Grant Number: 5U24DK110791-04
FAIN: U24DK110791

Principal Investigator(s):
(b)(6)

Project Title: University of Pittsburgh as the GUDMAP Tissue Hub and Collection Site

(b)(6)
University of Pittsburgh
(b)(6)
Pittsburgh, PA 152132303

Award e-mailed to: ornih@offres.pitt.edu

Period Of Performance:
Budget Period: 06/01/2019 – 05/31/2020
Project Period: 09/15/2016 – 05/31/2021

Dear Business Official:

The National Institutes of Health hereby awards a grant in the amount of $0 (see "Award Calculation" in Section I and "Terms and Conditions" in Section III) to UNIVERSITY OF PITTSBURGH AT PITTSBURGH in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 31 USC 6305 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award including the "Terms and Conditions" is acknowledged by the grantee when funds are drawn down or otherwise obtained from the grant payment system.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as "Research reported in this publication was supported by the National Institute Of Diabetes And Digestive And Kidney Diseases of the National Institutes of Health under Award Number U24DK110791. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health." Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Award recipients must promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under NIH awards will be free from bias resulting from an Investigator's Financial Conflict of Interest (FCOI), in accordance with the 2011 revised regulation at 42 CFR Part 50 Subpart F. The Institution shall submit all FCOI reports to the NIH through the eRA Commons FCOI Module. The regulation does not apply to Phase I Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) awards. Consult the NIH website http://grants.nih.gov/grants/policy/coi/ for a link to the regulation and additional important information.

If you have any questions about this award, please contact the individual(s) referenced in Section IV.

Sincerely yours,

(b)(6)

Grants Management Officer
NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

Additional information follows

SECTION I – AWARD DATA – 5U24DK110791-04

Award Calculation (U.S. Dollars)

Salaries and Wages	$39,353
Fringe Benefits	$12,354
Personnel Costs (Subtotal)	$51,707
Materials & Supplies	$4,497
Travel	$1,697
Other	$7,528
Federal Direct Costs	$65,429
Federal F&A Costs	$34,571
Approved Budget	$100,000
Total Amount of Federal Funds Obligated (Federal Share)	$100,000
Less Unobligated Balance	$100,000
TOTAL FEDERAL AWARD AMOUNT	$0
AMOUNT OF THIS ACTION (FEDERAL SHARE)	$0

SUMMARY TOTALS FOR ALL YEARS		
YR	**THIS AWARD**	**CUMULATIVE TOTALS**
4	$0	$0
5	$613,000	$613,000

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

Fiscal Information:

CFDA Name:	Diabetes, Digestive, and Kidney Diseases Extramural Research
CFDA Number:	93.847
EIN:	1250965591A1
Document Number:	UDK110791A
PMS Account Type:	P (Subaccount)
Fiscal Year:	2019

IC	CAN	2019	2020
DK	8472288	$0	$613,000

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

NIH Administrative Data:
PCC: KDH KDB / **OC**: 414P / **Released**: (b)(6) 06/04/2019
Award Processed: 06/05/2019 12:08:14 AM

SECTION II – PAYMENT/HOTLINE INFORMATION – 5U24DK110791-04

For payment and HHS Office of Inspector General Hotline information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

SECTION III – TERMS AND CONDITIONS – 5U24DK110791-04

This award is based on the application submitted to, and as approved by, NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

a. The grant program legislation and program regulation cited in this Notice of Award.
b. Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.
c. 45 CFR Part 75.
d. National Policy Requirements and all other requirements described in the NIH Grants Policy Statement, including addenda in effect as of the beginning date of the budget

period.

e. Federal Award Performance Goals: As required by the periodic report in the RPPR or in the final progress report when applicable.
f. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(See NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm for certain references cited above.)

Research and Development (R&D): All awards issued by the National Institutes of Health (NIH) meet the definition of "Research and Development" at 45 CFR Part§ 75.2**.** As such, auditees should identify NIH awards as part of the R&D cluster on the Schedule of Expenditures of Federal Awards (SEFA). The auditor should test NIH awards for compliance as instructed in Part V, Clusters of Programs. NIH recognizes that some awards may have another classification for purposes of indirect costs. The auditor is not required to report the disconnect (i.e., the award is classified as R&D for Federal Audit Requirement purposes but non-research for indirect cost rate purposes), unless the auditee is charging indirect costs at a rate other than the rate(s) specified in the award document(s).

Carry over of an unobligated balance into the next budget period requires Grants Management Officer prior approval.

This award is subject to the requirements of 2 CFR Part 25 for institutions to receive a Dun & Bradstreet Universal Numbering System (DUNS) number and maintain an active registration in the System for Award Management (SAM). Should a consortium/subaward be issued under this award, a DUNS requirement must be included. See http://grants.nih.gov/grants/policy/awardconditions.htm for the full NIH award term implementing this requirement and other additional information.

This award has been assigned the Federal Award Identification Number (FAIN) U24DK110791. Recipients must document the assigned FAIN on each consortium/subaward issued under this award.

Based on the project period start date of this project, this award is likely subject to the Transparency Act subaward and executive compensation reporting requirement of 2 CFR Part 170. There are conditions that may exclude this award; see http://grants.nih.gov/grants/policy/awardconditions.htm for additional award applicability information.

In accordance with P.L. 110-161, compliance with the NIH Public Access Policy is now mandatory. For more information, see NOT-OD-08-033 and the Public Access website: http://publicaccess.nih.gov/.

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts with cumulative total value greater than $10,000,000 must report and maintain information in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made publicly available in the designated integrity and performance system (currently the Federal Awardee Performance and Integrity Information System (FAPIIS)). Full reporting requirements and procedures are found in Appendix XII to 45 CFR Part 75. This term does not apply to NIH fellowships.

Treatment of Program Income:
Other Research (Add/Deduct Option)

Clinical Trial Indicator: No
This award does not support any NIH-defined Clinical Trials. See the NIH Grants Policy Statement Section 1.2 for NIH definition of Clinical Trial.

RESTRICTION: Funds may only be used to pay for the cost of processing, shipping and handling tissue samples from external sources to the GUDMAP atlas projects.

Notice: Under governing regulations, Federal funds administered by the Department of Health and Human Services shall not be expended for research involving human subjects, and individuals shall not be enrolled in such research, without prior approval by the Office of Human Research Protections (OHRP) of an assurance to comply with the requirements of 45 CFR 46 to protect human research subjects. This restriction applies to all collaborating sites without OHRP-approved assurances, whether domestic or foreign, and compliance must be ensured by the awardee.

Notice: Under governing policy, federal funds administered by the Public Health Service (PHS) shall not be expended for research involving live vertebrate animals without prior approval by the Office of Laboratory Animal Welfare (OLAW) of an assurance to comply with the PHS policy on humane care and use of laboratory animals. This restriction applies to all performance sites (e.g., collaborating institutions, subcontractors, subgrantees) without OLAW-approved assurances, whether domestic or foreign.

The issuance of this award has been delayed due to administrative funding considerations. According to NIH policy, if pre-award costs are necessary, they may be approved by the authorized Institution
Official(s).

This award uses as an offset the unobligated balance ($100,000) from the -02 year Federal Financial Report.

In addition to the PI, the following individuals are named as key personnel:

(b)(6)

Written prior approval is required if any of the individual(s) named above withdraws from the project entirely, is absent from the project during any continuous period of 3 months or more, or reduces time devoted to the project by 25 percent or more from the level that was approved at the time of award.

This grant is in response to RFA/PA DK15-016. Acceptance of this award requires compliance with this solicitation. See the NIH Guide at http://grants.nih.gov/grants/guide/index.html for copy of the RFA/PA that includes administrative and programmatic requirements specific to this award.

In accordance with the Salary Limitation in NIH Guide Notice NOT-OD-19-031, Notice of Fiscal Policies in Effect for FY2019, none of the funds in this award shall be used to pay the salary of an individual at a rate in excess of Executive Level II. Therefore, this award and/or future years are adjusted accordingly, if applicable. See the Salary Cap Summary for a historical record of the salary cap, including effective dates.

Grantees can determine which progress reports are due through the website located at https://public.era.nih.gov/chl/public/search/index.jsp and should periodically check the site, which is updated on or around the 30th of each month. Progress report due dates are also available in the eRA Commons Status system. In addition, automatic e-mail notifications are sent to the PD/PI prior to due date.

As of October 17, 2014, the National Institutes of Health (NIH) requires grantees to submit all type 5 progress reports using the eRA Research Performance Progress Report (RPPR) module. Annual progress reports submitted in any format other than the RPPR will not be processed by the NIH and will require resubmission through the RPPR module in accordance with NIH Guide Notice NOT-OD-15-014 released October 16, 2014.

The following special terms of award are in addition to, and not in lieu of, otherwise applicable U.S. Office of Management and Budget (OMB) administrative guidelines, U.S. Department of Health and Human Services (DHHS) grant administration regulations at 45 CFR Parts 74 and 92 (Part 92 is applicable when State and local Governments are eligible to apply), and other HHS, PHS, and NIH grant administration policies.

The administrative and funding instrument used for this program will be the cooperative agreement, an "assistance" mechanism (rather than an "acquisition" mechanism), in which substantial NIH programmatic involvement with the awardees is anticipated during the performance of the activities.

Under the cooperative agreement, the NIH purpose is to support and stimulate the recipients' activities by involvement in and otherwise working jointly with the award recipients in a partnership role; it is not to assume direction, prime responsibility, or a dominant role in the activities. Consistent with this concept, the dominant role and prime responsibility resides with the awardees for the project as a whole, although specific tasks and activities may be shared among the awardees and the NIH as defined below.

The PD(s)/PI(s) will have the primary responsibility for:

- All aspects of the scientific activities, including defining the objectives and approaches, planning, conduct, analysis, and publication of results, interpretations, and conclusions of studies conducted under the terms and conditions of the cooperative agreement award.
- Collaborating with other investigators in the program for protocol development, sample, reagents and data sharing as appropriate, data quality control, and data organization
- Accountability towards the applicant organization officials and to the NIDDK for the performance and proper conduct of the research supported by the project in accordance with the terms and conditions of the award.
- Serving as a voting member of the Steering Committee and will attend the Planning Meeting and a Steering Committee meeting in the first year, two Steering Committee meetings a year in subsequent years and monthly teleconference calls.
- Accepting and implementing the goals, priorities, procedures, protocols, and policies agreed upon by the Steering Committee and subcommittees, and be responsible for close coordination and cooperation with the components of the GUDMAP consortium and with NIDDK staff.
- Adhering to PHS policy for the distribution of unique research resources produced with PHS funding as described under Special Requirements.
- Establishing written milestones for the project, in negotiation with NIDDK Project Staff prior to funding.
- Release all study design materials and procedure manuals into the public domain and/or make them available to other investigators, according to the approved plan for making data and materials available to the scientific community and the NIDDK, for the conduct of research at no charge other than the costs of reproduction and distribution, consistent with achieving the goals of this program initiative.
- Awardees will retain custody of and have primary rights to the data and software developed under these awards, subject to Government rights of access consistent with current DHHS, PHS, and NIH policies.

NIH staff will have substantial programmatic involvement that is above and beyond the normal stewardship role in awards, as described below:

- An NIH Project Scientist will have substantial programmatic involvement that is above and beyond the normal stewardship role in awards, as described below. However, the dominant role and prime responsibility for the project as a whole resides with the awardees, although specific tasks and activities in carrying out the studies will be shared by awardees and the NIDDK.
- NIDDK will designate a Project Officer and a Grants Management Specialist to provide normal program stewardship and administrative oversight of the cooperative agreement.
- NIDDK will form an External Advisory Committee (EAC), comprised of the NIDDK Project Scientist and other NIH extramural staff with relevant scientific expertise or who manage research grant programs that relate scientifically to the goals of the GUDMAP projects, and outside advisors selected by the NIDDK. The EAC will meet annually with the GUDMAP Steering Committee to review and assess GUDMAP and to advise NIDDK of

scientific developments and opportunities that may enhance the achievement of the GUDMAP goals.

- The NIDDK Project Scientist will attend and participate as a voting member in all meetings of the Steering Committee, and provide liaison between the Steering Committee and the External Advisory Committee.
- The NIDDK Project Scientist will help the Steering Committee develop and draft operating policies.
- The NIDDK Project Officer will review the scientific progress of the individual GUDMAP components, for compliance with operating policies developed by the Steering Committee, and may recommend to the NIDDK to withhold support, suspend, or terminate an award for lack of scientific progress or failure to adhere to policies established by the Steering Committee.
- An agency program official or IC program director will be responsible for the normal scientific and programmatic stewardship of the award and will be named in the award notice. The assigned Program Officer may also serve as an NIDDK Project Scientist.

Areas of Joint Responsibility include:

- Steering Committee - The NIDDK Project Scientist, PIs from the project funded through this FOA and RFA-DK-15-014, and RFA-DK-15-015 and voluntary representatives from the previously funded GUDMAP atlas projects funded under RFA-DK-11-001 will be responsible for forming a Steering Committee as defined below. An arbitration system, as detailed below, will be available to resolve disagreements among members of the Steering Committee. The Steering Committee will be the main governing board of the GUDMAP consortium. It will develop collaborative protocols, identify technological impediments to success and strategies to overcome them, develop shared software tools for disseminating information about the projects, and identify opportunities for sharing techniques and tools that might be developed in future GUDMAP atlas projects.
- The Steering Committee will be composed of the PIs from the project funded through this FOA, RFA-DK-15-014, and RFA-DK-15-015, representatives from the previously funded GUDMAP projects, and the NIDDK Project Scientist. The representatives and the PIs will each have one vote. The NIDDK Project Scientist for this project will have one vote. The Steering Committee will select a chairperson who will be someone other than an NIH staff member.
- The Steering Committee may, as it deems necessary, invite additional, non-voting scientific advisors to meetings at which research priorities and opportunities are discussed. The NIH reserves the right to augment the scientific or consumer expertise of the Steering Committee when necessary.
- There will be two Steering Committee meetings annually. The first meeting will be a Planning Meeting to be held in the Washington, DC area on **June 20-21, 2016**. At the Planning Meeting, the Steering Committee will be formed and a chairperson selected from among the members. At the Planning Meeting, the Steering Committee may: (a) draft a charter to detail policies and procedures, a process for monitoring compliance with the policies and procedures, and a process for recommending that the NIDDK Project Administrators act on evidence of non-compliance of any Consortium component with Steering Committee policies; (b) agree upon the terms of the charter; and (c) devise a plan for working with the GUDMAP database developers to provide ongoing input into database and website design.
- At the second and subsequent meetings, the Steering Committee will refine the GUDMAP scientific objectives and implementation as necessary, consistent with data produced by former and possible future GUDMAP atlas projects and from other laboratories.
- The Steering Committee will plan workshops, to which non-GUDMAP participants will also be invited, to inform the research community of the progress made toward development of the atlas, and to inform the research community of any technological advances related to the implementation of the GUDMAP website/database. The NIDDK Project Scientist, the External Advisory Committee, and other NIH staff as appropriate will provide the Steering Committee with advice on participants for the workshops and symposia.
- The Steering Committee may establish subcommittees as it deems appropriate.
- Awardee members of the Steering Committee will be required to accept and implement policies approved by the Steering Committee.

- The EAC will meet annually with the GUDMAP Steering Committee to review and assess the progress of the GUDMAP consortium and to advise NIDDK of scientific developments and opportunities that may enhance the achievement of the GUDMAP goals.

Dispute Resolution
Any disagreements that may arise in scientific or programmatic matters (within the scope of the award) between award recipients and the NIH may be brought to Dispute Resolution. A Dispute Resolution Panel will have three members: a designee of the Steering Committee chosen without NIH staff voting, one NIH designee, and a third designee with expertise in the relevant area who is chosen by the other two; in the case of individual disagreement, the first member may be chosen by the individual awardee. This special dispute resolution procedure does not alter the awardee's right to appeal an adverse action that is otherwise appealable in accordance with PHS regulation 42 CFR Part 50, Subpart D and DHHS regulation 45 CFR Part 16.

STAFF CONTACTS

The Grants Management Specialist is responsible for the negotiation, award and administration of this project and for interpretation of Grants Administration policies and provisions. The Program Official is responsible for the scientific, programmatic and technical aspects of this project. These individuals work together in overall project administration. Prior approval requests (signed by an Authorized Organizational Representative) should be submitted in writing to the Grants Management Specialist. Requests may be made via e-mail.

Grants Management Specialist: (b)(6)
Email: (b)(6) @extra.niddk.nih.gov **Phone**: (b)(6) **Fax**: (b)(6)

Program Official: (b)(6)
Email: (b)(6) @niddk.nih.gov **Phone**: (b)(6)

SPREADSHEET SUMMARY
GRANT NUMBER: 5U24DK110791-04

INSTITUTION: UNIVERSITY OF PITTSBURGH AT PITTSBURGH

Budget	Year 4	Year 5
Salaries and Wages	$39,353	$236,510
Fringe Benefits	$12,354	$74,246
Personnel Costs (Subtotal)	$51,707	$310,756
Materials & Supplies	$4,497	$27,027
Travel	$1,697	$10,200
Other	$7,528	$45,242
TOTAL FEDERAL DC	$65,429	$393,225
TOTAL FEDERAL F&A	$34,571	$219,775
TOTAL COST	$0	$613,000

Facilities and Administrative Costs	Year 4	Year 5
F&A Cost Rate 1	56.5%	56.5%
F&A Cost Base 1	$61,187	$388,983
F&A Costs 1	$34,571	$219,775

A. COVER PAGE

Project Title: University of Pittsburgh as the GUDMAP Tissue Hub and Collection Site	
Grant Number: 5U24DK110791-04	**Project/Grant Period:** 09/15/2016 - 05/31/2021
Reporting Period: 06/01/2018 - 05/31/2019	**Requested Budget Period:** 06/01/2019 - 05/31/2020
Report Term Frequency: Annual	**Date Submitted:** 04/02/2019
Program Director/Principal Investigator Information: (b)(6) **Phone number:** (b)(6) **Email:** (b)(6) @upmc.edu	**Recipient Organization:** UNIVERSITY OF PITTSBURGH AT PITTSBURGH UNIVERSITY OF PITTSBURGH OFFICE OF RESEARCH PITTSBURGH, PA 152132303 **DUNS:** 004514360 **EIN:** 1250965591A1 **RECIPIENT ID:**
Change of Contact PD/PI: N/A	
Administrative Official: (b)(6) UNIVERSITY OF PITTSBURGH 123 University Place (b)(6) PITTSBURGH, PA 15213 **Phone number:** (b)(6) **Email:** (b)(6) @pitt.edu	**Signing Official:** (b)(6) 123 University Place (b)(6) Pittsburgh, PA 15213 **Phone number:** (b)(6) **Email:** (b)(6) @pitt.edu
Human Subjects: Yes HS Exempt: No Exemption Number: Phase III Clinical Trial:	**Vertebrate Animals:** No
hESC: No	**Inventions/Patents:** No

B. ACCOMPLISHMENTS

B.1 WHAT ARE THE MAJOR GOALS OF THE PROJECT?

Aim 1: To generate an inventory of genitourinary tissue throughout normal human development The main goal of this aim is to develop a pipeline for the acquisition, quality control and distribution of human genitourinary samples obtained throughout development (6-42 weeks gestation). We currently have access to 6-24 week samples through the HSTB. However, for later gestational stages (25-42 weeks gestation) we have partnered with the International institute for the Advancement of Medicine. This will provide access to a novel resource for neonatal donation. We aim to collect and store a minimum of 5 samples per developmental week. Each of these samples will have histology, immunohistochemistry and in situ hybridization performed to assess tissue quality, protein and RNA integrity. Furthermore, we will obtain maternal blood, urine and amniotic fluid; based on the clinical situation and ability to procure. Based on our current experience, we get these biological
materials in most cases. Anonymized demographic information of each specimen will also be provided.

Aim 2: To provide fresh genitourinary tissue and biological research specimens This aim will generate an ongoing resource to distribute fresh developmental human genitourinary samples
from various stages (6-42 weeks) to the GUDMAP Atlas projects. The samples will be procured by a pathologist and inspected for mechanical damage. Samples will be collected from all qualified cases. The samples will then be subdivided based on the demand for fresh/frozen aliquots; the validation laboratory for quality control will keep a portion of each sample. The tissue samples will be immediately sent out for live cell use or immediately separated into distinct cellular populations before shipping based on researcher demands. Permissible annotating information; including demographics of each specimen, will also be provided.

B.1.a Have the major goals changed since the initial competing award or previous report?

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: ACCOMPLISHMENTS_2019 FINAL.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

For this reporting period, is there one or more Revision/Supplement associated with this award for which reporting is required?

No

B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

NOTHING TO REPORT

B.5 HOW HAVE THE RESULTS BEEN DISSEMINATED TO COMMUNITIES OF INTEREST?

There is very active e-mail and phone communication between the GUDMAP investigators, the Data Hub and the Tissue Hub. In addition, the Tissue Hub activities account for approximately 50% of the 90 minute long monthly consortium video conference calls.

B.6 WHAT DO YOU PLAN TO DO DURING THE NEXT REPORTING PERIOD TO ACCOMPLISH THE GOALS?

Continue providing materials to requesting investigators within the consortia. We will be performing extensive analyses on collected specimens both from a quality assessment perspective as well as to potentially assist GUDMAP investigators with specific pathology needs related to either localization studies and/or imaging.

ACCOMPLISHMENTS

Summary

The goal of this project is to provide human genitourinary tissues (kidneys, ureters, bladders and genital structures) to research projects funded in the GenitoUrinary Development Molecular Anatomy Project (GUDMAP), as part of a consortium to build a molecular atlas of human genitourinary development.

Biospecimen Collection/Quality Control:

The Tissue Hub has been shipping biospecimens to GUDMAP consortium members since June 2017. The Tissue Hub participates in monthly GUDMAP consortium phone calls for updates regarding the provision of tissue provided to GUDMAP Atlas projects, which provide a mechanism for feedback from consortium members about current tissue specimens, and to ascertain specific biospecimen and processing needs as projects evolve. The interface between the Tissue Hub and the Atlas projects remains collaborative in nature, and the Tissue Hub continues to strive to facilitate individual projects in this manner.

As part of the quality control process, the Validation Laboratory has been performing PCR-based genotyping on all biospecimens to document gender, in addition to an anatomical assessment performed by pathology since June 2018, in response to feedback from an investigator who had received one specimen of the incorrect gender in the prior grant year. Since that time, all PCR genotypes have corresponded to the gender determined by anatomical assessment. The Validation Laboratory has also performed pilot studies in collaboration with project PIs to identify optimal means of sample processing for the downstream applications for individual organs. For example, the validation laboratory performed tests of RNA quality following biospecimen collection in RPMI, storage and RNA isolation, compared to placing biospecimens in OCT, isolation of a subset of the tissue and RNA isolation. We recently received interest from the Cohn lab for additional biospecimens that can be provided by the Tissue Hub for single cell RNA sequencing, and engaged in technical discussions regarding the best way to generate viable single cell suspensions for single cell RNA sequencing from these tissues. The monthly feedback from GUDMAP investigators has been consistently positive regarding the tissue quality that has been received.

