rigorous QC/QA measures?
    - Does the application adequately consider the current KPMP tissue processing protocols and analytic pipelines and discuss feasible approaches to develop and validate a phantom(s)?
    - Are the proposed milestones, deliverables and timeline appropriate and feasible?
    - Does the applicant(s) state a willingness to travel key personnel two times a year to the Bethesda, MD area for KPMP meetings?
    - Does the applicant(s) state a willingness to adhere to all KPMP practices, protocols, and policies?
- Applications that are incomplete, non-compliant and/or nonresponsive will not be reviewed.
- No additional materials may be submitted after the receipt date.
- Scientists from the applicant institution are in conflict and excluded from review.
- Written comments will be provided for all reviewed applications.
- Reviewed applications will be considered by the KPMP Steering Committee (SC) and approved the KPMP External Expert Panel (EEP). Final funding decisions will be made by the NIDDK.
- All decisions are final, and appeals will not be accepted for applications submitted in response to this solicitation.

Timetable

Five (5) page applications requesting up to **$100,000 total costs per year for three years** are due **June 28, 2019 by 5 p.m. Pacific**.

Peer review: July 2019

Projected award date: August 2019

Attend first KPMP Meeting: Sept 24-25, 2019

Eligible Project Directors/Principal Investigators

- Applicants can NOT be currently supported by the KPMP.
- Current KPMP investigators are eligible to serve as unpaid consultants IF the application is proposing to form a NEW collaborative partnership. Overlap with existing funded activities is NOT allowed.

- 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.
- Early Stage Investigators are encouraged to apply, but they must have a full-time faculty position or an equivalent position at non-academic institutions.

Eligible Organizations

Higher Education Institutions

- Public/State Controlled Institution of Higher Education
- Private Institution of Higher Education

The following types of Higher Education Institutions are encouraged to apply for support as Public or Private Institutions of Higher Education:

- Hispanic-serving Institution; Historically Black Colleges and Universities (HBCUs);
- Tribally Controlled Colleges and Universities (TCCUs)
- Alaska Native and Native Hawaiian Serving Institutions; Nonprofit with 501(c)(3) IRS Status (Other than Institution of Higher Education)

Nonprofits Other Than Institutions of Higher Education

- Nonprofits with 501(c)(3) IRS Status (Other than Institutions of Higher Education)
- Nonprofits without 501(c)(3) IRS Status (Other than Institution of Higher Education)

For-Profit Organizations

- Small Businesses
- For-Profit Organization (Other than Small Businesses)

Foreign Institutions

- Non-domestic (non-U.S.) Entities (Foreign Institutions) are eligible to apply.
- Non-domestic (non-U.S.) components of U.S. Organizations are eligible to apply.
- Foreign components, as defined in the NIH Grants Policy Statement, are allowed.

Policies

Human Subjects. If the proposed research involves human subjects, then applicants must have approval from their local IRB prior to award to obtain consent for people to participate in the KPMP and for the collection, use, and sharing of human samples and appropriate affiliated metadata for research purposes.

Progress Reports. A written summary of progress of funded projects is due annually and following the completion of the funding period.

Sharing. Awardees must comply with the Public Health Service (PHS) policies relating to distribution of unique research resources produced with PHS funding and sharing of all research protocols, data, samples, and other research resources. Appropriate agreements must be executed prior to resource and data sharing. For further information, see the NIH Data Sharing Policy at https://grants.nih.gov/grants/policy/data_sharing/.

- The NIDDK intends the resource sharing plans for the data and samples generated under the KPMP to follow the policy and objectives stated in the original KPMP FOAs. Specifically, consistent with achieving the objectives of the KPMP, all study data (including, but not limited to, raw data, metadata, digital pathology images, and computational data sets), protocols (including analytical methods), technologies, biological samples (including but not limited to biopsies, nephrectomy tissue, tissue blocks, all slides in any form, blood, urine and stool) and other research resources are to be shared immediately across the consortium, and made publicly available to the larger community as soon as quality control procedures have been completed, and in accordance with KPMP Steering Committee (SC) policies, subject to approval by the NIDDK. Data derived from participant clinical records linked to biological data will only be made publicly available once risk of explicit or inferred identification has been mitigated in consultation with the KPMP Community Engagement Working Group and the Data and Safety Monitoring Board. Limited exceptions to the requirement for community dissemination may be identified by the KPMP SC and are subject to approval by the NIDDK. The NIDDK, in consultation with the SC for this project, will make all final decisions concerning data and sample deposition and data access policies, and all policies are subject to change by the NIDDK as deemed necessary to sustain program principles and priorities, or to ensure the highest standards for responsible research conduct within the project.
- Awardees will comply with and implement the recommendations and decisions of the SC with respect to the sharing of information, data, biosamples, protocols, resources, methods and analyses developed by the KPMP investigators under the KPMP.

Acknowledgment. Awardees must acknowledge the KPMP in all posters, manuscripts or scientific materials generated in part or whole using funds from the KPMP using the following text: “Research reported in this [poster/manuscript] was supported by the National Institute of Diabetes and Digestive and the Kidney Diseases (NIDDK) Kidney Precision Medicine Project (KPMP) Opportunity Pool, (www.kpmp.org), under award number U2CDK114886.”

Contact Information

For questions, contact: KPMP Administrator at kpmp@uw.edu