PRODUCTS

With the appropriate regulatory approvals and MTAs in place, the Tissue Hub is actively providing biospecimens to the GUDMAP investigators, with the current numbers from this funding year outlined in Table 1.

Table 1. Biospecimen disbursements from Tissue Hub to GUDMAP investigators.

GUDMAP Investigator	Fresh Tissue Disbursements June 1, 2018- March 1, 2019	
(b)(6)		(b)(4)
Totals		

In the prior grant funding year, the GUDMAP investigators identified a research need for biospecimens that could not be provided through the Health Sciences Tissue Bank at the University of Pittsburgh given how the biospecimens are collected. Given this, the Tissue Hub

developed a mechanism by which GUDMAP investigators can obtain these tissues through the Human Developmental Biology Resource (HDBR), and currently covers all the costs to the GUDMAP investigators for these shipments. The current numbers for this funding year are provided in Table 2.

Table 2. Shipments from Human Developmental Biology Resource (HDBR) to GUDMAP investigators.

GUDMAP Investigator	June 1, 2018- March 1, 2019	
(b)(6)		(b)(4)
Totals		

CHANGES/PROBLEMS

(b)(6); who was the (b)(6) Dr. (b)(6) was recruited by the Unviersity of Pittsburgh as (b)(6) replacement; and as the (b)(6) (b)(6) is replacing (b)(6) on the GUDMAP grant. This transition has been smooth and uneventful.

The Health Sciences Tissue Bank has been re-named the Pittsburgh Biospecimen Core in the past year. We do not anticipate that this will impact the function of the Tissue Hub in the GUDMAP consortium in any way.

For unclear reasons, the numbers of consents (N=29) from normal cases (N=81) in the last year has decreased significantly, which has impacted the number of specimens shipped from the Tissue Hub.

Due to the nature of the consenting process that is ethically and legally required for this type of tissue, we cannot be actively engaged in consenting. We have maintained active communication with our clinical partners in Obstetrics, and have not identified any significant changes that have occurred regarding the consenting process. Internally, we have reviewed our data monthly to evaluate other potential remediable factors, but the barrier is at the time of consent.

Our source for the younger time points is HDBR, which has been working hard with the investigators to provide the necessary samples. The quality of the specimens is sometimes not ideal for all groups and purposes, but the tissue shipments have in general increased. We act as a liason for this interaction and continue to work closely with HDBR.

BUDGETARY INFORMATION

The budget for Year 4 has minor adjustments in % effort and supplies; to maintain the total direct costs of the grant.

C. PRODUCTS

C.1 PUBLICATIONS

Are there publications or manuscripts accepted for publication in a journal or other publication (e.g., book, one-time publication, monograph) during the reporting period resulting directly from this award?

No

C.2 WEBSITE(S) OR OTHER INTERNET SITE(S)

Nothing to report

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

C.4 INVENTIONS, PATENT APPLICATIONS, AND/OR LICENSES

Have inventions, patent applications and/or licenses resulted from the award during the reporting period? No

If yes, has this information been previously provided to the PHS or to the official responsible for patent matters at the grantee organization?

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Category	Explanation
Research Material	The Tissue Hub will collect specimens as per the needs of the GUDMAP investigators. The biospecimens will be both from surgical pathology specimens (products of conception) as well as autopsy material (still-births). In addition, additional specimens may be collected depending on investigator and programmatic needs and direction. The specimen types that can be accrued, and possible specimen accrual limitations, have been discussed with consortia members. Collection protocols will continue to be modified and fine-tuned to reflect the needs and the reality of human biospecimen collections; since diagnostic assessment is the primary purpose.
Data or Databases	The data collected and provided by the Hub will be in two broad categories. Firstly, we will provide annotation information related to the specimens collected for the GUDMAP investigators. The data elements to be collected have been defined by the consortium. The data will be securely provided to the Data Hub, which will host this information. The second major data component will be imaging data generated from the specimens and slides etc. In addition, molecular data will also be generated from select specimens.

D. PARTICIPANTS

D.1 WHAT INDIVIDUALS HAVE WORKED ON THE PROJECT?

Commons ID	S/K	Name	Degree(s)	Role	Cal	Aca	Sum	Foreign Org	Country	SS
(b)(6)	Y	(b)(6)	MD	PD/PI	(b)(6)					NA
	N			QC Manager						NA
	N			HSTB Supervisor						NA
	N			Project Manager						NA
	N			Data Coordinator						NA
(b)(6)	N			Co-Investigator						NA
	N			Technician						NA
	N			Technician						NA
(b)(6)	N		BS,OTH,PHD	Co-Investigator						NA
	N		BS,MS,MD	Co-Investigator						NA
	N			Co-Investigator						NA
	N			Student						NA
	N			Technician						NA

Glossary of acronyms:
S/K - Senior/Key
DOB - Date of Birth
Cal - Person Months (Calendar)
Aca - Person Months (Academic)
Sum - Person Months (Summer)
Foreign Org - Foreign Organization Affiliation
SS - Supplement Support
RE - Reentry Supplement
DI - Diversity Supplement
OT - Other
NA - Not Applicable

D.2 PERSONNEL UPDATES

D.2.a Level of Effort

Will there be, in the next budget period, either (1) a reduction of 25% or more in the level of effort from what was approved by the agency for the PD/PI(s) or other senior/key personnel designated in the Notice of Award, or (2) a reduction in the level of effort below the minimum amount of effort required by the Notice of Award?

No

D.2.b New Senior/Key Personnel

Are there, or will there be, new senior/key personnel?

Yes

File uploaded: New_Investigator_(b)(6) pdf

D.2.c Changes in Other Support

Has there been a change in the active other support of senior/key personnel since the last reporting period?

Yes

File uploaded: Other Support RPPR.pdf

D.2.d New Other Significant Contributors

Are there, or will there be, new other significant contributors?

No

D.2.e Multi-PI (MPI) Leadership Plan

Will there be a change in the MPI Leadership Plan for the next budget period?

NA

For New and Renewal Applications (PHS 398) – DO NOT SUBMIT UNLESS REQUESTED

PHS 398 OTHER SUPPORT

Provide active and pending support for all senior/key personnel. **Other Support includes all financial resources, whether Federal, non-Federal, commercial or institutional, available in direct support of an individual's research endeavors, including but not limited to research grants, cooperative agreements, contracts, and/or institutional awards.** Training awards, prizes, or gifts do not need to be included.

There is no "form page" for other support. Information on other support should be provided in the *format* shown below, using continuation pages as necessary. ***Include the principal investigator's name at the top and number consecutively with the rest of the application.*** The sample below is intended to provide guidance regarding the type and extent of information requested.
For instructions and information pertaining to the use of and policy for other support, see Other Support in the Supplemental Instructions, Part III, Policies, Assurances, Definitions, and Other Information.
Effort devoted to projects must be measured using person months. Indicate calendar, academic, and/or summer months associated with each project.

Format

NAME OF INDIVIDUAL (b)(6)
ACTIVE/PENDING

ACTIVE

(b)(6)

(b)(6)

PENDING

NONE

OVERLAP: No Overlap

OTHER SUPPORT

(b)(6)

ACTIVE

(b)(6)

PENDING

None

OVERLAP

None

E. IMPACT

E.1 WHAT IS THE IMPACT ON THE DEVELOPMENT OF HUMAN RESOURCES?

Not Applicable

E.2 WHAT IS THE IMPACT ON PHYSICAL, INSTITUTIONAL, OR INFORMATION RESOURCES THAT FORM INFRASTRUCTURE?

NOTHING TO REPORT

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

Not Applicable

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?

NOTHING TO REPORT

F. CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

F.2 ACTUAL OR ANTICIPATED CHALLENGES OR DELAYS AND ACTIONS OR PLANS TO RESOLVE THEM

NOTHING TO REPORT

F.3 SIGNIFICANT CHANGES TO HUMAN SUBJECTS, VERTEBRATE ANIMALS, BIOHAZARDS, AND/OR SELECT AGENTS

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. SPECIAL REPORTING REQUIREMENTS

G.1 SPECIAL NOTICE OF AWARD TERMS AND FUNDING OPPORTUNITIES ANNOUNCEMENT REPORTING REQUIREMENTS

NOTHING TO REPORT

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

G.4.a Does the project involve human subjects?

Yes

Is the research exempt from Federal regulations?

No

Does this project involve a clinical trial?

No

G.4.b Inclusion Enrollment Data

Report Attached: Research on tissue from an elective or spontaneous abortion < 24 weeks gestation

G.4.c ClinicalTrials.gov

Does this project include one or more applicable clinical trials that must be registered in ClinicalTrials.gov under FDAAA?

No

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Are there personnel on this project who are newly involved in the design or conduct of human subjects research?

No

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

Does this project involve human embryonic stem cells (only hESC lines listed as approved in the NIH Registry may be used in NIH funded research)?

No

G.7 VERTEBRATE ANIMALS

Does this project involve vertebrate animals?

No

G.8 PROJECT/PERFORMANCE SITES

Organization Name:	DUNS	Congressional	Address

		District	
Primary: University of Pittsburgh	004514360	PA-018	(b)(6)
University of Pittsburgh	004514360	PA-018	
University of Pittsburgh	004514360	PA-018	(b)(4); (b)(6)
UNIVERSITY OF PITTSBURGH AT PITTSBURGH	004514360	PA-018	UNIVERSITY OF PITTSBURGH OFFICE OF RESEARCH PITTSBURGH PA 152132303
UNIVERSITY OF PITTSBURGH AT PITTSBURGH	004514360		UNIVERSITY OF PITTSBURGH OFFICE OF RESEARCH PITTSBURGH PA 152132303
University of Pittsburgh	004514360	PA-014	(b)(6)
University of Pittsburgh	004514360	PA-014	
University of Pittsburgh	004514360	PA-014	(b)(4); (b)(6)
UNIVERSITY OF PITTSBURGH AT PITTSBURGH	004514360		UNIVERSITY OF PITTSBURGH OFFICE OF RESEARCH PITTSBURGH PA 152132303

G.9 FOREIGN COMPONENT

No foreign component

G.10 ESTIMATED UNOBLIGATED BALANCE

G.10.a Is it anticipated that an estimated unobligated balance (including prior year carryover) will be greater than 25% of the current year's total approved budget?

No

G.11 PROGRAM INCOME

Is program income anticipated during the next budget period?

No

G.12 F&A COSTS

Is there a change in performance sites that will affect F&A costs?

No

Inclusion Enrollment Report

Inclusion Data Record (IDR) #: 132193

Using an Existing Dataset or Resource: No

Delayed Onset Study ?: No

Clinical Trial: No

Enrollment Location: Domestic

NIH Defined Phase III Clinical Trial: No

Study Title: Research on tissue from an elective or spontaneous abortion < 24 weeks gestation

Planned Enrollment

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/Alaska Native	0	0		0	0					0
Asian	50	0		0	0					50
Native Hawaiian or Other Pacific Islander	0	0		0	0					0
Black or African American	100	0		10	0					110
White	200	0		20	0					220
More than One Race	0	0		20	0					20
Unknown or Not Reported										
Total	**350**	**0**		**50**	**0**					**400**

Cumulative Enrollment

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/Alaska Native	0	0	0	0	0	0	0	0	0	0
Asian	0	50	0	0	0	0	0	0	0	50
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0
Black or African American	0	100	0	10	0	0	0	0	0	110
White	0	200	0	20	0	0	0	0	0	220
More than One Race	0	0	0	20	0	0	0	0	0	20
Unknown or Not Reported	0	0	0	0	0	0	0	0	0	0
Total	**0**	**350**	**0**	**50**	**0**	**0**	**0**	**0**	**0**	**400**

RESEARCH & RELATED BUDGET - SECTION A & B

ORGANIZATIONAL DUNS*: 004514360

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: UNIVERSITY OF PITTSBURGH AT PITTSBURGH

Start Date*: 06-01-2019 **End Date*:** 05-31-2020

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1.		(b)(6)				Project Lead	(b)(6)				37,920.00	9,809.00	47,729.00
2.						Co-Investigator					3,083.00	797.00	3,880.00
3.						Co-Investigator					6,165.00	1,595.00	7,760.00
4.						Co-Investigator					30,956.00	8,007.00	38,963.00
5.						Co-Investigator					23,540.00	6,089.00	29,629.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **127,961.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
9	Supervisors, Techs, and Data Coordinator	(b)(6)			134,846.00	47,949.00	182,795.00
9	**Total Number Other Personnel**					**Total Other Personnel**	**182,795.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**310,756.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E

ORGANIZATIONAL DUNS*: 004514360

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: UNIVERSITY OF PITTSBURGH AT PITTSBURGH

Start Date*: 06-01-2019 **End Date*:** 05-31-2020

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	10,200.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**10,200.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		0.00
2. Stipends		0.00
3. Travel		0.00
4. Subsistence		0.00
5. Other:		
0 Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**0.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K

ORGANIZATIONAL DUNS*: 004514360

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: UNIVERSITY OF PITTSBURGH AT PITTSBURGH

Start Date*: 06-01-2019 **End Date*:** 05-31-2020

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	27,027.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. PBC Tissue embedding/processing, storage and disbursement	4,242.00
9. Website maintenance, project management tool, BIOS	8,000.00
10. New Castle Shipping costs	33,000.00
Total Other Direct Costs	**72,269.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**393,225.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. MTDC	56.5	388,983.00	219,776.00
		Total Indirect Costs	**219,776.00**

Cognizant Federal Agency U.S. Department of Health and Human Services, (b)(6)

(Agency Name, POC Name, and POC Phone Number) (b)(6)

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**613,001.00**

J. Fee	Funds Requested ($)*
	0.00

K. Budget Justification* File Name: Budget Justification Final Year 4.pdf

(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

BUDGET JUSTIFICATION – Year 4

Personnel

(b)(6): PI, Effort = (b)(6) is the (b)(6) of the University of Pittsburgh and a practicing pathologist with subspecialty training in Genitourinary Pathology. He will be responsible for the oversight of the project. This will include interfacing and working with internal collaborators to ensure accrual and annotation of the appropriate specimens. He will also interact with the external collaborators and clients to ensure appropriate specimen aggregation and disbursement. He will work closely with NIDDK to ensure successful execution of the project, meeting the mission and goals of the Tissue Core. Annual effort of (b)(6) is requested.

(b)(6): Effort = (b)(6) This (b)(6) will be responsible for coordination and management of day to day operations. She supervises PBC staff members and will manage the overall efforts of the PBC and set operational standards related to the PBC scope of work. She will assure proper communication and resolution conflicts and issues.

1. Tissue Hub Infrastructure Support

A crucial component of this application is the infrastructure for the Tissue Hub, which will include personnel for the development and maintenance of a secure web-based interface for GUDMAP investigators, assurance of regulatory compliance, data collection and record-keeping, and management of the quality assurance program associated with this project.

(b)(6): Co-I, Effort = (b)(6) is the (b)(6) and will be the director of the Tissue hub Infrastructure. He also serves as the faculty in-charge of the informatics requirements of PBC. He provides direction and advice related to the different Information systems and tools used by PBC. He is also the director of the Imaging core; a subsidiary of PBC. The imaging core will perform whole slide image acquisition and provide access to these images for the Tissue Core clients. Annual effort of (b)(6) is requested.

(b)(6) Effort = (b)(6) This (b)(6) will be responsible for project intake, tracking and recording keeping. She will coordinate the GUDMAP investigator requests to the GUDMAP-Human Tissue Repository including documenting the needs of the investigator, assuring regulatory compliance, coordinating with tissue and data collection staff members and assuring proper completion and shipping of requests. Annual effort of (b)(6) is requested.

(b)(6): Effort = (b)(6) This (b)(6) will be responsible for the quality program. He will manage all aspects of quality management including record keeping, training of staff members to standard operating procedures (SOPs), data entry practices and audits, and quality related events. He will coordinate the overall record keeping and management of the quality metrics from the tissue collection and data entry processes with the quality measurements performed through the Department of Pediatrics team.

(b)(6) Effort = (b)(6) This (b)(6) will be responsible for overall management of the Biospecimen Inventory and Operations System with regard to the this project. He will manage the specimen search process, control the data entry lexicon as needed, and provide reports of collection activity for investigators who request samples and as needed for other purposes. He will maintain the data integrity and make corrections and amendments based on the quality control activities. In the case that new fields and library elements are required he will manage that process in conjunction with the Project Manager and Quality Manager. He will be required to produce final sample pick lists as specimens are disbursed.

(b)(6): Effort = (b)(6) is the technician responsible for processing tissues, immunohistochemistry and immunofluorescence needs of the project. He is also the supervisor of the Research Histology core facility and is responsible for the development of specialized techniques required by the program and for processes not included in the fee-for-service activity.

(b)(6): Effort = (b)(6) The (b)(6) will be responsible for aggregating information from the different information systems on the specimens offered as part of the Tissue Core. This will include pathology information as well as more specialized information (like cytogenetics); if applicable. The data coordinator will work with the Project manager on cohort identification for

the different requests. In addition the data coordinator will also be responsible for providing data to the clients of the Tissue Core.

2. Fetal Tissue Procurement Laboratory ((b)(4); (b)(6)

All of the fetal tissue will be collected at (b)(4) undergo a gross examination, and then be transported to the validation laboratory for further assessment prior to distribution.

(b)(6) **:** Co-I, Effort = (b)(6) is the (b)(6) (b)(6) He will be responsible for evaluating appropriate surgical pathology and autopsy specimens, and overseeing collection of the biological materials for the Tissue Core and will act as the director of the tissue procurement laboratory. He will perform the clinical evaluation of the gross genitourinary specimen and ensure quality control of the dissection to minimize mechanical disruption. He will train the staff to obtain early gestational age genitourinary specimens, and work closely with (b)(6) to perform routine and specialized histological assessment of the appropriate specimens. Annual effort of (b)(6) s requested.

Kindly note that (b)(6) **retired and** (b)(6) **was recruited by the Unviersity of Pittsburgh as** (b)(6) **replacement.** (b)(6) **is replacing** (b)(6) **on the GUDMAP grant.**

(b)(6) **:** Effort = (b)(6) This PBC tissue bank technician and will perform the day-to-day tasks associated with the collection of specimens. This includes maintaining a working knowledge of all SOPs related to the ongoing collections that are requested by the GUDMAP investigators. She will coordinate with the clinical departments within (b)(4); (b)(6) interface with the Pathology and other hospital staff members as required to obtain the requested specimens and enter data related to each case in the BIOS.

(b)(6) Effort = (b)(6) This (b)(6) will perform the day-to-day tasks associated with the collection of specimens. This includes maintaining a working knowledge of all SOPs related to the ongoing collections that are requested by the GUDMAP investigators. She will coordinate with the clinical departments within (b)(4); (b)(6) interface with the Pathology and other hospital staff members as required to obtain the requested specimens and enter data related to each case in the BIOS.

3. Validation Laboratory (b)(6)

The validation laboratory will perform quality assurance measures, as per GUDMAP project needs (eg. histological assessment, *in situ* hybridization and RNA isolation).

(b)(6) Co-I, Effort = (b)(6) is a kidney developmental biologist with over (b)(6) studying the genitourinary tract and will act as the director of the validation laboratory. Furthermore, he is also a classically trained human anatomist, histologist and embryologist. The quality assurance of the specimens will be performed by at least two independent evaluations (b)(6) for GUDMAP project needs. (b)(6) will work closely with (b)(6) to train staff to perform the gross dissection for early gestational age genitourinary tissues, and tissues not currently being obtained by the Tissue Bank, as per GUDMAP project needs. He will also oversee the training of (b)(6) (tissue hub technician) in all aspects of dissection, histology and molecular evaluation of the fetal tissues.

(b)(6) **:** Co-I, Effort = (b)(6) is a clinician scientist (Pediatric Nephrologist) with a research program related to kidney development and will act as the co-director of the validation laboratory. She has a thorough understanding of genitourinary development. She will participate in quality assurance of specimens as noted above. Furthermore, (b)(6) will provide direction and advice regarding the clinical parameters that will be used to screen fetal and neonatal tissues to exclude pathological specimens, and will evaluate individual cases as needed.

(b)(6) **:** Effort = (b)(6) This grant will fund (b)(6) of the technicians salary. This technician will perform all the required validation of the specimens including: histology, immunohistochemistry, in situ hybridization, cell isolation and real time PCR.

Supplies

PBC Consumable Laboratory Supplies: (b)(4) is requested for sample collections, integrity, maintenance, and transport including sample and shipping containers, dry ice, and other basic supplies.

Shipping: Funds are requested for the shipment of tissue from (b)(4) to the participating GUDMAP investigators, (b)(4) is requested in year 4.

Validation Laboratory Consumable Laboratory Supplies: (b)(4) monthly will be required to purchase reagents for staining, immunohistochemistry and in situ reagents as well as cell, culture medium and consumable plastics related to these processes. These processes will be performed in response to the needs of the GUDMAP investigators.

Travel

Pathology: The Project PI and PBC staff will need to travel to GUDMAP consortia meetings, to be held twice a year. A total of $4,200 is allocated for this travel in year 4.

Validation Laboratories: The Project co-investigators will need to travel to GUDMAP consortia meetings, to be held twice a year. (b)(6) will also attend the American Society of Nephrology meeting where GUDMAP typically has a booth. A total of $6,000 is allocated for this travel in year 4.

Other Expenses

Tissue embedding/processing, storage, and disbursement: (b)(4) for year 4. These are billable services based on the fiscal parameters in place within the University of Pittsburgh for the PBC. Tissue embedding and processing will be required at all levels for quality management and to provide product to GUDMAP investigators. Storage costs are based on the partial cost of a freezer with a 10 year life span plus projected maintenance and certification costs. The cost for disbursement of samples to GUDMAP investigators will be charged to the account award for this project.

Website maintenance, project management tool, BIOS, image acquisition: $8,000. Resources will be required to maintain and update our internally developed inventory management system (BIOS). The project management tool is internally developed and is the mechanism for starting and following the progress of the request from the client. The clients will be provided access to the contents of the resource via a Sharepoint link that will be password protected. Whole slide image acquisition will be done to offer clients access to high quality images of the specimens in the resource. These images will be from routine and specialized histologic and immunohistochemical/ in-situ protocols. We also have capabilities for image analysis and will offer, if required.

Grant Number: 5U24DK110791-03 REVISED
FAIN: U24DK110791

Principal Investigator(s):
(b)(6)

Project Title: University of Pittsburgh as the GUDMAP Tissue Hub and Collection Site

(b)(6)
University of Pittsburgh
123 University Place, (b)(6)
(b)(6)
Pittsburgh, PA 152132303

Award e-mailed to: ornih@offres.pitt.edu

Period Of Performance:
Budget Period: 06/01/2018 – 05/31/2019
Project Period: 09/15/2016 – 05/31/2021

Dear Business Official:

The National Institutes of Health hereby revises this award (see "Award Calculation" in Section I and "Terms and Conditions" in Section III) to UNIVERSITY OF PITTSBURGH AT PITTSBURGH in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 31 USC 6305 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award including the "Terms and Conditions" is acknowledged by the grantee when funds are drawn down or otherwise obtained from the grant payment system.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as "Research reported in this publication was supported by the National Institute Of Diabetes And Digestive And Kidney Diseases of the National Institutes of Health under Award Number U24DK110791. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health." Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Award recipients must promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under NIH awards will be free from bias resulting from an Investigator's Financial Conflict of Interest (FCOI), in accordance with the 2011 revised regulation at 42 CFR Part 50 Subpart F. The Institution shall submit all FCOI reports to the NIH through the eRA Commons FCOI Module. The regulation does not apply to Phase I Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) awards. Consult the NIH website http://grants.nih.gov/grants/policy/coi/ for a link to the regulation and additional important information.

If you have any questions about this award, please contact the individual(s) referenced in Section IV.

Sincerely yours,

(b)(6)

Grants Management Officer
NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

Additional information follows

SECTION I – AWARD DATA – 5U24DK110791-03 REVISED

Award Calculation (U.S. Dollars)

Salaries and Wages	$208,341
Fringe Benefits	$65,717
Personnel Costs (Subtotal)	$274,058
Materials & Supplies	$18,980
Travel	$7,451
Other	$32,729
ADP/Computer Services	$5,499
Federal Direct Costs	$338,717
Federal F&A Costs	$188,668
Approved Budget	$527,385
Total Amount of Federal Funds Obligated (Federal Share)	$527,385
Less Unobligated Balance	$106,761
TOTAL FEDERAL AWARD AMOUNT	$420,624
AMOUNT OF THIS ACTION (FEDERAL SHARE)	$0

SUMMARY TOTALS FOR ALL YEARS		
YR	**THIS AWARD**	**CUMULATIVE TOTALS**
3	$420,624	$420,624
4	$613,001	$613,001
5	$613,001	$613,001

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

Fiscal Information:

CFDA Name:	Diabetes, Digestive, and Kidney Diseases Extramural Research
CFDA Number:	93.847
EIN:	1250965591A1
Document Number:	UDK110791A
PMS Account Type:	P (Subaccount)
Fiscal Year:	2018

IC	CAN	2018	2019	2020
DK	8472288	$420,624	$613,001	$613,001

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

NIH Administrative Data:
PCC: KDH KDB / **OC**: 41029 / **Released**: (b)(6) 01/15/2020
Award Processed: 01/15/2020 07:00:54 PM

SECTION II – PAYMENT/HOTLINE INFORMATION – 5U24DK110791-03 REVISED

For payment and HHS Office of Inspector General Hotline information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

SECTION III – TERMS AND CONDITIONS – 5U24DK110791-03 REVISED

This award is based on the application submitted to, and as approved by, NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

a. The grant program legislation and program regulation cited in this Notice of Award.
b. Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.
c. 45 CFR Part 75.

d. National Policy Requirements and all other requirements described in the NIH Grants Policy Statement, including addenda in effect as of the beginning date of the budget period.
e. Federal Award Performance Goals: As required by the periodic report in the RPPR or in the final progress report when applicable.
f. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(See NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm for certain references cited above.)

Research and Development (R&D): All awards issued by the National Institutes of Health (NIH) meet the definition of "Research and Development" at 45 CFR Part§ 75.2**.** As such, auditees should identify NIH awards as part of the R&D cluster on the Schedule of Expenditures of Federal Awards (SEFA). The auditor should test NIH awards for compliance as instructed in Part V, Clusters of Programs. NIH recognizes that some awards may have another classification for purposes of indirect costs. The auditor is not required to report the disconnect (i.e., the award is classified as R&D for Federal Audit Requirement purposes but non-research for indirect cost rate purposes), unless the auditee is charging indirect costs at a rate other than the rate(s) specified in the award document(s).

Carry over of an unobligated balance into the next budget period requires Grants Management Officer prior approval.

This award is subject to the requirements of 2 CFR Part 25 for institutions to receive a Dun & Bradstreet Universal Numbering System (DUNS) number and maintain an active registration in the System for Award Management (SAM). Should a consortium/subaward be issued under this award, a DUNS requirement must be included. See http://grants.nih.gov/grants/policy/awardconditions.htm for the full NIH award term implementing this requirement and other additional information.

This award has been assigned the Federal Award Identification Number (FAIN) U24DK110791. Recipients must document the assigned FAIN on each consortium/subaward issued under this award.

Based on the project period start date of this project, this award is likely subject to the Transparency Act subaward and executive compensation reporting requirement of 2 CFR Part 170. There are conditions that may exclude this award; see http://grants.nih.gov/grants/policy/awardconditions.htm for additional award applicability information.

In accordance with P.L. 110-161, compliance with the NIH Public Access Policy is now mandatory. For more information, see NOT-OD-08-033 and the Public Access website: http://publicaccess.nih.gov/.

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts with cumulative total value greater than $10,000,000 must report and maintain information in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made publicly available in the designated integrity and performance system (currently the Federal Awardee Performance and Integrity Information System (FAPIIS)). Full reporting requirements and procedures are found in Appendix XII to 45 CFR Part 75. This term does not apply to NIH fellowships.

Treatment of Program Income:
Other Research (Add/Deduct Option)

Clinical Trial Indicator: No
This award does not support any NIH-defined Clinical Trials. See the NIH Grants Policy Statement Section 1.2 for NIH definition of Clinical Trial.

This revision reflects an authorized carryover of $106,761 ($68,275 direct costs and $38,486 F&A costs) from the -02 year as requested on and may be used for the stated purpose only.

The following terms from the previous Notice of Award also apply to this award:

RESTRICTION: Funds may only be used to pay for the cost of acquiring, processing and shipping tissue samples to the GUDMAP atlas projects. This includes covering the cost of processing and shipping tissue from external sources.

Notice: Under governing regulations, Federal funds administered by the Department of Health and Human Services shall not be expended for research involving human subjects, and individuals shall not be enrolled in such research, without prior approval by the Office of Human Research Protections (OHRP) of an assurance to comply with the requirements of 45 CFR 46 to protect human research subjects. This restriction applies to all collaborating sites without OHRP-approved assurances, whether domestic or foreign, and compliance must be ensured by the awardee.

Notice: Under governing policy, federal funds administered by the Public Health Service (PHS) shall not be expended for research involving live vertebrate animals without prior approval by the Office of Laboratory Animal Welfare (OLAW) of an assurance to comply with the PHS policy on humane care and use of laboratory animals. This restriction applies to all performance sites (e.g., collaborating institutions, subcontractors, subgrantees) without OLAW-approved assurances, whether domestic or foreign.

The issuance of this award has been delayed due to administrative funding considerations. According to NIH policy, if pre-award costs are necessary, they may be approved by the authorized Institution Official(s).

In addition to the PI, the following individuals are named as key personnel:

(b)(6)

Written prior approval is required if any of the individual(s) named above withdraws from the project entirely, is absent from the project during any continuous period of 3 months or more, or reduces time devoted to the project by 25 percent or more from the level that was approved at the time of award.

This grant is in response to RFA/PA DK15-016. Acceptance of this award requires compliance with this solicitation. See the NIH Guide at http://grants.nih.gov/grants/guide/index.html for copy of the RFA/PA that includes administrative and programmatic requirements specific to this award.

In accordance with NIH Guide Notice NOT-OD-18-137, Notice of Salary Limitation on Grants, Cooperative Agreements, and Contracts, none of the funds in this award shall be used to pay the salary of an individual at a rate in excess of the applicable salary cap. Therefore, this award and/or future years are adjusted accordingly, if applicable. See the Salary Cap Summary for a historical record of the salary cap, including effective dates.

Grantees can determine which progress reports are due through the website located at https://public.era.nih.gov/chl/public/search/index.jsp and should periodically check the site, which is updated on or around the 30th of each month. Progress report due dates are also available in the eRA Commons Status system. In addition, automatic e-mail notifications are sent to the PD/PI prior to due date.

As of October 17, 2014, the National Institutes of Health (NIH) requires grantees to submit all type 5 progress reports using the eRA Research Performance Progress Report (RPPR) module. Annual progress reports submitted in any format other than the RPPR will not be

processed by the NIH and will require resubmission through the RPPR module in accordance with NIH Guide Notice NOT-OD-15-014 released October 16, 2014.

The following special terms of award are in addition to, and not in lieu of, otherwise applicable U.S. Office of Management and Budget (OMB) administrative guidelines, U.S. Department of Health and Human Services (DHHS) grant administration regulations at 45 CFR Parts 74 and 92 (Part 92 is applicable when State and local Governments are eligible to apply), and other HHS, PHS, and NIH grant administration policies.

The administrative and funding instrument used for this program will be the cooperative agreement, an "assistance" mechanism (rather than an "acquisition" mechanism), in which substantial NIH programmatic involvement with the awardees is anticipated during the performance of the activities.

Under the cooperative agreement, the NIH purpose is to support and stimulate the recipients' activities by involvement in and otherwise working jointly with the award recipients in a partnership role; it is not to assume direction, prime responsibility, or a dominant role in the activities. Consistent with this concept, the dominant role and prime responsibility resides with the awardees for the project as a whole, although specific tasks and activities may be shared among the awardees and the NIH as defined below.

The PD(s)/PI(s) will have the primary responsibility for:

- All aspects of the scientific activities, including defining the objectives and approaches, planning, conduct, analysis, and publication of results, interpretations, and conclusions of studies conducted under the terms and conditions of the cooperative agreement award.
- Collaborating with other investigators in the program for protocol development, sample, reagents and data sharing as appropriate, data quality control, and data organization
- Accountability towards the applicant organization officials and to the NIDDK for the performance and proper conduct of the research supported by the project in accordance with the terms and conditions of the award.
- Serving as a voting member of the Steering Committee and will attend the Planning Meeting and a Steering Committee meeting in the first year, two Steering Committee meetings a year in subsequent years and monthly teleconference calls.
- Accepting and implementing the goals, priorities, procedures, protocols, and policies agreed upon by the Steering Committee and subcommittees, and be responsible for close coordination and cooperation with the components of the GUDMAP consortium and with NIDDK staff.
- Adhering to PHS policy for the distribution of unique research resources produced with PHS funding as described under Special Requirements.
- Establishing written milestones for the project, in negotiation with NIDDK Project Staff prior to funding.
- Release all study design materials and procedure manuals into the public domain and/or make them available to other investigators, according to the approved plan for making data and materials available to the scientific community and the NIDDK, for the conduct of research at no charge other than the costs of reproduction and distribution, consistent with achieving the goals of this program initiative.
- Awardees will retain custody of and have primary rights to the data and software developed under these awards, subject to Government rights of access consistent with current DHHS, PHS, and NIH policies.

NIH staff will have substantial programmatic involvement that is above and beyond the normal stewardship role in awards, as described below:

- An NIH Project Scientist will have substantial programmatic involvement that is above and beyond the normal stewardship role in awards, as described below. However, the dominant role and prime responsibility for the project as a whole resides with the awardees, although specific tasks and activities in carrying out the studies will be shared by awardees and the NIDDK.
- NIDDK will designate a Project Officer and a Grants Management Specialist to provide normal program stewardship and administrative oversight of the cooperative agreement.
- NIDDK will form an External Advisory Committee (EAC), comprised of the NIDDK Project Scientist and other NIH extramural staff with relevant scientific expertise or who manage research grant programs that relate scientifically to the goals of the GUDMAP projects,

and outside advisors selected by the NIDDK. The EAC will meet annually with the GUDMAP Steering Committee to review and assess GUDMAP and to advise NIDDK of scientific developments and opportunities that may enhance the achievement of the GUDMAP goals.

- The NIDDK Project Scientist will attend and participate as a voting member in all meetings of the Steering Committee, and provide liaison between the Steering Committee and the External Advisory Committee.
- The NIDDK Project Scientist will help the Steering Committee develop and draft operating policies.
- The NIDDK Project Officer will review the scientific progress of the individual GUDMAP components, for compliance with operating policies developed by the Steering Committee, and may recommend to the NIDDK to withhold support, suspend, or terminate an award for lack of scientific progress or failure to adhere to policies established by the Steering Committee.
- An agency program official or IC program director will be responsible for the normal scientific and programmatic stewardship of the award and will be named in the award notice. The assigned Program Officer may also serve as an NIDDK Project Scientist.

Areas of Joint Responsibility include:

- Steering Committee - The NIDDK Project Scientist, PIs from the project funded through this FOA and RFA-DK-15-014, and RFA-DK-15-015 and voluntary representatives from the previously funded GUDMAP atlas projects funded under RFA-DK-11-001 will be responsible for forming a Steering Committee as defined below. An arbitration system, as detailed below, will be available to resolve disagreements among members of the Steering Committee. The Steering Committee will be the main governing board of the GUDMAP consortium. It will develop collaborative protocols, identify technological impediments to success and strategies to overcome them, develop shared software tools for disseminating information about the projects, and identify opportunities for sharing techniques and tools that might be developed in future GUDMAP atlas projects.
- The Steering Committee will be composed of the PIs from the project funded through this FOA, RFA-DK-15-014, and RFA-DK-15-015, representatives from the previously funded GUDMAP projects, and the NIDDK Project Scientist. The representatives and the PIs will each have one vote. The NIDDK Project Scientist for this project will have one vote. The Steering Committee will select a chairperson who will be someone other than an NIH staff member.
- The Steering Committee may, as it deems necessary, invite additional, non-voting scientific advisors to meetings at which research priorities and opportunities are discussed. The NIH reserves the right to augment the scientific or consumer expertise of the Steering Committee when necessary.
- There will be two Steering Committee meetings annually. The first meeting will be a Planning Meeting to be held in the Washington, DC area on **June 20-21, 2016**. At the Planning Meeting, the Steering Committee will be formed and a chairperson selected from among the members. At the Planning Meeting, the Steering Committee may: (a) draft a charter to detail policies and procedures, a process for monitoring compliance with the policies and procedures, and a process for recommending that the NIDDK Project Administrators act on evidence of non-compliance of any Consortium component with Steering Committee policies; (b) agree upon the terms of the charter; and (c) devise a plan for working with the GUDMAP database developers to provide ongoing input into database and website design.
- At the second and subsequent meetings, the Steering Committee will refine the GUDMAP scientific objectives and implementation as necessary, consistent with data produced by former and possible future GUDMAP atlas projects and from other laboratories.
- The Steering Committee will plan workshops, to which non-GUDMAP participants will also be invited, to inform the research community of the progress made toward development of the atlas, and to inform the research community of any technological advances related to the implementation of the GUDMAP website/database. The NIDDK Project Scientist, the External Advisory Committee, and other NIH staff as appropriate will provide the Steering Committee with advice on participants for the workshops and symposia.
- The Steering Committee may establish subcommittees as it deems appropriate.
- Awardee members of the Steering Committee will be required to accept and implement policies approved by the Steering Committee.

- The EAC will meet annually with the GUDMAP Steering Committee to review and assess the progress of the GUDMAP consortium and to advise NIDDK of scientific developments and opportunities that may enhance the achievement of the GUDMAP goals.

Dispute Resolution
Any disagreements that may arise in scientific or programmatic matters (within the scope of the award) between award recipients and the NIH may be brought to Dispute Resolution. A Dispute Resolution Panel will have three members: a designee of the Steering Committee chosen without NIH staff voting, one NIH designee, and a third designee with expertise in the relevant area who is chosen by the other two; in the case of individual disagreement, the first member may be chosen by the individual awardee. This special dispute resolution procedure does not alter the awardee's right to appeal an adverse action that is otherwise appealable in accordance with PHS regulation 42 CFR Part 50, Subpart D and DHHS regulation 45 CFR Part 16.
- See more at: http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-15-016.html#sthash.UY9M5nfL.dpuf

STAFF CONTACTS

The Grants Management Specialist is responsible for the negotiation, award and administration of this project and for interpretation of Grants Administration policies and provisions. The Program Official is responsible for the scientific, programmatic and technical aspects of this project. These individuals work together in overall project administration. Prior approval requests (signed by an Authorized Organizational Representative) should be submitted in writing to the Grants Management Specialist. Requests may be made via e-mail.

Grants Management Specialist: (b)(6)
Email: (b)(6) @extra.niddk.nih.gov **Phone**: (b)(6) **Fax**: (b)(6)

Program Official: (b)(6)
Email: (b)(6) @niddk.nih.gov **Phone**: (b)(6)

SPREADSHEET SUMMARY
GRANT NUMBER: 5U24DK110791-03 REVISED

INSTITUTION: UNIVERSITY OF PITTSBURGH AT PITTSBURGH

Budget	Year 3	Year 4	Year 5
Salaries and Wages	$208,341	$226,544	$226,544
Fringe Benefits	$65,717	$71,911	$71,911
Personnel Costs (Subtotal)	$274,058	$298,455	$298,455
Materials & Supplies	$18,980	$27,490	$27,490
Travel	$7,451	$10,792	$10,792
Other	$32,729	$46,992	$46,992
ADP/Computer Services	$5,499	$7,965	$7,965
TOTAL FEDERAL DC	$338,717	$391,694	$391,694
TOTAL FEDERAL F&A	$188,668	$221,307	$221,307
TOTAL COST	$420,624	$613,001	$613,001

Facilities and Administrative Costs	Year 3	Year 4	Year 5
F&A Cost Rate 1	55.5%	56.5%	56.5%
F&A Cost Base 1	$31,095	$391,694	$391,694
F&A Costs 1	$17,258	$221,307	$221,307
F&A Cost Rate 2	56.5%		
F&A Cost Base 2	$303,380		
F&A Costs 2	$171,410		

A. OVERALL COVER PAGE

Project Title: University of Pittsburgh as the GUDMAP Tissue Hub and Collection Site	
Grant Number: 5U24DK110791-03	**Project/Grant Period:** 09/15/2016 - 05/31/2021
Reporting Period: 06/01/2017 - 05/31/2018	**Requested Budget Period:** 06/01/2018 - 05/31/2019
Report Term Frequency: Annual	**Date Submitted:** 04/02/2018
Program Director/Principal Investigator Information: (b)(6) **Phone number:** (b)(6) **Email:** (b)(6) @upmc.edu	**Recipient Organization:** UNIVERSITY OF PITTSBURGH AT PITTSBURGH UNIVERSITY OF PITTSBURGH OFFICE OF RESEARCH PITTSBURGH, PA 152132303 **DUNS:** 004514360 **EIN:** 1250965591A1 **RECIPIENT ID:**
Change of Contact PD/PI: N/A	
Administrative Official: (b)(6) UNIVERSITY OF PITTSBURGH 123 University Place (b)(6) PITTSBURGH, PA 15213 **Phone number:** (b)(6) **Email:** (b)(6) @pitt.edu	**Signing Official:** (b)(6) UNIVERSITY OF PITTSBURGH 123 University Place (b)(6) PITTSBURGH, PA 15213 **Phone number:** (b)(6) **Email:** (b)(6) @pitt.edu
Human Subjects: Yes HS Exempt: No Exemption Number: Phase III Clinical Trial:	**Vertebrate Animals:** No
hESC: No	**Inventions/Patents:** No

B. OVERALL ACCOMPLISHMENTS

B.1 WHAT ARE THE MAJOR GOALS OF THE PROJECT?

Aim 1: To generate an inventory of genitourinary tissue throughout normal human development The main goal of this aim is to develop a pipeline for the acquisition, quality control and distribution of human genitourinary samples obtained throughout development (6-42 weeks gestation). We currently have access to 6-24 week samples through the HSTB. However, for later gestational stages (25-42 weeks gestation) we have partnered with the International institute for the Advancement of Medicine. This will provide access to a novel resource for neonatal donation. We aim to collect and store a minimum of 5 samples per developmental week. Each of these samples will have histology, immunohistochemistry and in situ hybridization performed to assess tissue quality, protein and RNA integrity. Furthermore, we will obtain maternal blood, urine and amniotic fluid; based on the clinical situation and ability to procure. Based on our current experience, we get these biological
materials in most cases. Anonymized demographic information of each specimen will also be provided.

Aim 2: To provide fresh genitourinary tissue and biological research specimens This aim will generate an ongoing resource to distribute fresh developmental human genitourinary samples
from various stages (6-42 weeks) to the GUDMAP Atlas projects. The samples will be procured by a pathologist and inspected for mechanical damage. Samples will be collected from all qualified cases. The samples will then be subdivided based on the demand for fresh/frozen aliquots; the validation laboratory for quality control will keep a portion of each sample. The tissue samples will be immediately sent out for live cell use or immediately separated into distinct cellular populations before shipping based on researcher demands. Permissible annotating information; including demographics of each specimen, will also be provided.

B.1.a Have the major goals changed since the initial competing award or previous report?

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

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B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

For this reporting period, is there one or more Revision/Supplement associated with this award for which reporting is required?

No

B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

NOTHING TO REPORT

B.5 HOW HAVE THE RESULTS BEEN DISSEMINATED TO COMMUNITIES OF INTEREST?

There is very active e-mail and phone communication between the GUDMAP investigators, the Data Hub and the Tissue Hub. In addition, the Tissue Hub activities account for approximately 50% of the 90 minute long monthly consortium video conference calls.

B.6 WHAT DO YOU PLAN TO DO DURING THE NEXT REPORTING PERIOD TO ACCOMPLISH THE GOALS?

Continue providing materials to requesting investigators within the consortia. We will be performing extensive analyses on collected specimens both from a quality assessment perspective as well as to potentially assist GUDMAP investigators with specific pathology needs related to either localization studies and/or imaging.

ACCOMPLISHMENTS

Summary

The goal of this project is to provide human genitourinary tissues (kidneys, ureters, bladders and genital structures) to research projects funded in the GenitoUrinary Development Molecular Anatomy Project (GUDMAP), as part of a consortium to build a molecular atlas of human genitourinary development.

Institutional Review Board (IRB) and Material Transfer Agreement (MTA):

The IRB for the Health Sciences Tissue Bank at the University of Pittsburgh for the collection of biospecimens from products of conception has been approved with the following modifications: (1) to allow for sharing with external investigators, (2) to include verbiage related to genomic and molecular testing in the consents; and (3) to include a new consent form for specimens from autopsy materials/ stillbirths. As per regulations, the autopsy material needed appropriate Committee for Oversight of Research and Clinical Training Involving Decedents (CORID) vetting. The IRB for the GUDMAP consortium was an expedited submission working off the biospecimen collection IRB and is approved. The MTAs for sharing biospecimens with GUDMAP consortium members are in place.

Biospecimen Collection/Quality Control:

The Tissue Hub has been actively shipping biospecimens to GUDMAP consortium members since June 2017. The Tissue Hub maintains active monthly communications with the consortium members to ascertain specific biospecimen and processing needs. These have typically comprised monthly emails or phone calls between Health Sciences Tissue Bank staff, GUDMAP PIs, and (b)(6) The interface between the Tissue Hub and the tissue projects is very collaborative in nature and decisions in the best interest of the individual investigators is easily facilitated in this manner. (b)(6) has been overseeing the collection and dissection of the specimens to accrue genitourinary specimens.

As part of the quality control process, the Validation Laboratory performs genotyping on all biospecimens to document gender, in addition to an anatomical assessment. The Validation Laboratory has also performed pilot studies in collaboration with project PIs to identify optimal means of sample processing for the downstream applications for individual organs. For example, the validation laboratory performed tests of RNA quality following biospecimen collection in RPMI, storage and RNA isolation, compared to placing biospecimens in OCT, isolation of a subset of the tissue and RNA isolation. (b)(6) and his lab have been receiving and utilizing specimens and assessing different modalities to ensure the highest quality specimens for the consortium members for their respective needs. The monthly feedback from GUDMAP investigators has been consistently positive regarding the tissue quality that has been received. With the appropriate regulatory approvals and MTAs in place, the Tissue Hub is actively providing biospecimens to the GUDMAP investigators as outlined in Table 1.

Table 1. Biospecimen disbursements from Tissue Hub to GUDMAP investigators.

GUDMAP Investigator	Fresh Tissue Disbursements June 1, 2017- March 1, 2018	Frozen Tissue Disbursements June 1, 2017- March 1, 2018
(b)(6)	(b)(4)	

(b)(6)	(b)(4)
Totals	

The GUDMAP investigators identified a research need for biospecimens that could not be provided through the Health Sciences Tissue Bank at the University of Pittsburgh given how the biospecimens are collected. Given this, the Tissue Hub developed a mechanism by which GUDMAP investigators can obtain these tissues through the Human Developmental Biology Resource (HDBR), and currently covers all the costs to the GUDMAP investigators for these shipments. The current numbers are provided in Table 2. The volume of shipments from HDBR to GUDMAP investigators is expected to increase significantly in the next funding cycle, as GUDMAP investigators have requested that they receive shipments of individual fresh biospecimens in culture media, as opposed to shipments of frozen tissue that can be grouped together. In pilot data, this method of tissue preservation and shipping has been most robust for downstream applications, particularly as it pertains to highthroughput RNA sequencing.

Table 2. Shipments from Human Developmental Biology Resource (HDBR) to GUDMAP investigators.

GUDMAP Investigator	June 1, 2017- March 1, 2018
(b)(6)	(b)(4)
Totals	

Information Technology Initiatives:
The Tissue Hub has developed inventory and data management tools internally to appropriately annotate the GUDMAP tissue collections. The Tissue Hub, in concert with the PIs of the GUDMAP projects, have defined de-identified clinical information that is collected for each of the biospecimens. Biospecimens are linked to barcodes, and provided to GUDMAP PIs, which allows for access to de-identified clinical information should it be required for the individual projects.

C. OVERALL PRODUCTS

C.1 PUBLICATIONS

Are there publications or manuscripts accepted for publication in a journal or other publication (e.g., book, one-time publication, monograph) during the reporting period resulting directly from this award?

No

C.2 WEBSITE(S) OR OTHER INTERNET SITE(S)

Nothing to report

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

C.4 INVENTIONS, PATENT APPLICATIONS, AND/OR LICENSES

Have inventions, patent applications and/or licenses resulted from the award during the reporting period? No

If yes, has this information been previously provided to the PHS or to the official responsible for patent matters at the grantee organization?

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Category	Explanation
Data or Databases	The data collected and provided by the Hub will be in two broad categories. Firstly, we will provide annotation information related to the specimens collected for the GUDMAP investigators. The data elements to be collected have been defined by the consortium. The data will be securely provided to the Data Hub, which will host this information. The second major data component will be imaging data generated from the specimens and slides etc. In addition, molecular data will also be generated from select specimens.
Research Material	The Tissue Hub will collect specimens as per the needs of the GUDMAP investigators. The biospecimens will be both from surgical pathology specimens (products of conception) as well as autopsy material (still-births). In addition, additional specimens may be collected depending on investigator and programmatic needs and direction. The specimen types that can be accrued, and possible specimen accrual limitations, have been discussed with consortia members. Collection protocols will continue to be modified and fine-tuned to reflect the needs and the reality of human biospecimen collections; since diagnostic assessment is the primary purpose.

D. OVERALL PARTICIPANTS

D.1 WHAT INDIVIDUALS HAVE WORKED ON THE PROJECT?

Commons ID	S/K	Name	Degree(s)	Role	Cal	Aca	Sum	Foreign Org	Country	SS
(b)(6)	Y	(b)(6)	MD	PD/PI	(b)(6)					NA
	N			Technician						NA
	N			Technician						NA
	N			Technician						NA
(b)(6)	N		BS,MS,MD	Co-Investigator						NA
	N			QC Manager						NA
(b)(6)	Y		BS,OTH,PHD	Co-Investigator						NA
	N			Data Coordinator						NA
	N			HSTB Supervisor						NA
	N			Project Manager						NA
	N			Co-Investigator						NA
(b)(6)	N			Co-Investigator						NA

Glossary of acronyms:
S/K - Senior/Key
DOB - Date of Birth
Cal - Person Months (Calendar)
Aca - Person Months (Academic)
Sum - Person Months (Summer)
Foreign Org - Foreign Organization Affiliation
SS - Supplement Support
RE - Reentry Supplement
DI - Diversity Supplement
OT - Other
NA - Not Applicable

D.2 PERSONNEL UPDATES

D.2.a Level of Effort

Will there be, in the next budget period, either (1) a reduction of 25% or more in the level of effort from what was approved by the agency for the PD/PI(s) or other senior/key personnel designated in the Notice of Award, or (2) a reduction in the level of effort below the minimum amount of effort required by the Notice of Award?

No

D.2.b New Senior/Key Personnel

Are there, or will there be, new senior/key personnel?

No

D.2.c Changes in Other Support

Has there been a change in the active other support of senior/key personnel since the last reporting period?

Yes

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D.2.d New Other Significant Contributors

Are there, or will there be, new other significant contributors?

No

D.2.e Multi-PI (MPI) Leadership Plan

Will there be a change in the MPI Leadership Plan for the next budget period?

NA

For New and Renewal Applications (PHS 398) – DO NOT SUBMIT UNLESS REQUESTED

PHS 398 OTHER SUPPORT

Provide active and pending support for all senior/key personnel. **Other Support includes all financial resources, whether Federal, non-Federal, commercial or institutional, available in direct support of an individual's research endeavors, including but not limited to research grants, cooperative agreements, contracts, and/or institutional awards.** Training awards, prizes, or gifts do not need to be included.

There is no "form page" for other support. Information on other support should be provided in the *format* shown below, using continuation pages as necessary. ***Include the principal investigator's name at the top and number consecutively with the rest of the application.*** The sample below is intended to provide guidance regarding the type and extent of information requested.
For instructions and information pertaining to the use of and policy for other support, see Other Support in the Supplemental Instructions, Part III, Policies, Assurances, Definitions, and Other Information.
Effort devoted to projects must be measured using person months. Indicate calendar, academic, and/or summer months associated with each project.

Format

NAME OF INDIVIDUAL (b)(6)
ACTIVE/PENDING

ACTIVE

(b)(6)

(b)(4); (b)(6)

PENDING

(b)(4); (b)(6)

OVERLAP: No Overlap

Other Support

(b)(6)

ACTIVE

(b)(4); (b)(6)

E. OVERALL IMPACT

E.1 WHAT IS THE IMPACT ON THE DEVELOPMENT OF HUMAN RESOURCES?

Not Applicable

E.2 WHAT IS THE IMPACT ON PHYSICAL, INSTITUTIONAL, OR INFORMATION RESOURCES THAT FORM INFRASTRUCTURE?

NOTHING TO REPORT

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

Not Applicable

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?

NOTHING TO REPORT

F. OVERALL CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

F.2 ACTUAL OR ANTICIPATED CHALLENGES OR DELAYS AND ACTIONS OR PLANS TO RESOLVE THEM

NOTHING TO REPORT

F.3 SIGNIFICANT CHANGES TO HUMAN SUBJECTS, VERTEBRATE ANIMALS, BIOHAZARDS, AND/OR SELECT AGENTS

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. OVERALL SPECIAL REPORTING REQUIREMENTS

G.1 SPECIAL NOTICE OF AWARD TERMS AND FUNDING OPPORTUNITIES ANNOUNCEMENT REPORTING REQUIREMENTS

NOTHING TO REPORT

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

G.4.a Does the project involve human subjects?

Yes

Is the research exempt from Federal regulations?

No

Does this project involve a clinical trial?

No

G.4.b Inclusion Enrollment Data

Report Attached: Research on tissue from an elective or spontaneous abortion < 24 weeks gestation

G.4.c ClinicalTrials.gov

Does this project include one or more applicable clinical trials that must be registered in ClinicalTrials.gov under FDAAA?

No

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Are there personnel on this project who are newly involved in the design or conduct of human subjects research?

No

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

Does this project involve human embryonic stem cells (only hESC lines listed as approved in the NIH Registry may be used in NIH funded research)?

No

G.7 VERTEBRATE ANIMALS

Does this project involve vertebrate animals?

No

G.8 PROJECT/PERFORMANCE SITES

Organization Name:	DUNS	Congressional District	Address

Primary: University of Pittsburgh	004514360	PA-014	(b)(6)	
University of Pittsburgh	004514360	PA-014		
University of Pittsburgh	004514360	PA-014	(b)(4); (b)(6)	
UNIVERSITY OF PITTSBURGH AT PITTSBURGH	004514360		UNIVERSITY OF PITTSBURGH OFFICE OF RESEARCH PITTSBURGH PA 152132303	

G.9 FOREIGN COMPONENT

No foreign component

G.10 ESTIMATED UNOBLIGATED BALANCE

G.10.a Is it anticipated that an estimated unobligated balance (including prior year carryover) will be greater than 25% of the current year's total approved budget?

No

G.11 PROGRAM INCOME

Is program income anticipated during the next budget period?

No

G.12 F&A COSTS

Not Applicable

Inclusion Enrollment Report

Inclusion Data Record (IDR) #: 1078054

Using an Existing Dataset or Resource: No

Delayed Onset Study ?: No

Clinical Trial: No

Enrollment Location: Domestic

NIH Defined Phase III Clinical Trial: No

Study Title: Research on tissue from an elective or spontaneous abortion < 24 weeks gestation

Planned Enrollment

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/Alaska Native	0	0		0	0					**0**
Asian	50	0		0	0					**50**
Native Hawaiian or Other Pacific Islander	0	0		0	0					**0**
Black or African American	100	0		10	0					**110**
White	200	0		20	0					**220**
More than One Race	0	0		20	0					**20**
Unknown or Not Reported										
Total	**350**	**0**		**50**	**0**					**400**

Cumulative Enrollment

Only planned enrollment data exists for this data record. The PD/PI did not enter cumulative inclusion enrollment data.

RESEARCH & RELATED BUDGET - SECTION A & B

ORGANIZATIONAL DUNS*: 004514360

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: UNIVERSITY OF PITTSBURGH AT PITTSBURGH

Start Date*: 06-01-2018 **End Date*:** 05-31-2019

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1.		(b)(6)				Project Lead	(b)(6)				37,920.00	9,651.00	47,571.00
2.						Co-investigator					3,000.00	764.00	3,764.00
3.						Co-investigator					26,846.00	6,832.00	33,678.00
4.						Co-investigator					6,000.00	1,527.00	7,527.00
5.						Co-investigator					21,012.00	5,348.00	26,360.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **118,900.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
9	Supervisors, Techs, and Data Coord	(b)(6)			132,773.00	48,108.00	180,881.00
9	**Total Number Other Personnel**					**Total Other Personnel**	**180,881.00**

Total Salary, Wages and Fringe Benefits (A+B) **299,781.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E

ORGANIZATIONAL DUNS*: 004514360

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: UNIVERSITY OF PITTSBURGH AT PITTSBURGH

Start Date*: 06-01-2018 **End Date*:** 05-31-2019

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	10,840.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**10,840.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		0.00
2. Stipends		0.00
3. Travel		0.00
4. Subsistence		0.00
5. Other:		
0 Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**0.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K

ORGANIZATIONAL DUNS*: 004514360

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: UNIVERSITY OF PITTSBURGH AT PITTSBURGH

Start Date*: 06-01-2018 **End Date*:** 05-31-2019

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	27,612.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	8,000.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. HSTB Services	4,242.00
9. New Castle, UK Shipping Costs to consortium sites	42,959.00
Total Other Direct Costs	**82,813.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**393,434.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. MTDC	0.0	389,192.00	219,569.00
		Total Indirect Costs	**219,569.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): U.S. Department of Health and Human Services (b)(6) (b)(6)

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**613,003.00**

J. Fee	Funds Requested ($)*
	0.00

K. Budget Justification* File Name: budget justification _yr 3.pdf

(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

BUDGET JUSTIFICATION – Year 3

Personnel

(b)(6) PI, Effort = (b)(6) is the (b)(6) (b)(6) of the University of Pittsburgh and a practicing pathologist with subspecialty training in Genitourinary Pathology. He will be responsible for the oversight of the project. This will include interfacing and working with internal collaborators to ensure accrual and annotation of the appropriate specimens. He will also interact with the external collaborators and clients to ensure appropriate specimen aggregation and disbursement. He will work closely with NIDDK to ensure successful execution of the project, meeting the mission and goals of the Tissue Core. Annual effort of (b)(6) is requested.

(b)(6) Effort = (b)(6) This (b)(6) will be responsible for coordination and management of day to day operations. She supervises HSTB staff members and will manage the overall efforts of the HSTB and set operational standards related to the HSTB scope of work. She will assure proper communication and resolution conflicts and issues.

1. **Tissue Hub Infrastructure Support**

A crucial component of this application is the infrastructure for the Tissue Hub, which will include personnel for the development and maintenance of a secure web-based interface for GUDMAP investigators, assurance of regulatory compliance, data collection and record-keeping, and management of the quality assurance program associated with this project.

(b)(6): Co-I, Effort = (b)(6) is the (b)(6) (b)(6) and will be the director of the Tissue hub Infrastructure. He also serves as the faculty in-charge of the informatics requirements of HSTB. He provides direction and advice related to the different Information systems and tools used by HSTB. He is also the director of the Imaging core; a subsidiary of HSTB. The imaging core will perform whole slide image acquisition and provide access to these images for the Tissue Core clients. Annual effort of (b)(6) is requested.

(b)(6) Effort = (b)(6) This (b)(6) will be responsible for project intake, tracking and recording keeping. She will coordinate the GUDMAP investigator requests to the GUDMAP-Human Tissue Repository including documenting the needs of the investigator, assuring regulatory compliance, coordinating with tissue and data collection staff members and assuring proper completion and shipping of requests. Annual effort of (b)(6) is requested.

(b)(6) Effort = (b)(6) This (b)(6) will be responsible for the quality program. He will manage all aspects of quality management including record keeping, training of staff members to standard operating procedures (SOPs), data entry practices and audits, and quality related events. He will coordinate the overall record keeping and management of the quality metrics from the tissue collection and data entry processes with the quality measurements performed through the Department of Pediatrics team.

(b)(6) Effort = (b)(6) This (b)(6) specialist will be responsible for overall management of the Biospecimen Inventory and Operations System with regard to the this project. He will manage the specimen search process, control the data entry lexicon as needed, and provide reports of collection activity for investigators who request samples and as needed for other purposes. He will maintain the data integrity and make corrections and amendments based on the quality control activities. In the case that new fields and library elements are required he will manage that process in conjunction with the Project Manager and Quality Manager. He will be required to produce final sample pick lists as specimens are disbursed.

(b)(6): Effort = (b)(6) is the technician responsible for processing tissues, immunohistochemistry and immunofluorescence needs of the project. He is also the supervisor of the Research Histology core facility and is responsible for the development of specialized techniques required by the program and for processes not included in the fee-for-service activity.

(b)(6): Effort = (b)(6) The (b)(6) will be responsible for aggregating information from the different information systems on the specimens offered as part of the Tissue Core. This will include pathology information as well as more specialized information (like cytogenetics); if applicable. The data coordinator will work with the Project manager on cohort identification for

the different requests. In addition the data coordinator will also be responsible for providing data to the clients of the Tissue Core.

2. Fetal Tissue Procurement Laboratory ((b)(4); (b)(6)

All of the fetal tissue will be collected at (b)(4); (b)(6) undergo a gross examination, and then be transported to the validation laboratory for further assessment prior to distribution.

(b)(6) **:** Co-I, Effort = (b)(6) is the (b)(6) (b)(6) He will be responsible for evaluating appropriate surgical pathology and autopsy specimens, and overseeing collection of the biological materials for the Tissue Core and will act as the director of the tissue procurement laboratory. He will perform the clinical evaluation of the gross genitourinary specimen and ensure quality control of the dissection to minimize mechanical disruption. He will train the staff to obtain early gestational age genitourinary specimens, and work closely with (b)(6) to perform routine and specialized histological assessment of the appropriate specimens. Annual effort of (b)(6) is requested.

(b)(6) **:** Effort = (b)(6) This HSTB tissue bank technician and will perform the day-to-day tasks associated with the collection of specimens. This includes maintaining a working knowledge of all SOPs related to the ongoing collections that are requested by the GUDMAP investigators. She will coordinate with the clinical departments within (b)(4) interface with the Pathology and other hospital staff members as required to obtain the requested specimens and enter data related to each case in the BIOS.

(b)(6) Effort = (b)(6) This (b)(6) will perform the day-to-day tasks associated with the collection of specimens. This includes maintaining a working knowledge of all SOPs related to the ongoing collections that are requested by the GUDMAP investigators. She will coordinate with the clinical departments within (b)(4); (b)(6) interface with the Pathology and other hospital staff members as required to obtain the requested specimens and enter data related to each case in the BIOS.

3. Validation Laboratory (b)(6)

The validation laboratory will perform quality assurance measures, as per GUDMAP project needs (eg. histological assessment, *in situ* hybridization and RNA isolation).

(b)(6) Co-I, Effort = (b)(6) is a kidney developmental biologist with over (b)(6) studying the genitourinary tract and will act as the director of the validation laboratory. Furthermore, he is also a classically trained human anatomist, histologist and embryologist. The quality assurance of the specimens will be performed by at least two independent evaluations (b)(6) for GUDMAP project needs. (b)(6) will work closely with (b)(6) to train staff to perform the gross dissection for early gestational age genitourinary tissues, and tissues not currently being obtained by the Tissue Bank, as per GUDMAP project needs. He will also oversee the training of (b)(6) (tissue hub technician) in all aspects of dissection, histology and molecular evaluation of the fetal tissues.

(b)(6) **:** Co-I, Effort = (b)(6) is a clinician scientist (Pediatric Nephrologist) with a research program related to kidney development and will act as the co-director of the validation laboratory. She has a thorough understanding of genitourinary development. She will participate in quality assurance of specimens as noted above. Furthermore, (b)(6) will provide direction and advice regarding the clinical parameters that will be used to screen fetal and neonatal tissues to exclude pathological specimens, and will evaluate individual cases as needed.

(b)(6) Effort = (b)(6) This grant will fund (b)(6) of the technicians salary. This technician will perform all the required validation of the specimens including: histology, immunohistochemistry, in situ hybridization, cell isolation and real time PCR.

Supplies

HSTB Consumable Laboratory Supplies: (b)(4) is requested for sample collections, integrity, maintenance, and transport including sample and shipping containers, dry ice, and other basic supplies.

Shipping: Funds are requested for the shipment of tissue from (b)(4) to the participating GUDMAP investigators, (b)(4) is requested in year 3.

Validation Laboratory Consumable Laboratory Supplies: (b)(4) monthly will be required to purchase reagents for staining, immunohistochemistry and in situ reagents as well as cell, culture medium and consumable plastics related to these processes. These processes will be performed in response to the needs of the GUDMAP investigators.

Travel

Pathology: The Project PI and HSTB staff will need to travel to GUDMAP consortia meetings, to be held twice a year. A total of $4,840 is allocated for this travel in year 3.

Validation Laboratories: The Project co-investigators will need to travel to GUDMAP consortia meetings, to be held twice a year. (b)(6) will also attend the American Society of Nephrology meeting where GUDMAP typically has a booth. A total of $6,000 is allocated for this travel in year 3.

(b)(6) will also attend the International Meeting on Development Nephrology to be held in 2018, where GUDMAP will hold workshops.

Other Expenses

Tissue embedding/processing, storage, and disbursement: (b)(4) for year 3. These are billable services based on the fiscal parameters in place within the University of Pittsburgh for the HSTB. Tissue embedding and processing will be required at all levels for quality management and to provide product to GUDMAP investigators. Storage costs are based on the partial cost of a freezer with a 10 year life span plus projected maintenance and certification costs. The cost for disbursement of samples to GUDMAP investigators will be charged to the account award for this project.

Website maintenance, project management tool, BIOS, image acquisition: $8,000. Resources will be required to maintain and update our internally developed inventory management system (BIOS). The project management tool is internally developed and is the mechanism for starting and following the progress of the request from the client. The clients will be provided access to the contents of the resource via a Sharepoint link that will be password protected. Whole slide image acquisition will be done to offer clients access to high quality images of the specimens in the resource. These images will be from routine and specialized histologic and immunohistochemical/ in-situ protocols. We also have capabilities for image analysis and will offer, if required.

Notice of Award

RESOURCE-RELATED COOPERATIVE AGREEMENT PROJECTS **Federal Award Date:** 07/03/2017

Department of Health and Human Services
National Institutes of Health
NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

Grant Number: 5U24DK110791-02
FAIN: U24DK110791

Principal Investigator(s):
(b)(6)

Project Title: University of Pittsburgh as the GUDMAP Tissue Hub and Collection Site

(b)(6)
University of Pittsburgh
(b)(6)
Grants and Contracts Officer
Pittsburgh, PA 152132303

Award e-mailed to: ornih@offres.pitt.edu

Period Of Performance:
Budget Period: 06/01/2017 – 05/31/2018
Project Period: 09/15/2016 – 05/31/2021

Dear Business Official:

The National Institutes of Health hereby awards a grant in the amount of $479,336 (see "Award Calculation" in Section I and "Terms and Conditions" in Section III) to UNIVERSITY OF PITTSBURGH AT PITTSBURGH in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 31 USC 6305 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award including the "Terms and Conditions" is acknowledged by the grantee when funds are drawn down or otherwise obtained from the grant payment system.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as "Research reported in this publication was supported by the National Institute Of Diabetes And Digestive And Kidney Diseases of the National Institutes of Health under Award Number U24DK110791. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health." Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Award recipients must promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under NIH awards will be free from bias resulting from an Investigator's Financial Conflict of Interest (FCOI), in accordance with the 2011 revised regulation at 42 CFR Part 50 Subpart F. The Institution shall submit all FCOI reports to the NIH through the eRA Commons FCOI Module. The regulation does not apply to Phase I Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) awards. Consult the NIH website http://grants.nih.gov/grants/policy/coi/ for a link to the regulation and additional important information.

If you have any questions about this award, please contact the individual(s) referenced in Section IV.

Sincerely yours,

(b)(6)

Grants Management Officer
NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

Additional information follows

SECTION I – AWARD DATA – 5U24DK110791-02

Award Calculation (U.S. Dollars)

Salaries and Wages	$178,322
Fringe Benefits	$56,043
Personnel Costs (Subtotal)	$234,365
Materials & Supplies	$39,960
Travel	$9,798
Other	$27,300
Federal Direct Costs	$311,423
Federal F&A Costs	$167,913
Approved Budget	$479,336
Total Amount of Federal Funds Obligated (Federal Share)	$479,336
TOTAL FEDERAL AWARD AMOUNT	$479,336
AMOUNT OF THIS ACTION (FEDERAL SHARE)	$479,336

SUMMARY TOTALS FOR ALL YEARS		
YR	**THIS AWARD**	**CUMULATIVE TOTALS**
2	$479,336	$479,336
3	$613,002	$613,002
4	$613,001	$613,001
5	$613,001	$613,001

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

Fiscal Information:

CFDA Name: Diabetes, Digestive, and Kidney Diseases Extramural Research
CFDA Number: 93.847
EIN: 1250965591A1
Document Number: UDK110791A
PMS Account Type: P (Subaccount)
Fiscal Year: 2017

IC	CAN	2017	2018	2019	2020
DK	8472288	$479,336	$613,002	$613,001	$613,001

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

NIH Administrative Data:
PCC: KDH KDB / **OC**: 414P / **Released**: (b)(6) 06/30/2017
Award Processed: 07/03/2017 11:21:15 AM

SECTION II – PAYMENT/HOTLINE INFORMATION – 5U24DK110791-02

For payment and HHS Office of Inspector General Hotline information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

SECTION III – TERMS AND CONDITIONS – 5U24DK110791-02

This award is based on the application submitted to, and as approved by, NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

a. The grant program legislation and program regulation cited in this Notice of Award.
b. Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.
c. 45 CFR Part 75.
d. National Policy Requirements and all other requirements described in the NIH Grants

Policy Statement, including addenda in effect as of the beginning date of the budget period.

e. Federal Award Performance Goals: As required by the periodic report in the RPPR or in the final progress report when applicable.
f. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(See NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm for certain references cited above.)

Research and Development (R&D): All awards issued by the National Institutes of Health (NIH) meet the definition of "Research and Development" at 45 CFR Part§ 75.2**.** As such, auditees should identify NIH awards as part of the R&D cluster on the Schedule of Expenditures of Federal Awards (SEFA). The auditor should test NIH awards for compliance as instructed in Part V, Clusters of Programs. NIH recognizes that some awards may have another classification for purposes of indirect costs. The auditor is not required to report the disconnect (i.e., the award is classified as R&D for Federal Audit Requirement purposes but non-research for indirect cost rate purposes), unless the auditee is charging indirect costs at a rate other than the rate(s) specified in the award document(s).

Carry over of an unobligated balance into the next budget period requires Grants Management Officer prior approval.

This award is subject to the requirements of 2 CFR Part 25 for institutions to receive a Dun & Bradstreet Universal Numbering System (DUNS) number and maintain an active registration in the System for Award Management (SAM). Should a consortium/subaward be issued under this award, a DUNS requirement must be included. See http://grants.nih.gov/grants/policy/awardconditions.htm for the full NIH award term implementing this requirement and other additional information.

This award has been assigned the Federal Award Identification Number (FAIN) U24DK110791. Recipients must document the assigned FAIN on each consortium/subaward issued under this award.

Based on the project period start date of this project, this award is likely subject to the Transparency Act subaward and executive compensation reporting requirement of 2 CFR Part 170. There are conditions that may exclude this award; see http://grants.nih.gov/grants/policy/awardconditions.htm for additional award applicability information.

In accordance with P.L. 110-161, compliance with the NIH Public Access Policy is now mandatory. For more information, see NOT-OD-08-033 and the Public Access website: http://publicaccess.nih.gov/.

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts with cumulative total value greater than $10,000,000 must report and maintain information in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made publicly available in the designated integrity and performance system (currently the Federal Awardee Performance and Integrity Information System (FAPIIS)). Full reporting requirements and procedures are found in Appendix XII to 45 CFR Part 75. This term does not apply to NIH fellowships.

Treatment of Program Income:
Other Research (Add/Deduct Option)

RESTRICTION: Funds may only be used to offset the cost of acquiring, processing and shipping tissue samples to the GUDMAP atlas projects. This includes covering the cost of processing and shipping tissue from external sources.

Notice: Under governing regulations, Federal funds administered by the Department of Health and Human Services shall not be expended for research involving human subjects, and individuals shall not be enrolled in such research, without prior approval by the Office of Human Research Protections (OHRP) of an assurance to comply with the requirements of 45 CFR 46 to protect human research subjects. This restriction applies to all collaborating sites without OHRP-approved assurances, whether domestic or foreign, and compliance must be ensured by the awardee.

Notice: Under governing policy, federal funds administered by the Public Health Service (PHS) shall not be expended for research involving live vertebrate animals without prior approval by the Office of Laboratory Animal Welfare (OLAW) of an assurance to comply with the PHS policy on humane care and use of laboratory animals. This restriction applies to all performance sites (e.g., collaborating institutions, subcontractors, subgrantees) without OLAW-approved assurances, whether domestic or foreign.

The issuance of this award has been delayed due to administrative funding considerations. According to NIH policy, if pre-award costs are necessary, they may be approved by the authorized Institution Official(s).

In addition to the PI, the following individuals are named as key personnel:

(b)(6)

Written prior approval is required if any of the individual(s) named above withdraws from the project entirely, is absent from the project during any continuous period of 3 months or more, or reduces time devoted to the project by 25 percent or more from the level that was approved at the time of award.

This grant is in response to RFA/PA DK15-016. Acceptance of this award requires compliance with this solicitation. See the NIH Guide at http://grants.nih.gov/grants/guide/index.html for copy of the RFA/PA that includes administrative and programmatic requirements specific to this award.

The following special terms of award are in addition to, and not in lieu of, otherwise applicable U.S. Office of Management and Budget (OMB) administrative guidelines, U.S. Department of Health and Human Services (DHHS) grant administration regulations at 45 CFR Parts 74 and 92 (Part 92 is applicable when State and local Governments are eligible to apply), and other HHS, PHS, and NIH grant administration policies.

The administrative and funding instrument used for this program will be the cooperative agreement, an "assistance" mechanism (rather than an "acquisition" mechanism), in which substantial NIH programmatic involvement with the awardees is anticipated during the performance of the activities.

Under the cooperative agreement, the NIH purpose is to support and stimulate the recipients' activities by involvement in and otherwise working jointly with the award recipients in a partnership role; it is not to assume direction, prime responsibility, or a dominant role in the activities. Consistent with this concept, the dominant role and prime responsibility resides with the awardees for the project as a whole, although specific tasks and activities may be shared among the awardees and the NIH as defined below.

The PD(s)/PI(s) will have the primary responsibility for:

- All aspects of the scientific activities, including defining the objectives and approaches, planning, conduct, analysis, and publication of results, interpretations, and conclusions of studies conducted under the terms and conditions of the cooperative agreement award.
- Collaborating with other investigators in the program for protocol development, sample, reagents and data sharing as appropriate, data quality control, and data organization

- Accountability towards the applicant organization officials and to the NIDDK for the performance and proper conduct of the research supported by the project in accordance with the terms and conditions of the award.
- Serving as a voting member of the Steering Committee and will attend the Planning Meeting and a Steering Committee meeting in the first year, two Steering Committee meetings a year in subsequent years and monthly teleconference calls.
- Accepting and implementing the goals, priorities, procedures, protocols, and policies agreed upon by the Steering Committee and subcommittees, and be responsible for close coordination and cooperation with the components of the GUDMAP consortium and with NIDDK staff.
- Adhering to PHS policy for the distribution of unique research resources produced with PHS funding as described under Special Requirements.
- Establishing written milestones for the project, in negotiation with NIDDK Project Staff prior to funding.
- Release all study design materials and procedure manuals into the public domain and/or make them available to other investigators, according to the approved plan for making data and materials available to the scientific community and the NIDDK, for the conduct of research at no charge other than the costs of reproduction and distribution, consistent with achieving the goals of this program initiative.
- Awardees will retain custody of and have primary rights to the data and software developed under these awards, subject to Government rights of access consistent with current DHHS, PHS, and NIH policies.

NIH staff will have substantial programmatic involvement that is above and beyond the normal stewardship role in awards, as described below:

- An NIH Project Scientist will have substantial programmatic involvement that is above and beyond the normal stewardship role in awards, as described below. However, the dominant role and prime responsibility for the project as a whole resides with the awardees, although specific tasks and activities in carrying out the studies will be shared by awardees and the NIDDK.
- NIDDK will designate a Project Officer and a Grants Management Specialist to provide normal program stewardship and administrative oversight of the cooperative agreement.
- NIDDK will form an External Advisory Committee (EAC), comprised of the NIDDK Project Scientist and other NIH extramural staff with relevant scientific expertise or who manage research grant programs that relate scientifically to the goals of the GUDMAP projects, and outside advisors selected by the NIDDK. The EAC will meet annually with the GUDMAP Steering Committee to review and assess GUDMAP and to advise NIDDK of scientific developments and opportunities that may enhance the achievement of the GUDMAP goals.
- The NIDDK Project Scientist will attend and participate as a voting member in all meetings of the Steering Committee, and provide liaison between the Steering Committee and the External Advisory Committee.
- The NIDDK Project Scientist will help the Steering Committee develop and draft operating policies.
- The NIDDK Project Officer will review the scientific progress of the individual GUDMAP components, for compliance with operating policies developed by the Steering Committee, and may recommend to the NIDDK to withhold support, suspend, or terminate an award for lack of scientific progress or failure to adhere to policies established by the Steering Committee.
- An agency program official or IC program director will be responsible for the normal scientific and programmatic stewardship of the award and will be named in the award notice. The assigned Program Officer may also serve as an NIDDK Project Scientist.

Areas of Joint Responsibility include:

- Steering Committee - The NIDDK Project Scientist, PIs from the project funded through this FOA and RFA-DK-15-014, and RFA-DK-15-015 and voluntary representatives from the previously funded GUDMAP atlas projects funded under RFA-DK-11-001 will be responsible for forming a Steering Committee as defined below. An arbitration system, as detailed below, will be available to resolve disagreements among members of the Steering Committee. The Steering Committee will be the main governing board of the GUDMAP consortium. It will develop collaborative protocols, identify technological impediments to success and strategies to overcome them, develop shared software tools

for disseminating information about the projects, and identify opportunities for sharing techniques and tools that might be developed in future GUDMAP atlas projects.

- The Steering Committee will be composed of the PIs from the project funded through this FOA, RFA-DK-15-014, and RFA-DK-15-015, representatives from the previously funded GUDMAP projects, and the NIDDK Project Scientist. The representatives and the PIs will each have one vote. The NIDDK Project Scientist for this project will have one vote. The Steering Committee will select a chairperson who will be someone other than an NIH staff member.
- The Steering Committee may, as it deems necessary, invite additional, non-voting scientific advisors to meetings at which research priorities and opportunities are discussed. The NIH reserves the right to augment the scientific or consumer expertise of the Steering Committee when necessary.
- There will be two Steering Committee meetings annually. The first meeting will be a Planning Meeting to be held in the Washington, DC area on **June 20-21, 2016**. At the Planning Meeting, the Steering Committee will be formed and a chairperson selected from among the members. At the Planning Meeting, the Steering Committee may: (a) draft a charter to detail policies and procedures, a process for monitoring compliance with the policies and procedures, and a process for recommending that the NIDDK Project Administrators act on evidence of non-compliance of any Consortium component with Steering Committee policies; (b) agree upon the terms of the charter; and (c) devise a plan for working with the GUDMAP database developers to provide ongoing input into database and website design.
- At the second and subsequent meetings, the Steering Committee will refine the GUDMAP scientific objectives and implementation as necessary, consistent with data produced by former and possible future GUDMAP atlas projects and from other laboratories.
- The Steering Committee will plan workshops, to which non-GUDMAP participants will also be invited, to inform the research community of the progress made toward development of the atlas, and to inform the research community of any technological advances related to the implementation of the GUDMAP website/database. The NIDDK Project Scientist, the External Advisory Committee, and other NIH staff as appropriate will provide the Steering Committee with advice on participants for the workshops and symposia.
- The Steering Committee may establish subcommittees as it deems appropriate.
- Awardee members of the Steering Committee will be required to accept and implement policies approved by the Steering Committee.
- The EAC will meet annually with the GUDMAP Steering Committee to review and assess the progress of the GUDMAP consortium and to advise NIDDK of scientific developments and opportunities that may enhance the achievement of the GUDMAP goals.

Dispute Resolution

Any disagreements that may arise in scientific or programmatic matters (within the scope of the award) between award recipients and the NIH may be brought to Dispute Resolution. A Dispute Resolution Panel will have three members: a designee of the Steering Committee chosen without NIH staff voting, one NIH designee, and a third designee with expertise in the relevant area who is chosen by the other two; in the case of individual disagreement, the first member may be chosen by the individual awardee. This special dispute resolution procedure does not alter the awardee's right to appeal an adverse action that is otherwise appealable in accordance with PHS regulation 42 CFR Part 50, Subpart D and DHHS regulation 45 CFR Part 16.
- See more at: http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-15-016.html#sthash.UY9M5nfL.dpuf

STAFF CONTACTS

The Grants Management Specialist is responsible for the negotiation, award and administration of this project and for interpretation of Grants Administration policies and provisions. The Program Official is responsible for the scientific, programmatic and technical aspects of this project. These individuals work together in overall project administration. Prior approval requests (signed by an Authorized Organizational Representative) should be submitted in writing to the Grants Management Specialist. Requests may be made via e-mail.

Grants Management Specialist: (b)(6)
Email: (b)(6) @extra.niddk.nih.gov **Phone**: (b)(6) **Fax**: (b)(6)

Program Official: (b)(6)
Email: (b)(6)@niddk.nih.gov **Phone:** (b)(6)

SPREADSHEET SUMMARY
GRANT NUMBER: 5U24DK110791-02

INSTITUTION: UNIVERSITY OF PITTSBURGH AT PITTSBURGH

Budget	Year 2	Year 3	Year 4	Year 5
Salaries and Wages	$178,322	$224,405	$224,284	$224,284
Fringe Benefits	$56,043	$70,527	$70,489	$70,489
Personnel Costs (Subtotal)	$234,365	$294,932	$294,773	$294,773
Materials & Supplies	$39,960	$50,288	$50,261	$50,261
Travel	$9,798	$12,331	$12,324	$12,324
Other	$27,300	$34,355	$34,336	$34,336
TOTAL FEDERAL DC	$311,423	$391,906	$391,694	$391,694
TOTAL FEDERAL F&A	$167,913	$221,096	$221,307	$221,307
TOTAL COST	$479,336	$613,002	$613,001	$613,001

Facilities and Administrative Costs	Year 2	Year 3	Year 4	Year 5
F&A Cost Rate 1	54%	55.5%	56.5%	56.5%
F&A Cost Base 1	$32,448	$33,115	$391,694	$391,694
F&A Costs 1	$17,522	$18,379	$221,307	$221,307
F&A Cost Rate 2	55.5%	56.5%		
F&A Cost Base 2	$270,975	$358,791		
F&A Costs 2	$150,391	$202,717		

A. OVERALL COVER PAGE

Project Title: University of Pittsburgh as the GUDMAP Tissue Hub and Collection Site	
Grant Number: 5U24DK110791-02	**Project/Grant Period:** 09/15/2016 - 05/31/2021
Reporting Period: 09/15/2016 - 05/31/2017	**Requested Budget Period:** 06/01/2017 - 05/31/2018
Report Term Frequency: Annual	**Date Submitted:** 04/03/2017
Program Director/Principal Investigator Information: (b)(6) **Phone number:** (b)(6) **Email:** (b)(6) @upmc.edu	**Recipient Organization:** UNIVERSITY OF PITTSBURGH AT PITTSBURGH UNIVERSITY OF PITTSBURGH OFFICE OF RESEARCH 123 UNIVERSITY PL, B21 PITTSBURGH, PA 152132303 **DUNS:** 004514360 **EIN:** 1250965591A1 **RECIPIENT ID:**
Change of Contact PD/PI: N/A	
Administrative Official: (b)(6) University of Pittsburgh 123 University Place Pittsburgh, PA 15213 **Phone number:** (b)(6) **Email:** (b)(6) @pitt.edu	**Signing Official:** (b)(6) University of Pittsburgh 123 University Place Pittsburgh, PA 15213 **Phone number:** (b)(6) **Email:** (b)(6) @pitt.edu
Human Subjects: Yes HS Exempt: No Exemption Number: Phase III Clinical Trial:	**Vertebrate Animals:** No
hESC: No	**Inventions/Patents:** No

B. OVERALL ACCOMPLISHMENTS

B.1 WHAT ARE THE MAJOR GOALS OF THE PROJECT?

Aim 1: To generate an inventory of genitourinary tissue throughout normal human development The main goal of this aim is to develop a pipeline for the acquisition, quality control and distribution of human genitourinary samples obtained throughout development (6-42 weeks gestation). We currently have access to 6-24 week samples through the HSTB. However, for later gestational stages (25-42 weeks gestation) we have partnered with the International institute for the Advancement of Medicine. This will provide access to a novel resource for neonatal donation. We aim to collect and store a minimum of 5 samples per developmental week. Each of these samples will have histology, immunohistochemistry and in situ hybridization performed to assess tissue quality, protein and RNA integrity. Furthermore, we will obtain maternal blood, urine and amniotic fluid; based on the clinical situation and ability to procure. Based on our current experience, we get these biological
materials in most cases. Anonymized demographic information of each specimen will also be provided.

Aim 2: To provide fresh genitourinary tissue and biological research specimens This aim will generate an ongoing resource to distribute fresh developmental human genitourinary samples
from various stages (6-42 weeks) to the GUDMAP Atlas projects. The samples will be procured by a pathologist and inspected for mechanical damage. Samples will be collected from all qualified cases. The samples will then be subdivided based on the demand for fresh/frozen aliquots; the validation laboratory for quality control will keep a portion of each sample. The tissue samples will be immediately sent out for live cell use or immediately separated into distinct cellular populations before shipping based on researcher demands. Permissible annotating information; including demographics of each specimen, will also be provided.

B.1.a Have the major goals changed since the initial competing award or previous report?

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: ACCOMPLISHMENTS.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

For this reporting period, is there one or more Revision/Supplement associated with this award for which reporting is required?

No

B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

NOTHING TO REPORT

B.5 HOW HAVE THE RESULTS BEEN DISSEMINATED TO COMMUNITIES OF INTEREST?

There is very active e-mail and phone communication between the GUDMAP investigators, the Data Hub and the Tissue Hub. In addition, the Tissue Hub activities account for approximately 50% of the 90 minute long monthly consortium video conference calls.

B.6 WHAT DO YOU PLAN TO DO DURING THE NEXT REPORTING PERIOD TO ACCOMPLISH THE GOALS?

With the IRB and MTA processes accomplished, the Tissue Hub will start providing materials to the investigators. In addition, we are engaged in developing appropriate protocols to specifically address the needs of different projects. Finally, we will be performing extensive analyses on collected specimens both from a quality assessment perspective as well as to potentially assist GUDMAP investigators with specific pathology needs related to either localization studies and/or imaging.

ACCOMPLISHMENTS

Summary
The goal of this project is to provide human genitourinary tissues (kidneys, ureters, bladders and genital structures) to research projects funded in the GenitoUrinary Development Molecular Anatomy Project (GUDMAP), as part of a consortium to build a molecular atlas of human genitourinary development.

Institutional Review Board (IRB) and Material Transfer Agreement (MTA):
The existing IRB for the Health Sciences Tissue Bank at the University of Pittsburgh for the collection of biospecimens from products of conception required significant modifications to allow for sharing with external investigators. In addition, the verbiage related to genomic and molecular testing in the consents was updated. Finally, since there is an anticipated need for specimens from autopsy materials/ stillbirths; a new consent form was created to address tissue accrual from those specific clinical encounters rather than products of gestation. As per regulations, the autopsy material needed appropriate Committee for Oversight of Research and Clinical Training Involving Decedents (CORID) vetting. This IRB has been approved. The IRB for the GUDMAP consortium is an expedited submission working off the biospecimen collection IRB. This GUDMAP IRB is now in the final stages of institutional vetting and approval.

The draft MTA for sharing biospecimens with consortium members was sent out to the NIDDK and the GUDMAP funded investigators for review, and subsequent processing. The MTA documents should be in place in the near future. We anticipate that the legal and IRB processes should be accomplished in the next few weeks. Following that, the GUDMAP Tissue Hub and Collection site will be ready to start sharing biospecimens.

Biospecimen Collection/Quality Control:
The Tissue Hub has been in active communication with the consortium members to ascertain specific biospecimen and processing needs. We have been engaging in pilot studies internally, both from a collection as well as a quality control/quality assurance perspective. With the approval of the collection IRB, the collection of biospecimens that can be shared with GUDMAP consortia members is happening with the new consent forms in place. (b)(6) has been overseeing the collection and dissection of the specimens to accrue genitourinary specimens. (b)(6) and his lab have been receiving and utilizing specimens and assessing different modalities to ensure the highest quality specimens for the consortium members.

Information Technology Initiatives:
The Tissue Hub has been engaged in creating inventory and data management tools internally to appropriately annotate the GUDMAP tissue collections. In addition, local efforts have also focused on imaging of slides/ specimens to provide data and analysis. The Tissue Hub has been actively working with (b)(6) and the University of Southern California, as the GUDMAP Data Hub, to set up a portal and data transfer mechanism for collection and data annotation information to be securely transferred and available to GUDMAP investigators.

C. OVERALL PRODUCTS

C.1 PUBLICATIONS

Are there publications or manuscripts accepted for publication in a journal or other publication (e.g., book, one-time publication, monograph) during the reporting period resulting directly from this award?

No

C.2 WEBSITE(S) OR OTHER INTERNET SITE(S)

Nothing to report

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

C.4 INVENTIONS, PATENT APPLICATIONS, AND/OR LICENSES

Have inventions, patent applications and/or licenses resulted from the award during the reporting period?

No

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Category	Explanation
Data or Databases	The data collected and provided by the Hub will be in two broad categories. Firstly, we will provide annotation information related to the specimens collected for the GUDMAP investigators. The data elements to be collected have been defined by the consortium. The data will be securely provided to the Data Hub, which will host this information. The second major data component will be imaging data generated from the specimens and slides etc. In addition, molecular data will also be generated from select specimens.
Research Material	The Tissue Hub will collect specimens as per the needs of the GUDMAP investigators. The biospecimens will be both from surgical pathology specimens (products of conception) as well as autopsy material (still-births). In addition, additional specimens may be collected depending on investigator and programmatic needs and direction. The specimen types that can be accrued, and possible specimen accrual limitations, have been discussed with consortia members. Collection protocols will continue to be modified and fine-tuned to reflect the needs and the reality of human biospecimen collections; since diagnostic assessment is the primary purpose.

D. OVERALL PARTICIPANTS

D.1 WHAT INDIVIDUALS HAVE WORKED ON THE PROJECT?

Commons ID	S/K	Name	Degree(s)	Role	Cal	Aca	Sum	Foreign Org	Country	SS
(b)(6)	Y	(b)(6)	MD	PD/PI	(b)(6)					NA
	N			Technician						NA
	N			Technician						NA
	N			Technician						NA
	N			QC Manager						NA
(b)(6)	N			Co-Investigator						NA
	Y		BS,OTH,PHD	Co-Investigator						NA
	N			HSTB Supervisor						NA
	N			Project Manager						NA
	N			Co-Investigator						NA
(b)(6)	N		BS,MS,MD	Co-Investigator						NA

Glossary of acronyms:
S/K - Senior/Key
DOB - Date of Birth
Cal - Person Months (Calendar)
Aca - Person Months (Academic)
Sum - Person Months (Summer)
Foreign Org - Foreign Organization Affiliation
SS - Supplement Support
RE - Reentry Supplement
DI - Diversity Supplement
OT - Other
NA - Not Applicable

D.2 PERSONNEL UPDATES

D.2.a Level of Effort

Will there be, in the next budget period, either (1) a reduction of 25% or more in the level of effort from what was approved by the agency for the PD/PI(s) or other senior/key personnel designated in the Notice of Award, or (2) a reduction in the level of effort below the minimum amount of effort required by the Notice of Award?

No

D.2.b New Senior/Key Personnel

Are there, or will there be, new senior/key personnel?

No

D.2.c Changes in Other Support

Has there been a change in the active other support of senior/key personnel since the last reporting period?

Yes

File uploaded: (b)(6) Other Support Feb 2017.pdf

D.2.d New Other Significant Contributors

Are there, or will there be, new other significant contributors?

No

D.2.e Multi-PI (MPI) Leadership Plan

Will there be a change in the MPI Leadership Plan for the next budget period?

NA

For New and Renewal Applications (PHS 398) – DO NOT SUBMIT UNLESS REQUESTED

PHS 398 OTHER SUPPORT

Provide active and pending support for all senior/key personnel. **Other Support includes all financial resources, whether Federal, non-Federal, commercial or institutional, available in direct support of an individual's research endeavors, including but not limited to research grants, cooperative agreements, contracts, and/or institutional awards.** Training awards, prizes, or gifts do not need to be included.

There is no "form page" for other support. Information on other support should be provided in the *format* shown below, using continuation pages as necessary. ***Include the principal investigator's name at the top and number consecutively with the rest of the application.*** The sample below is intended to provide guidance regarding the type and extent of information requested.
For instructions and information pertaining to the use of and policy for other support, see Other Support in the Supplemental Instructions, Part III, Policies, Assurances, Definitions, and Other Information.
Effort devoted to projects must be measured using person months. Indicate calendar, academic, and/or summer months associated with each project.

Format

NAME OF INDIVIDUAL (b)(6)
ACTIVE/PENDING

ACTIVE

(b)(6)

(b)(6)

PENDING

(b)(4); (b)(6)

OVERLAP: No Overlap

E. OVERALL IMPACT

E.1 WHAT IS THE IMPACT ON THE DEVELOPMENT OF HUMAN RESOURCES?

Not Applicable

E.2 WHAT IS THE IMPACT ON PHYSICAL, INSTITUTIONAL, OR INFORMATION RESOURCES THAT FORM INFRASTRUCTURE?

NOTHING TO REPORT

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

Not Applicable

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?

NOTHING TO REPORT

F. OVERALL CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

F.2 ACTUAL OR ANTICIPATED CHALLENGES OR DELAYS AND ACTIONS OR PLANS TO RESOLVE THEM

The IRB process is almost done for the Tissue Hub. We have worked very closely with the IRB and do not anticipate any issues; as these have already been addressed. The collection IRB has already been extensively revamped; and has been IRB approved for about 6 weeks. The collection of biospecimens, that can be shared with GUDMAP consortia members, are happening with the new consent forms in place. The GUDMAP IRB is going through a final review and should be approved in the next few weeks. The draft MTA has been sent to the NIDDK and to the GUDMAP consortium members. The respective consortia sites could have delays if their legal teams want significant changes to the MTA verbiage. That is the only possible challenge that we anticipate at this point.

F.3 SIGNIFICANT CHANGES TO HUMAN SUBJECTS, VERTEBRATE ANIMALS, BIOHAZARDS, AND/OR SELECT AGENTS

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. OVERALL SPECIAL REPORTING REQUIREMENTS

G.1 SPECIAL NOTICE OF AWARD TERMS AND FUNDING OPPORTUNITIES ANNOUNCEMENT REPORTING REQUIREMENTS

NOTHING TO REPORT

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

G.4.a Does the project involve human subjects?

Yes

Is the research exempt from Federal regulations?

No

Does this project involve a clinical trial?

No

G.4.b Inclusion Enrollment Data

Report Attached: Research on tissue from an elective or spontaneous abortion < 24 weeks gestation

G.4.c ClinicalTrials.gov

Does this project include one or more applicable clinical trials that must be registered in ClinicalTrials.gov under FDAAA?

No

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Are there personnel on this project who are newly involved in the design or conduct of human subjects research?

Yes

(b)(6) replaced (b)(6) who was a co-investigator on this grant and has left the University of Pittsburgh. (b)(6) completed the Collaborative Institutional Training Initiative (CITI) Biomedical Human Subjects Research on 09/14/2016 This course covers the historical development of human subject protections, as well as current regulatory information and ethical issues.

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

Does this project involve human embryonic stem cells (only hESC lines listed as approved in the NIH Registry may be used in NIH funded research)?

No

G.7 VERTEBRATE ANIMALS

Does this project involve vertebrate animals?

No

G.8 PROJECT/PERFORMANCE SITES

Organization Name:	DUNS	Congressional District	Address
Primary: University of Pittsburgh	004514360	PA-014	(b)(4); (b)(6)
University of Pittsburgh	004514360	PA-014	
University of Pittsburgh	004514360	PA-014	
UNIVERSITY OF PITTSBURGH AT PITTSBURGH	004514360		UNIVERSITY OF PITTSBURGH OFFICE OF RESEARCH PITTSBURGH PA 152132303

G.9 FOREIGN COMPONENT

No foreign component

G.10 ESTIMATED UNOBLIGATED BALANCE

G.10.a Is it anticipated that an estimated unobligated balance (including prior year carryover) will be greater than 25% of the current year's total approved budget?

Yes

Estimated unobligated balance: 261812

G.10.b Provide an explanation for unobligated balance:
It is expected we wil have greater than 25% carryover due to the delay in the IRB and MTA as well as pending invoices for IT professional services. Without the IRB and MTA in place, the work to prepare and ship samples could not be completed. We expect that in year 2 of the award, we will address all pending requests for tissue from year 1 as well as those needed in year 2. For this reason, we plan to formally request the carryover funds from year 1 from the NIDDK to ensure we have the funds to address all requests for year 2.

G.10.c If authorized to carryover the balance, provide a general description of how it is anticipated that the funds will be spent

G.11 PROGRAM INCOME

Is program income anticipated during the next budget period?

No

G.12 F&A COSTS

Not Applicable

Inclusion Enrollment Report

Inclusion Data Record (IDR) #: 1078054

Using an Existing Dataset or Resource: No

Delayed Onset Study ?: No

Clinical Trial: No

Enrollment Location: Domestic

NIH Defined Phase III Clinical Trial: No

Study Title: Research on tissue from an elective or spontaneous abortion < 24 weeks gestation

Planned Enrollment

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/Alaska Native	0	0		0	0					**0**
Asian	50	0		0	0					**50**
Native Hawaiian or Other Pacific Islander	0	0		0	0					**0**
Black or African American	100	0		10	0					**110**
White	200	0		20	0					**220**
More than One Race	0	0		20	0					**20**
Unknown or Not Reported										
Total	**350**	**0**		**50**	**0**					**400**

Cumulative Enrollment

Only planned enrollment data exists for this data record. The PD/PI did not enter cumulative inclusion enrollment data.

RESEARCH & RELATED BUDGET - SECTION A & B

ORGANIZATIONAL DUNS*: 004514360

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: UNIVERSITY OF PITTSBURGH AT PITTSBURGH

Start Date*: 06-01-2017 **End Date*:** 05-31-2018

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1.		(b)(6)				Project Lead	(b)(6)				37,400.00	9,278.00	46,678.00
2.						Co-investigator					20,550.00	5,098.00	25,648.00
3.						Co-investigator					26,846.00	6,660.00	33,506.00
4.						Co-investigator					9,000.00	2,233.00	11,233.00
5.						Co-investigator					6,000.00	1,489.00	7,489.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **124,554.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
9	Support staff	(b)(6)			127,745.00	46,755.00	174,500.00
9	**Total Number Other Personnel**					**Total Other Personnel**	**174,500.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**299,054.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E

ORGANIZATIONAL DUNS*: 004514360

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: UNIVERSITY OF PITTSBURGH AT PITTSBURGH

Start Date*: 06-01-2017 **End Date*:** 05-31-2018

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	12,502.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**12,502.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		0.00
2. Stipends		0.00
3. Travel		0.00
4. Subsistence		0.00
5. Other:		
0 Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**0.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K

ORGANIZATIONAL DUNS*: 004514360

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: UNIVERSITY OF PITTSBURGH AT PITTSBURGH

Start Date*: 06-01-2017 **End Date*:** 05-31-2018

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	50,991.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. HSTB Services	8,000.00
9. Project Management Tool, BIOS (IT Services)	26,335.00
10. Shipping costs	500.00
Total Other Direct Costs	**85,826.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**397,382.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. MTDC	54.0	32,448.00	17,522.00
2. MTDC	55.5	356,933.00	198,098.00
		Total Indirect Costs	**215,620.00**

Cognizant Federal Agency
(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**613,002.00**

J. Fee	Funds Requested ($)*
	0.00

K. Budget Justification*	File Name: Fetal budget justification _yr 2.pdf
	(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

BUDGET JUSTIFICATION

Personnel

(b)(6) PI, Effort = (b)(6) is the (b)(6) (b)(6) of the University of Pittsburgh and a practicing pathologist with subspecialty training in Genitourinary Pathology. He will be responsible for the oversight of the project. This will include interfacing and working with internal collaborators to ensure accrual and annotation of the appropriate specimens. He will also interact with the external collaborators and clients to ensure appropriate specimen aggregation and disbursement. He will work closely with NIDDK to ensure successful execution of the project, meeting the mission and goals of the Tissue Core (**Figure 1**: Proposed organizational structure of the Tissue Core). Annual effort of (b)(6) is requested.

(b)(6) Effort = (b)(6) This (b)(6) will be responsible for coordination and management of day to day operations. She supervises HSTB staff members and will manage the overall efforts of the HSTB and set operational standards related to the HSTB scope of work. She will assure proper communication and resolution conflicts and issues.

1. Tissue Hub Infrastructure Support

A crucial component of this application is the infrastructure for the Tissue Hub, which will include personnel for the development and maintenance of a secure web-based interface for GUDMAP investigators, assurance of regulatory compliance, data collection and record-keeping, and management of the quality assurance program associated with this project.

(b)(6) Co-I, Effort = (b)(6) is the Director of (b)(6) and will be the director of the Tissue hub Infrastructure. He also serves as the faculty in-charge of the informatics requirements of HSTB. He provides direction and advice related to the different Information systems and tools used by HSTB. He is also the director of the Imaging core; a subsidiary of HSTB. The imaging core will perform whole slide image acquisition and provide access to these images for the Tissue Core clients. Annual effort of (b)(6) is requested.

(b)(6) Effort = (b)(6) This (b)(6) will be responsible for project intake, tracking and recording keeping. She will coordinate the GUDMAP investigator requests to the GUDMAP-Human Tissue Repository including documenting the needs of the investigator, assuring regulatory compliance, coordinating with tissue and data collection staff members and assuring proper completion and shipping of requests. Annual effort of (b)(6) is requested.

(b)(6) Effort = (b)(6) This (b)(6) will be responsible for the quality program. He will manage all aspects of quality management including record keeping, training of staff members to standard operating procedures (SOPs), data entry practices and audits, and quality related events. He will coordinate the overall record keeping and management of the quality metrics from the tissue collection and data entry processes with the quality measurements performed through the Department of Pediatrics team.

(b)(6) Effort = (b)(6) This (b)(6) specialist will be responsible for overall management of the Biospecimen Inventory and Operations System with regard to the this project. He will manage the specimen search process, control the data entry lexicon as needed, and provide reports of collection activity for investigators who request samples and as needed for other purposes. He will maintain the data integrity and make corrections and amendments based on the quality control activities. In the case that new fields and library elements are required he will manage that process in conjunction with the Project Manager and Quality Manager. He will be required to produce final sample pick lists as specimens are disbursed.

(b)(6) **(Histology Supervisor):** Effort = (b)(6) is the technician responsible for processing tissues, immunohistochemistry and immunofluorescence needs of the project. He is also the supervisor of the Research Histology core facility and is responsible for the development of specialized techniques required by the program and for processes not included in the fee-for-service activity.

(b)(6) Effort = (b)(6) The (b)(6) will be responsible for aggregating information from the different information systems on the specimens offered as part of the Tissue Core. This will include pathology information as well as more specialized information (like

cytogenetics); if applicable. The data coordinator will work with the Project manager on cohort identification for the different requests. In addition the data coordinator will also be responsible for providing data to the clients of the Tissue Core.

2. Fetal Tissue Procurement Laboratory (b)(4); (b)(6)

All of the fetal tissue will be (b)(4); (b)(6) undergo a gross examination, and then be transported to the validation laboratory for further assessment prior to distribution.

(b)(6) **:** Co-I, Effort = (b)(6) is the (b)(6) (b)(6) He will be responsible for evaluating appropriate surgical pathology and autopsy specimens, and overseeing collection of the biological materials for the Tissue Core and will act as the director of the tissue procurement laboratory. He will perform the clinical evaluation of the gross genitourinary specimen and ensure quality control of the dissection to minimize mechanical disruption. He will train the staff to obtain early gestational age genitourinary specimens, and work closely with (b)(6) to perform routine and specialized histological assessment of the appropriate specimens. Annual effort of (b)(6) is requested.

(b)(6) Effort = (b)(6) This HSTB tissue bank technician and will perform the day-to-day tasks associated with the collection of specimens. This includes maintaining a working knowledge of all SOPs related to the ongoing collections that are requested by the GUDMAP investigators. She will coordinate with the clinical departments within (b)(4); (b)(6) interface with the Pathology and other hospital staff members as required to obtain the requested specimens and enter data related to each case in the BIOS.

(b)(6) **:** Effort = (b)(6) This HSTB tissue bank supervisor and technician will perform the day-to-day tasks associated with the collection of specimens. This includes maintaining a working knowledge of all SOPs related to the ongoing collections that are requested by the GUDMAP investigators. She will coordinate with the clinical departments within (b)(4); (b)(6), interface with the Pathology and other hospital staff members as required to obtain the requested specimens and enter data related to each case in the BIOS.

3. Validation Laboratory (b)(6)

The validation laboratory will perform quality assurance measures, as per GUDMAP project needs (eg. histological assessment, *in situ* hybridization and RNA isolation).

(b)(6) **:** Co-I, Effort = (b)(6) is a kidney developmental biologist with over (b)(6) studying the genitourinary tract and will act as the director of the validation laboratory. Furthermore, he is also a classically trained human anatomist, histologist and embryologist. The quality assurance of the specimens will be performed by at least two independent evaluations (b)(6) for GUDMAP project needs. (b)(6) will work closely with (b)(6) to train staff to perform the gross dissection for early gestational age genitourinary tissues, and tissues not currently being obtained by the Tissue Bank, as per GUDMAP project needs. He will also oversee the training of (b)(6) (tissue hub technician) in all aspects of dissection, histology and molecular evaluation of the fetal tissues.

(b)(6) **:** Co-I, Effort = (b)(6) is a clinician scientist (Pediatric Nephrologist) with a research program related to kidney development and will act as the co-director of the validation laboratory. She has a thorough understanding of genitourinary development. She will participate in quality assurance of specimens as noted above. Furthermore, (b)(6) will provide direction and advice regarding the clinical parameters that will be used to screen fetal and neonatal tissues to exclude pathological specimens, and will evaluate individual cases as needed.

(b)(6) **:** Effort = (b)(6) This grant will fund (b)(6) of the technicians salary. This technician will perform all the required validation of the specimens including: histology, immunohistochemistry, in situ hybridization, cell isolation and real time PCR.

Supplies

HSTB Consumable Laboratory Supplies: (b)(4) Or about (b)(4) monthly will be used for sample collections, integrity, maintenance, and transport including sample and shipping containers, dry ice, and other basic supplies.

Shipping: Funds are requested for the shipment of tissue (b)(4) is requested.

Validation Laboratory Consumable Laboratory Supplies: (b)(4) Or about (b)(4) monthly will be required to purchase reagents for staining, immunohistochemistry and in situ reagents as well as cell, culture medium and consumable plastics related to these processes. These processes will be performed in response to the needs of the GUDMAP investigators.

Travel

Pathology: The Project PI and HSTB staff will need to travel to GUDMAP consortia meetings, to be held twice a year. A total of $6,502 is allocated for this travel in year 2.

Validation Laboratories: The Project co-investigators will need to travel to GUDMAP consortia meetings, to be held twice a year. (b)(6) will also attend the American Society of Nephrology meeting where GUDMAP typically has a booth. A total of $6,000 is allocated for this travel in year 2.

(b)(6) will also attend the International Meeting on Development Nephrology to be held in 2018, where GUDMAP will hold workshops.

Other Expenses

Tissue embedding/processing, storage, and disbursement: (b)(4) for year 2. These are billable services based on the fiscal parameters in place within the University of Pittsburgh for the HSTB. Tissue embedding and processing will be required at all levels for quality management and to provide product to GUDMAP investigators. Storage costs are based on the partial cost of a freezer with a 10 year life span plus projected maintenance and certification costs. The cost for disbursement of samples to GUDMAP investigators will be charged to the account award for this project.

Website maintenance, project management tool, BIOS, image acquisition: $26,335. Resources will be required to maintain and update our internally developed inventory management system (BIOS). The project management tool is internally developed and is the mechanism for starting and following the progress of the request from the client. The clients will be provided access to the contents of the resource via a Sharepoint link that will be password protected. Whole slide image acquisition will be done to offer clients access to high quality images of the specimens in the resource. These images will be from routine and specialized histologic and immunohistochemical/ in-situ protocols. We also have capabilities for image analysis and will offer, if required.

Notice of Award

RESEARCH PROJECT COOPERATIVE AGREEMENT **Federal Award Date:** 07/03/2017

Department of Health and Human Services
National Institutes of Health

NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

Grant Number: 5U01DK110792-02
FAIN: U01DK110792

Principal Investigator(s):
(b)(6)

Project Title: Four-dimensional Modeling of Mouse and Human Nephrogenesis.

(b)(6)
2001 N. Soto Street
(b)(6)
Los Angeles, CA 900899235

Award e-mailed to: uscaward@usc.edu

Period Of Performance:
Budget Period: 06/01/2017 – 05/31/2018
Project Period: 09/15/2016 – 05/31/2021

Dear Business Official:

The National Institutes of Health hereby awards a grant in the amount of $387,083 (see "Award Calculation" in Section I and "Terms and Conditions" in Section III) to UNIVERSITY OF SOUTHERN CALIFORNIA in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 31 USC 6305 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award including the "Terms and Conditions" is acknowledged by the grantee when funds are drawn down or otherwise obtained from the grant payment system.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as "Research reported in this publication was supported by the National Institute Of Diabetes And Digestive And Kidney Diseases of the National Institutes of Health under Award Number U01DK110792. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health." Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Award recipients must promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under NIH awards will be free from bias resulting from an Investigator's Financial Conflict of Interest (FCOI), in accordance with the 2011 revised regulation at 42 CFR Part 50 Subpart F. The Institution shall submit all FCOI reports to the NIH through the eRA Commons FCOI Module. The regulation does not apply to Phase I Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) awards. Consult the NIH website http://grants.nih.gov/grants/policy/coi/ for a link to the regulation and additional important information.

If you have any questions about this award, please contact the individual(s) referenced in Section IV.

Sincerely yours,

(b)(6)

Grants Management Officer
NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

Additional information follows

SECTION I – AWARD DATA – 5U01DK110792-02

Award Calculation (U.S. Dollars)

Salaries and Wages	$98,758
Fringe Benefits	$32,787
Personnel Costs (Subtotal)	$131,545
Materials & Supplies	$32,495
Travel	$4,336
Other	$66,220
Federal Direct Costs	$234,596
Federal F&A Costs	$152,487
Approved Budget	$387,083
Total Amount of Federal Funds Obligated (Federal Share)	$387,083
TOTAL FEDERAL AWARD AMOUNT	$387,083
AMOUNT OF THIS ACTION (FEDERAL SHARE)	$387,083

SUMMARY TOTALS FOR ALL YEARS		
YR	**THIS AWARD**	**CUMULATIVE TOTALS**
2	$387,083	$387,083
3	$387,083	$387,083
4	$387,083	$387,083
5	$387,083	$387,083

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

Fiscal Information:

CFDA Name:	Diabetes, Digestive, and Kidney Diseases Extramural Research
CFDA Number:	93.847
EIN:	1951642394A1
Document Number:	UDK110792A
PMS Account Type:	P (Subaccount)
Fiscal Year:	2017

IC	CAN	2017	2018	2019	2020
DK	8472278	$387,083	$387,083	$387,083	$387,083

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

NIH Administrative Data:
PCC: KDH KDB / **OC**: 414P / **Released**: (b)(6) 06/30/2017
Award Processed: 07/03/2017 11:20:39 AM

SECTION II – PAYMENT/HOTLINE INFORMATION – 5U01DK110792-02

For payment and HHS Office of Inspector General Hotline information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

SECTION III – TERMS AND CONDITIONS – 5U01DK110792-02

This award is based on the application submitted to, and as approved by, NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

a. The grant program legislation and program regulation cited in this Notice of Award.
b. Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.
c. 45 CFR Part 75.
d. National Policy Requirements and all other requirements described in the NIH Grants

Policy Statement, including addenda in effect as of the beginning date of the budget period.

e. Federal Award Performance Goals: As required by the periodic report in the RPPR or in the final progress report when applicable.
f. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(See NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm for certain references cited above.)

Research and Development (R&D): All awards issued by the National Institutes of Health (NIH) meet the definition of "Research and Development" at 45 CFR Part§ 75.2**.** As such, auditees should identify NIH awards as part of the R&D cluster on the Schedule of Expenditures of Federal Awards (SEFA). The auditor should test NIH awards for compliance as instructed in Part V, Clusters of Programs. NIH recognizes that some awards may have another classification for purposes of indirect costs. The auditor is not required to report the disconnect (i.e., the award is classified as R&D for Federal Audit Requirement purposes but non-research for indirect cost rate purposes), unless the auditee is charging indirect costs at a rate other than the rate(s) specified in the award document(s).

This institution is a signatory to the Federal Demonstration Partnership (FDP) Phase VI Agreement which requires active institutional participation in new or ongoing FDP demonstrations and pilots.

Carry over of an unobligated balance into the next budget period requires Grants Management Officer prior approval.

This award is subject to the requirements of 2 CFR Part 25 for institutions to receive a Dun & Bradstreet Universal Numbering System (DUNS) number and maintain an active registration in the System for Award Management (SAM). Should a consortium/subaward be issued under this award, a DUNS requirement must be included. See http://grants.nih.gov/grants/policy/awardconditions.htm for the full NIH award term implementing this requirement and other additional information.

This award has been assigned the Federal Award Identification Number (FAIN) U01DK110792. Recipients must document the assigned FAIN on each consortium/subaward issued under this award.

Based on the project period start date of this project, this award is likely subject to the Transparency Act subaward and executive compensation reporting requirement of 2 CFR Part 170. There are conditions that may exclude this award; see http://grants.nih.gov/grants/policy/awardconditions.htm for additional award applicability information.

In accordance with P.L. 110-161, compliance with the NIH Public Access Policy is now mandatory. For more information, see NOT-OD-08-033 and the Public Access website: http://publicaccess.nih.gov/.

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts with cumulative total value greater than $10,000,000 must report and maintain information in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made publicly available in the designated integrity and performance system (currently the Federal Awardee Performance and Integrity Information System (FAPIIS)). Full reporting requirements and procedures are found in Appendix XII to 45 CFR Part 75. This term does not apply to NIH fellowships.

Treatment of Program Income:

SECTION IV – DK Special Terms and Conditions – 5U01DK110792-02

The issuance of this award has been delayed due to administrative funding considerations. According to NIH policy, if pre-award costs are necessary, they may be approved by the authorized Institution Official(s).

Notice: Under governing policy, federal funds administered by the Public Health Service (PHS) shall not be expended for research involving live vertebrate animals without prior approval by the Office of Laboratory Animal Welfare (OLAW) of an assurance to comply with the PHS policy on humane care and use of laboratory animals. This restriction applies to all performance sites (e.g., collaborating institutions, subcontractors, subgrantees) without OLAW-approved assurances, whether domestic or foreign.

The grantee is required to follow the model organism sharing plan included in the application and may not implement any changes in the plan without the written prior approval of the NIDDK.

Notice: Under governing regulations, Federal funds administered by the Department of Health and Human Services shall not be expended for research involving human subjects, and individuals shall not be enrolled in such research, without prior approval by the Office of Human Research Protections (OHRP) of an assurance to comply with the requirements of 45 CFR 46 to protect human research subjects. This restriction applies to all collaborating sites without OHRP-approved assurances, whether domestic or foreign, and compliance must be ensured by the awardee.

This award involves the use of human embryonic stem cells (hESCs). The grantee may use only those hESCs that appear on the NIH Human Embryonic Stem Cell Registry as eligible for NIH funding (http://grants.nih.gov/stem_cells/registry/current.htm) and in accord with any restrictions placed on the use of those lines.

This grant is in response to RFA/PA DK15-014. Acceptance of this award requires compliance with this solicitation. See the NIH Guide at http://grants.nih.gov/grants/guide/index.html for copy of the RFA/PA that includes administrative and programmatic requirements specific to this award.

In accordance with NIH Guide Notice NOT-OD-17-049, Notice of Salary Limitation on Grants, Cooperative Agreements, and Contracts, none of the funds in this award shall be used to pay the salary of an individual at a rate in excess of the applicable salary cap. Therefore, this award and/or future years are adjusted accordingly, if applicable. See the Salary Cap Summary for a historical record of the salary cap, including effective dates.

Grantees can determine which progress reports are due through the website located at https://public.era.nih.gov/chl/public/search/index.jsp and should periodically check the site, which is updated on or around the 30th of each month. Progress report due dates are also available in the eRA Commons Status system. In addition, automatic e-mail notifications are sent to the PD/PI prior to due date.

As of October 17, 2014, the National Institutes of Health (NIH) requires grantees to submit all type 5 progress reports using the eRA Research Performance Progress Report (RPPR) module. Annual progress reports submitted in any format other than the RPPR will not be processed by the NIH and will require resubmission through the RPPR module in accordance with NIH Guide Notice NOT-OD-15-014 released October 16, 2014.

The following special terms of award are in addition to, and not in lieu of, otherwise applicable U.S. Office of Management and Budget (OMB) administrative guidelines, U.S. Department of Health and Human Services (DHHS) grant administration regulations at 45 CFR Parts 74 and 92 (Part 92 is applicable when State and local Governments are eligible to apply), and other HHS, PHS, and NIH grant administration policies.

The administrative and funding instrument used for this program will be the cooperative agreement, an "assistance" mechanism (rather than an "acquisition" mechanism), in which substantial NIH programmatic involvement with the awardees is anticipated during the performance of the activities.

Under the cooperative agreement, the NIH purpose is to support and stimulate the recipients' activities by involvement in and otherwise working jointly with the award recipients in a partnership role; it is not to assume direction, prime responsibility, or a dominant role in the activities. Consistent with this concept, the dominant role and prime responsibility resides with the awardees for the project as a whole, although specific tasks and activities may be shared among the awardees and the NIH as defined below.

The PD(s)/PI(s) will have the primary responsibility for:

- All aspects of the scientific activities, including defining the objectives and approaches, planning, conduct, analysis, and publication of results, interpretations, and conclusions of studies conducted under the terms and conditions of the cooperative agreement award.
- Collaborating with other investigators in the program for protocol development, sample, reagents and data sharing as appropriate, data quality control, and data organization
- Accountability towards the applicant organization officials and to the NIDDK for the performance and proper conduct of the research supported by the project in accordance with the terms and conditions of the award.
- Serving as a voting member of the Steering Committee and will attend the Planning Meeting and a Steering Committee meeting in the first year, two Steering Committee meetings a year in subsequent years and monthly teleconference calls.
- Accepting and implementing the goals, priorities, procedures, protocols, and policies agreed upon by the Steering Committee and subcommittees, and be responsible for close coordination and cooperation with the components of the GUDMAP consortium and with NIH staff.
- Adhering to PHS policy for the distribution of unique research resources produced with PHS funding as described under Special Requirements.
- Establishing written milestones for the project, in negotiation with NIDDK Project Staff prior to funding.
- Release all study design materials and procedure manuals into the public domain and/or make them available to other investigators, according to the approved plan for making data and materials available to the scientific community and the NIDDK, for the conduct of research at no charge other than the costs of reproduction and distribution, consistent with achieving the goals of this program initiative.
- Awardees will retain custody of and have primary rights to the data and software developed under these awards, subject to Government rights of access consistent with current DHHS, PHS, and NIH policies.
  NIH staff will have substantial programmatic involvement that is above and beyond the normal stewardship role in awards, as described below:

- An NIH Project Scientist will have substantial programmatic involvement that is above and beyond the normal stewardship role in awards, as described below. However, the dominant role and prime responsibility for the project as a whole resides with the awardees, although specific tasks and activities in carrying out the studies will be shared by awardees and the NIDDK.
- NIDDK will designate a Project Officer and a Grants Management Specialist to provide normal program stewardship and administrative oversight of the cooperative agreement.
- NIDDK will form an External Advisory Committee (EAC), comprised of the NIDDK Project Scientist and other NIH extramural staff with relevant scientific expertise or who manage research grant programs that relate scientifically to the goals of the GUDMAP projects, and outside advisors selected by the NIDDK. The EAC will meet annually with the GUDMAP Steering Committee to review and assess GUDMAP and to advise NIDDK of scientific developments and opportunities that may enhance the achievement of the GUDMAP goals.
- The NIDDK Project Scientist will attend and participate as a voting member in all meetings of the Steering Committee, and provide liaison between the Steering Committee and the External Advisory Committee.
- The NIDDK Project Scientist will help the Steering Committee develop and draft operating policies.
- The NIDDK Project Officer will review the scientific progress of the individual GUDMAP components, for compliance with operating policies developed by the Steering Committee, and may recommend to the NIDDK to withhold support, suspend, or terminate an award for lack of scientific progress or failure to adhere to policies established by the Steering Committee.

- An agency program official or IC program director will be responsible for the normal scientific and programmatic stewardship of the award and will be named in the award notice. The assigned Program Officer may also serve as an NIH Project Scientist.
  Areas of Joint Responsibility include:

- Steering Committee - The NIH Project Scientist, PIs from the project funded through this FOA and RFA-DK-15-015, and RFA-DK-15-016 and voluntary representatives from the previously funded GUDMAP atlas projects funded under RFA-DK-11-001 will be responsible for forming a Steering Committee as defined below. An arbitration system, as detailed below, will be available to resolve disagreements among members of the Steering Committee. The Steering Committee will be the main governing board of the GUDMAP consortium. It will develop collaborative protocols, identify technological impediments to success and strategies to overcome them, develop shared software tools for disseminating information about the projects, and identify opportunities for sharing techniques and tools that might be developed in future GUDMAP atlas projects.
- The Steering Committee will be composed of the PIs from the project funded through this FOA, RFA-DK-15-015, and RFA-DK-15-016, representatives from the previously funded GUDMAP projects, and the NIDDK Project Scientist. The representatives and the PIs will each have one vote. The NIDDK Project Scientist for this project will have one vote. The Steering Committee will select a chairperson who will be someone other than an NIH staff member.
- The Steering Committee may, as it deems necessary, invite additional, non-voting scientific advisors to meetings at which research priorities and opportunities are discussed. The NIH reserves the right to augment the scientific or consumer expertise of the Steering Committee when necessary.
- There will be two Steering Committee meetings annually. The first meeting will be a Planning Meeting to be held in the Washington, DC area on June 20-21, 2016. At the Planning Meeting, the Steering Committee will be formed and a chairperson selected from among the members. At the Planning Meeting, the Steering Committee may: (a) draft a charter to detail policies and procedures, a process for monitoring compliance with the policies and procedures, and a process for recommending that the NIH Project Administrators act on evidence of non-compliance of any Consortium component with Steering Committee policies; (b) agree upon the terms of the charter; and (c) devise a plan for working with the GUDMAP database developers to provide ongoing input into database and website design.
- At the second and subsequent meetings, the Steering Committee will refine the GUDMAP scientific objectives and implementation as necessary, consistent with data produced by former and possible future GUDMAP atlas projects and from other laboratories.
- The Steering Committee will plan workshops, to which non-GUDMAP participants will also be invited, to inform the research community of the progress made toward development of the atlas, and to inform the research community of any technological advances related to the implementation of the GUDMAP website/database. The NIDDK Project Scientist, the External Advisory Committee, and other NIH staff as appropriate will provide the Steering Committee with advice on participants for the workshops and symposia.
- The Steering Committee may establish subcommittees as it deems appropriate.
- Awardee members of the Steering Committee will be required to accept and implement policies approved by the Steering Committee.
- The EAC will meet annually with the GUDMAP Steering Committee to review and assess the progress of the GUDMAP consortium and to advise NIDDK of scientific developments and opportunities that may enhance the achievement of the GUDMAP goals.
  Dispute Resolution
  Any disagreements that may arise in scientific or programmatic matters (within the scope of the award) between award recipients and the NIH may be brought to Dispute Resolution. A Dispute Resolution Panel will have three members: a designee of the Steering Committee chosen without NIH staff voting, one NIH designee, and a third designee with expertise in the relevant area who is chosen by the other two; in the case of individual disagreement, the first member may be chosen by the individual awardee. This special dispute resolution procedure does not alter the awardee's right to appeal an adverse action that is otherwise appealable in accordance with PHS regulation 42 CFR Part 50, Subpart D and DHHS regulation 45 CFR Part 16.

STAFF CONTACTS

The Grants Management Specialist is responsible for the negotiation, award and administration of this project and for interpretation of Grants Administration policies and provisions. The Program Official is responsible for the scientific, programmatic and technical aspects of this project. These individuals work together in overall project administration. Prior approval requests (signed by an Authorized Organizational Representative) should be submitted in writing to the Grants Management Specialist. Requests may be made via e-mail.

Grants Management Specialist: (b)(6)
Email: (b)(6) @extra.niddk.nih.gov **Phone**: (b)(6) **Fax**: (301) 480-3504

Program Official: (b)(6)
Email: (b)(6) @niddk.nih.gov **Phone**: (b)(6)

SPREADSHEET SUMMARY
GRANT NUMBER: 5U01DK110792-02

INSTITUTION: UNIVERSITY OF SOUTHERN CALIFORNIA

Budget	Year 2	Year 3	Year 4	Year 5
Salaries and Wages	$98,758	$98,758	$98,758	$98,758
Fringe Benefits	$32,787	$32,787	$32,787	$32,787
Personnel Costs (Subtotal)	$131,545	$131,545	$131,545	$131,545
Materials & Supplies	$32,495	$32,495	$32,495	$32,495
Travel	$4,336	$4,336	$4,336	$4,336
Other	$66,220	$66,220	$66,220	$66,220
TOTAL FEDERAL DC	$234,596	$234,596	$234,596	$234,596
TOTAL FEDERAL F&A	$152,487	$152,487	$152,487	$152,487
TOTAL COST	$387,083	$387,083	$387,083	$387,083

Facilities and Administrative Costs	Year 2	Year 3	Year 4	Year 5
F&A Cost Rate 1	65%	65%	65%	65%
F&A Cost Base 1	$234,596	$234,596	$234,596	$234,596
F&A Costs 1	$152,487	$152,487	$152,487	$152,487

A. OVERALL COVER PAGE

Project Title: Four-dimensional Modeling of Mouse and Human Nephrogenesis.	
Grant Number: 5U01DK110792-02	**Project/Grant Period:** 09/15/2016 - 05/31/2021
Reporting Period: 09/15/2016 - 05/31/2017	**Requested Budget Period:** 06/01/2017 - 05/31/2018
Report Term Frequency: Annual	**Date Submitted:** 04/03/2017
Program Director/Principal Investigator Information: (b)(6) **Phone number:** (b)(6) **Email:** (b)(6)@med.usc.edu	**Recipient Organization:** UNIVERSITY OF SOUTHERN CALIFORNIA DEPARTMENT OF CONTRACTS AND GRANTS 1640 Marengo Street, (b)(6) LOS ANGELES, CA 900339263 **DUNS:** 072933393 **EIN:** 1951642394A1 **RECIPIENT ID:**
Change of Contact PD/PI: N/A	
Administrative Official: (b)(6) 1640 Marengo Street (b)(6) Los Angeles, CA 900339263 **Phone number:** (b)(6) **Email:** (b)(6)@usc.edu	**Signing Official:** (b)(6) 1640 Marengo Street (b)(6) Los Angeles, CA 900339263 **Phone number:** (b)(6) **Email:** (b)(6)@usc.edu
Human Subjects: No	**Vertebrate Animals:** Yes
hESC: Yes	**Inventions/Patents:** No

B. OVERALL ACCOMPLISHMENTS

B.1 WHAT ARE THE MAJOR GOALS OF THE PROJECT?

Aim 1: To generate comparative 3D morphological maps of nephron progenitor and nephron patterning in the mouse and human kidney

Aim 2: To generate high-resolution dynamic views of mouse and human kidney development utilizing genetically modified mouse strains and genetically engineered human pluripotent stem cell lines

B.1.a Have the major goals changed since the initial competing award or previous report?

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

File uploaded: Progress Report and Appendix Combined.pdf

B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

For this reporting period, is there one or more Revision/Supplement associated with this award for which reporting is required?

No

B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

NOTHING TO REPORT

B.5 HOW HAVE THE RESULTS BEEN DISSEMINATED TO COMMUNITIES OF INTEREST?

(b)(6) has discussed data with the non profit organization, UKRO (University Kidney Research Organization).

B.6 WHAT DO YOU PLAN TO DO DURING THE NEXT REPORTING PERIOD TO ACCOMPLISH THE GOALS?

Aim 1. We will continue with efforts to segment and relationally map different stages of mouse and human nephron development with the end point of a connected (to the ureteric epithelium) S-shaped body. We will attempt to generate harmonized, accurate models of mouse and human nephrogenesis that embrace morphogenesis and patterning as visualized by our antibody sets.

Aim 2. Given the investment to date in generating reporter cell lines in HUESC9 cells (additional lines targeting SLC34a1 [proximal tubule], CITED1 and SIX2 [nephron progenitors] have also been generated and are also being characterized), we need to make an important strategic decision
a)do we continue with the (b)(6) protocol attempting to optimize with existing cell lines
b)do we continue with the protocol generating new knock-in reporters in a better suited cell line
c)or do we pursue other protocols form the (b)(6) laboratories that do not attempt to develop a model that generates all kidney cell types optimizing either ureteric bud and nephrogenic mesenchyme specification independently.
We will examine option “c” with the existing lines and utilizing stage-specific antibody markers before making a decision here.

(b)(6) Progress Report 1 U01DK110792-01

Four-dimensional Modeling of Mouse and Human Nephrogenesis

A) Specific Aims

Aim 1: To generate comparative 3D morphological maps of nephron progenitor and nephron patterning in the mouse and human kidney

The current view of mammalian genitourinary development is largely two-dimensional (2D). Addition of 3D gene expression maps generated by optical projection tomography has provided significant new insights into development of the external genitalia (b)(6) in GUDMAP2 round of funding). **We will generate detailed 3D insights into mouse and human nephrogenesis through optical imaging and secondary image analysis generating a comparative morphological atlas for mouse and human kidney development.**

Aim 2: To generate high-resolution dynamic views of mouse and human kidney development utilizing genetically modified mouse strains and genetically engineered human pluripotent stem cell lines

Time lapse imaging of the ureteric epithelium branching in kidney organ culture has provided important new insights into progenitor cell dynamics in the development of the collecting duct. **This Aim focuses on visualizing the cellular dynamics underlying mammalian nephrogenesis through live cell imaging. The data will complement studies in Aim1 that incorporate selected mutants into live cell imaging studies.** Recent advances in genome editing and directed differentiation of PSCs will enable imaging of human models of nephrogenesis.

B) Studies and Results

Aim 1. Generating comparative 3D morphological maps of nephron progenitor and nephron patterning in the mouse and human kidney

Our initial focus has been to generate a well-validated set of antibodies active across mouse and human kidney samples that can be used in strategic combinations to defined each stage of nephron patterning from nephron progenitor to mature nephron. The antibody list is appended (Table 1). With the understanding that no informative 3-D view will be possible without the best possible 2-D view, we have performed an extensive series of immunostaining to visualize and compare the nephrogenic program in the mouse and human kidney at different stages of development. We are currently working on manuscripts that will highlight key features that distinguish these two mammalian systems. A large number of high quality, multi-channel confocal images are available for uploading to the GUDMAP database though viewing these to maximum effect will require a browser interface that separates each channel. Examples of this data are provided in Figures 1 and 2. In moving to 3-D views, we have established whole-mount immunostaining procedures and confocal imaging on cleared material to perform deep (~200um) imaging from the cortical region into the nephrogenic zone. An example of the imaging is provided in the attached file Movie 1. With these whole views, we have started to quantify parameters such as nephron progenitor to niche ratios in the human kidney to get a comparative sense of mouse and human dynamics comparing our data with data from Short et al., 2014. These approaches reveal a dense array of different nephron structures at varying stages of development, as we would expect, with single cell resolution; a data quality comparable to the 2-D datasets. The next step has been to segment out nephron structures to visualize morphogenesis and patterning at different stages. The efforts have raised an important question that has never been addressed. Is nephrogenesis stereotyped within a species? That is do intermediates at equivalent stages of development at different positions within the developing kidney or at different times have similar number of cells, within distinct cell types positioned in reproducible ways within an invariant architecture? If this is the case, we should be able to resolve the structures of a large number of nephron stages and generate relational spatial maps that overlap creating a “stage model”. If this is possible, such maps will have long-reaching impact as they will provide the first high definition model for mammalian nephrogenesis and a platform for in depth relational mapping of other types of data, notably single cell RNA-seq. Thus far, we have segmented over 100 individual mouse or human nephron stages. Unfortunately, this cannot be automated and is time consuming and intensive for the “segmenting team”. However, initial results show a good degree of overlap in the shape and pattern of nephrons within a species

indicating this is likely to be time well-spent. Figure 3 gives an overview of a number of individually segmented mouse and human renal vesicle (RV) stages (note there are early and later RVs in this mix).

Aim 2. Generating high-resolution dynamic views of mouse and human kidney development utilizing genetically modified mouse strains and genetically engineered human pluripotent stem cell lines

With respect to the mouse, most work over the current funding period has been to obtain snapshot of individual mouse strains triaging these to determine which will be most effective to view *in vivo* processes of nephrogenesis and to optimize the culture and imaging of kidney explants. In addition, there has been extensive breeding over the last year to generate informative strains which has required for many examples bringing together three distinct genetic components over three generations of intercrosses (9 months) so that all components segregate within the progeny of an informative stud males. This is essential for containing animal costs in this program. We have made advances to the current state-of-the art of kidney explant imaging using bespoke metal supports for Transwell inserts in Ibidi glass bottom culture dishes using a 25x, long-working distance water immersion lens that is continuously supplied with water to prevent drying out over long periods if imaging. This system can be used over 24 hours to obtain high quality image datasets. Movie 2 provides an example of an 8hr visualization of ureteric branching to give a sense of the resolution. Table 2 provides a list of strain combinations and experimental goals for those strains. With regard to human kidney organoid models of nephrogenesis, we have focused on replicating and analyzing the self-assembly model reported by the (b)(6) 2015) using HUESC9 cells. We have shown that we can obtain similar nephron cell types to those reported though less effectively than in the published report. (b)(6) has suggested there may be cell line variability and notes that HUESC9 cells were sub-optimal in her group's hands. We have introduced eGFP under the control of the MAFB promoter, a podocyte specific transcriptional regulator, as a first step in developing systems for dynamic imaging. This highlights the emergence of podocyte-like cells late in kidney organoid culture (Figure 4) and comparative analysis of gene expression within these cells of key podocyte markers in isolated glomeruli from the fetal kidney highlights a podocyte-like cell identity (Figure 5).

In summary, there are a variety of quite different materials that can now be supplied to the GUDMAP database though for some of this data there are potentially challenges that will need to be resolved for effectively displaying that data. Data include:

1) Revised update of protocols for immunostaining and imagining (section and wholemount)
2) List of verified antibodies for cell specific resolution (supplied to GUDMAP and RBK datahubs)
3) Multichannel confocal images of immunostained mouse and kidney sections
4) Video images of primary 3-D confocal images of mouse and human kidney tissue
5) Video images of segmented 3-D nephron stages for mouse and human kidney

C) Significance

In thinking about the significance of our effort, we considered GUDMAP and, more broadly, current knowledge in the scientific literature to draw several conclusions. First, there is a need to incorporate more human data. Second, our understanding of kidney development is largely two-dimensional, whereas nephron structures have complex morphologies. Whether nephron morphogenesis is similar at different stages of mouse kidney development and how nephrogenic programs compare from mouse to human is not clear. Third, the GUDMAP database is centered on the normal mouse; analyzing mouse mutants that compromise nephron formation or patterning will expand and enhance the resource. Fourth, current data provides snapshots of specific stages that do not capture the fluid cellular dynamics of nephrogenesis. The absence of 3D and dynamic insight into the cellular events generating the mammalian nephron highlights a prominent deficiency in the literature. Our proposal directly addresses these limitations within GUDMAP. In addition, the human component herein will provide helpful insights to inform other NIDDK initiatives in particular the translation goals within the ReBuilding A Kidney Consortium.

D) Plans

Aim 1. We will continue with efforts to segment and relationally map different stages of mouse and human nephron development with the end point of a connected (to the ureteric epithelium) S-shaped body. We will attempt to generate harmonized, accurate models of mouse and human nephrogenesis that embrace morphogenesis and patterning as visualized by our antibody sets.

Aim 2. Given the investment to date in generating reporter cell lines in HUESC9 cells (additional lines targeting SLC34a1 [proximal tubule], CITED1 and SIX2 [nephron progenitors] have also been generated and are also being characterized), we need to make an important strategic decision

a) do we continue with the (b)(6) protocol attempting to optimize with existing cell lines
b) do we continue with the protocol generating new knock-in reporters in a better suited cell line
c) or do we pursue other protocols form the (b)(6) laboratories that do not attempt to develop a model that generates all kidney cell types optimizing either ureteric bud and nephrogenic mesenchyme specification independently.

We will examine option “c” with the existing lines and utilizing stage-specific antibody markers before making a decision here.

E) Publications

Research Publications
None

Reviews and commentaries
None

F) Project-Generated Resources

1) Revised update of protocols for immunostaining and imagining (section and wholemount)
2) List of verified antibodies for cell specific resolution (supplied to GUDMAP and RBK datahubs)
3) Multichannel confocal images of immunostained mouse and kidney sections
4) Video images of primary 3-D confocal images of mouse and human kidney tissue
5) Video images of segmented 3-D nephron stages for mouse and human kidney
6) HUESC9 cell line with eGFP knock-in into the MAFB locus

Appendix Items

Figure 1. Comparative analysis of mouse and human nephrogenesis identifies progenitor streaming as component in the temporal and spatial patterning of the renal vesicle

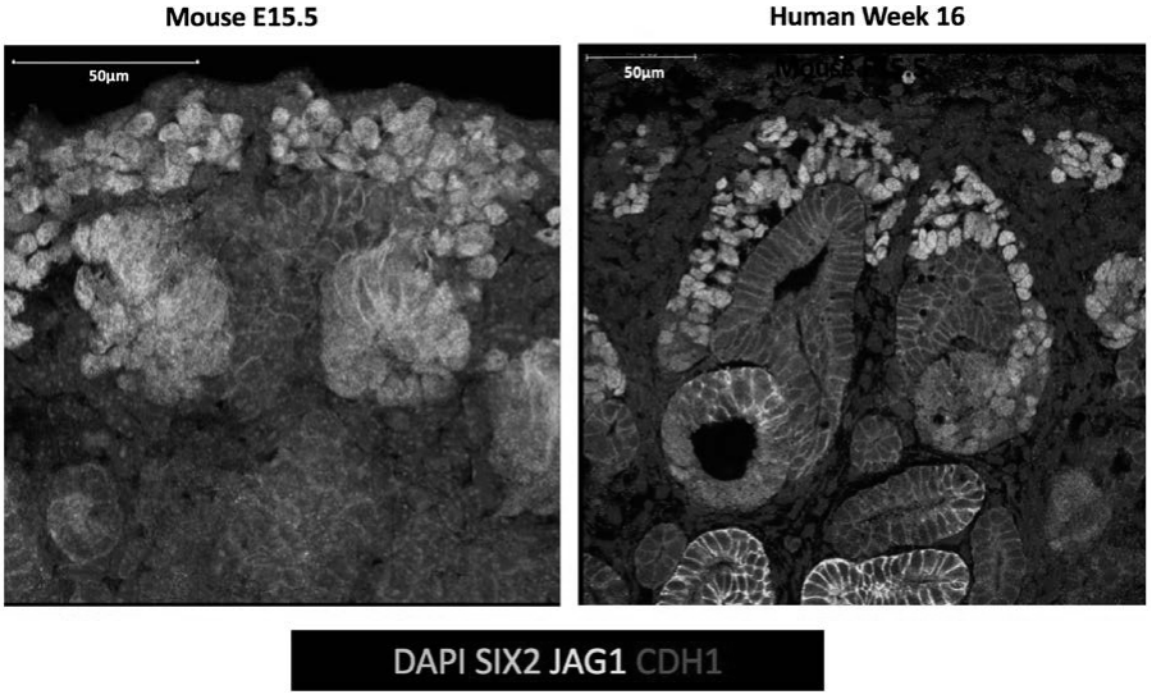


Figure 2. Progressive patterning of human nephron precursors

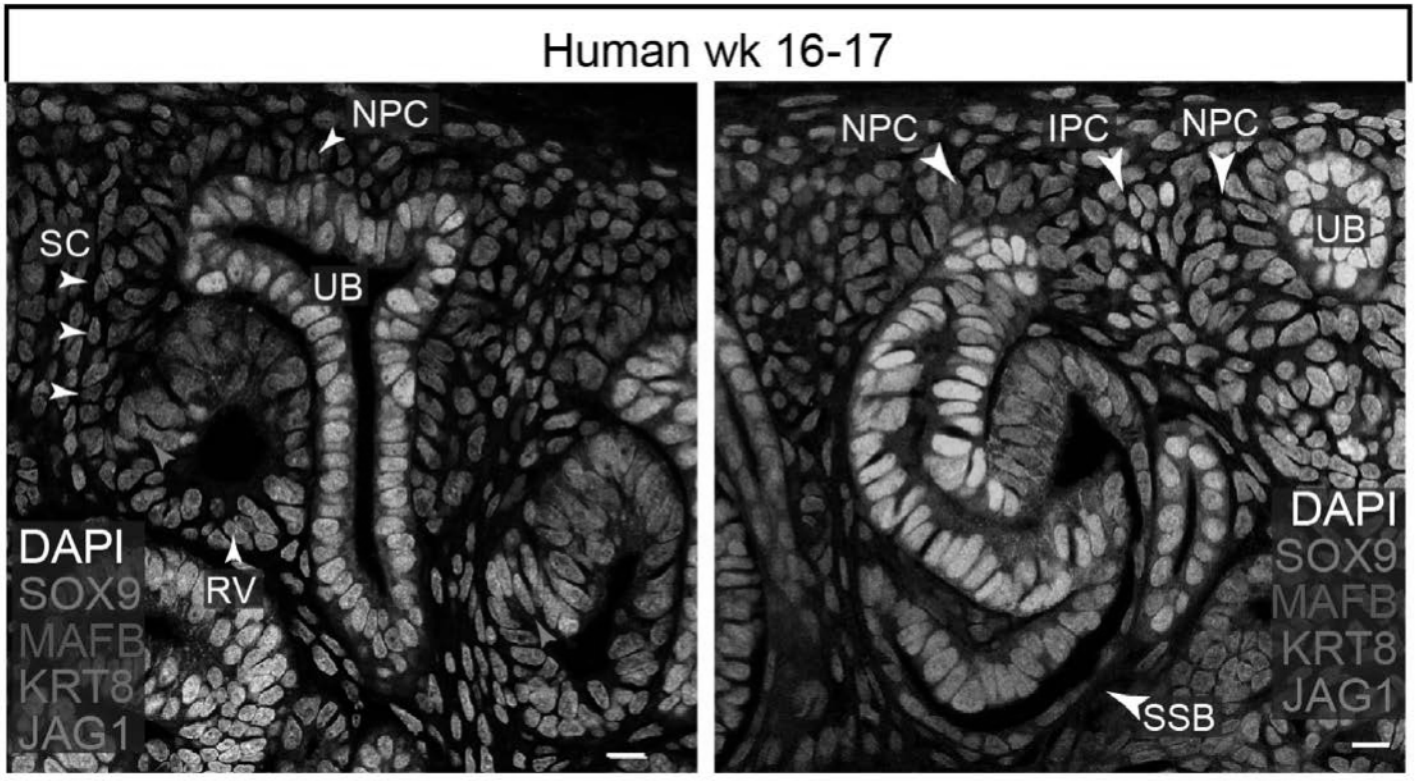


Figure 3. Overview of individually segmented mouse and human renal vesicles

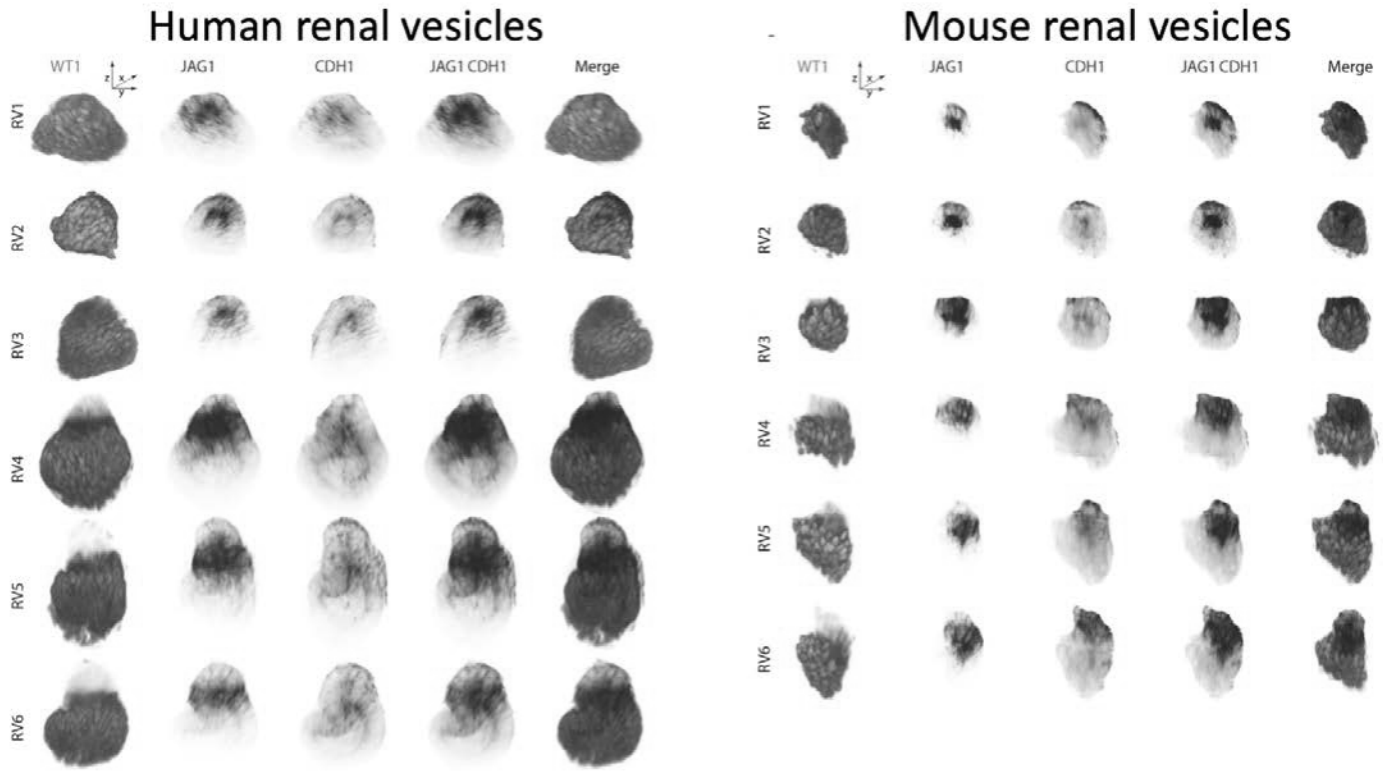


Figure 4. Progressive development of HUESC9 derived kidney organoid showing activation of eGFP reporter driven by the MAFB locus highlighting emerging podocyte like cells

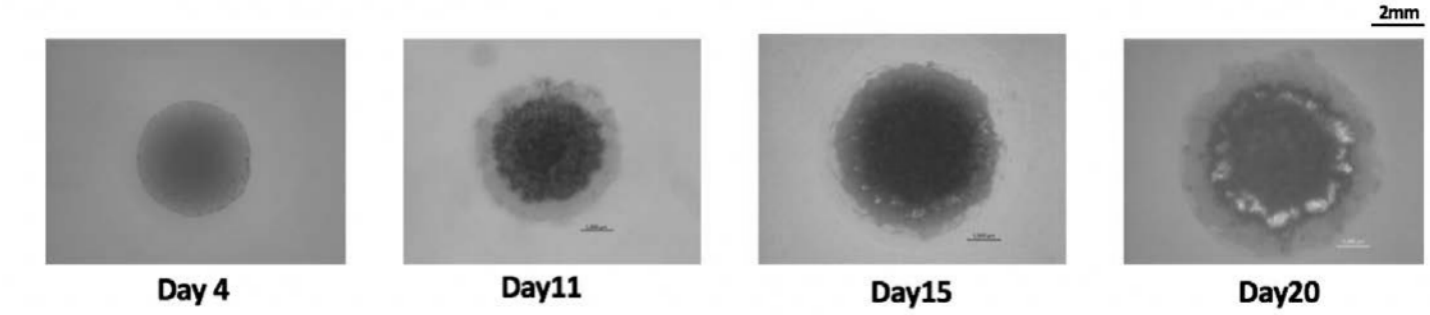


Figure 5. Expression profiling indicates MAFB-eGFP cells have elevated levels of key podocyte genes indicating an immature podocyte-like gene expression signature

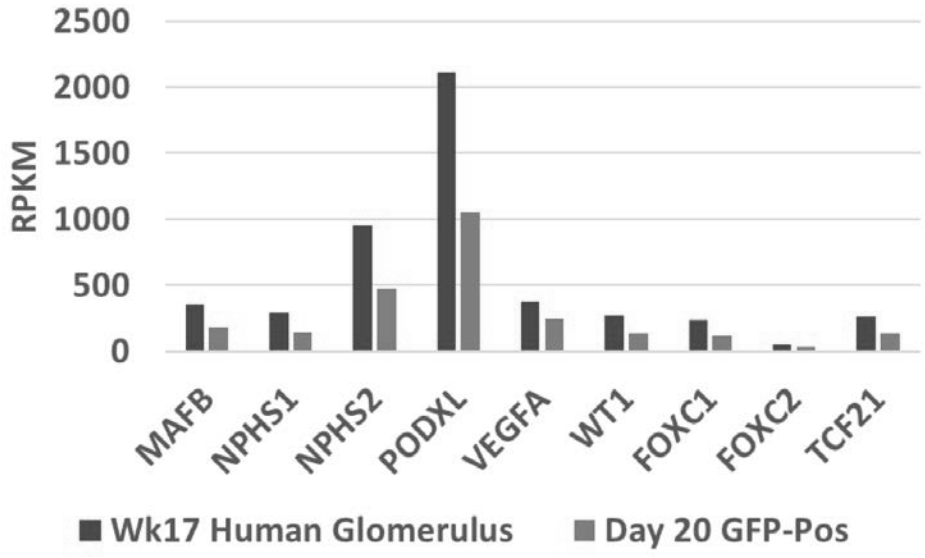


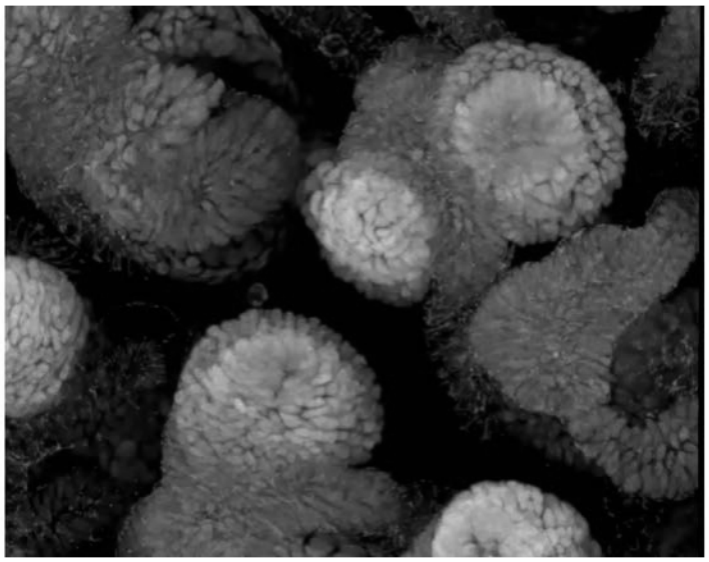
Table 1. Table of tested and validated antibodies for cell identification in the mouse and human kidney

Antibody	ost Specie	Species Reactivity	Expected region in kidney	Company	Catalog number	Working dilution
AQP1	rabbit	human and mouse	proximal tubule	Abcam	ab168387	1 to 1000
CALB1	mouse	human and mouse	collecting duct	Sigma	C9848	1 to 300
CITED1	mouse	human	cap mesenchyme	Abcam	ab55467	1 to 300
CITED1	rabbit	mouse	cap mesenchyme	Mybiosource	MBS2025863	1 to 300
FOXD1	goat	human and mouse	interstial progenitors and cap mesenchym	Santa Cruz	sc-47585	1 to 1000
JAG1	goat	human and mouse	renal vesical and SSB	R&D	AF599	1 to 500
KRT8	rat	human and mouse	collecting duct and distal segment SSB	DSHB	TROMA-1	1 to 50
LEF1	rabbit	human and mouse	induced cells in cap and developing nephrons	Cell Signaling	2230	1 to 300
LRP2	mouse	human	proximal tubule	Mybiosource	MBS690201	1 to 300
LRP2	goat	mouse	proximal tubule	Santa Cruz	sc-16478	1 to 1000
MAFB	rabbit	human and mouse	podocytes of glomerulus	Sigma	HPA005653	1 to 1000
NPHS1	sheep	human and mouse	podocytes of glomerulus	R&D	AF-4269	1 to 300
NPHS2	rabbit	human and mouse	podocytes of glomerulus	Abcam	ab50339	1 to 1000
PAX8	rabbit	human/weak in mouse	induced cells in cap and developing nephrons	Abcam	ab189249	1 to 1000
PODXL	goat	human	podocytes of glomerulus	R&D	AF1658	1 to 2000
PODXL	ouse IgG2	mouse	podocytes of glomerulus	R&D	MAB1556	1 to 1000
SIX1	rabbit	human and mouse	human cap mesenchyme/mouse early metanephric mesenchyme	Cell Signaling	12891S	1 to 1000
SIX2	rabbit	human and mouse	cap mesenchyme	Mybiosource	MBS610128	1 to 1000
SIX2	mouse	human and mouse	cap mesenchyme	Sigma	SAB1401533	1 to 500
SLC12A1	rabbit	human and mouse	loop of Henle distal tubule	Abcam	ab171747	1 to 2000
SLC12A3	rabbit	human and mouse	distal tubule	Sigma	HPA028748	1 to 1000
MEIS1/2/3	mouse	human and mouse	Cortical and medullary interstititum	ActiveMotif	39795	1:500
SOX9	rabbit	human and mouse	Ureteric tip and distal S-shaped body	Abcam	ab185230	1:1000
CUBN	goat	human and mouse	Proximal tubule	Santa Cruz	sc-20607	1:500
GATA3	goat	human and mouse	Collecting duct, connecting tubule, mesangial cells in human	R&D	AF2605	1:300

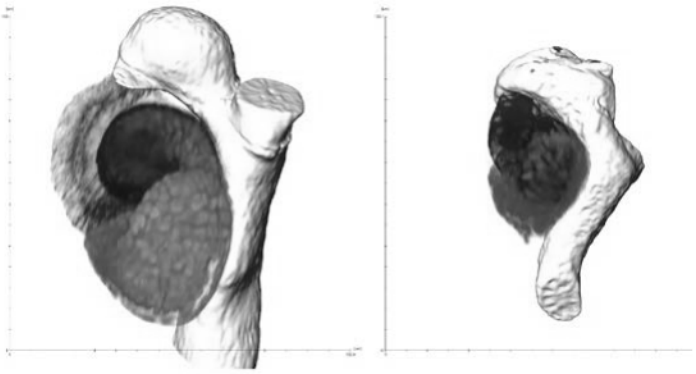
Table 2. List of mouse strain combinations for 4D-analysis of specific developmental events in the mouse kidney

Strain	Research Goal
$Six2^{CE/+}$; $Rosa26^{mTmG/mTmG}$; TgHoxb7-Venus	To enable visualization of nephron progenitor membrane dynamics within their niche and during nephrogenesis.
$Six2^{CE/+}$; $Rosa26^{mTmG/mTmG}$; $Cdh1^{CFP/CFP}$	To visualize nephron progenitor membrane dynamics within their niche and during epithelialization.
TgSix2TGC ; $Rosa26^{TDT/+}$	To visualize nephron progenitor behaviour within their niche and their differentiation and morphogenetic processes during nephrogenesis.
$Sox9^{CE/+}$; $Rosa26^{TDT/+}$	To be crossed with TgHoxb7Venus to visualize nephron fusion to the ureteric tip.
TgPax8YFP	To visualize upregulation of Pax8 during nephrogenesis.
TgLfngGFP	To visualize upregulation of Lfng during nephrogenesis and medial segment formation.
$Wnt11^{tm1a/tm1a}$; $Six2^{CE/+}$; $Rosa26^{mTmG/+}$	To visualize nephron progenitor membrane dynamics within their niche and during epithelialization in the absence of Wnt11.

Video 1. Unsegmented tiled views of Z stack through cortical region of human fetal kidney (~ 16 weeks)



Video 2. Segmented 3-D views of S-shaped bodies of mouse and human fetal kidney (~ 16 weeks) showing structure and pattern.



C. OVERALL PRODUCTS

C.1 PUBLICATIONS

Are there publications or manuscripts accepted for publication in a journal or other publication (e.g., book, one-time publication, monograph) during the reporting period resulting directly from this award?

No

C.2 WEBSITE(S) OR OTHER INTERNET SITE(S)

Category	Explanation
Data or Databases	www.gudmap.org

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

C.4 INVENTIONS, PATENT APPLICATIONS, AND/OR LICENSES

Have inventions, patent applications and/or licenses resulted from the award during the reporting period?

No

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Category	Explanation
Other	Nothing to Report. There were no requests for resources received.

D. OVERALL PARTICIPANTS

D.1 WHAT INDIVIDUALS HAVE WORKED ON THE PROJECT?

Commons ID	S/K	Name	Degree(s)	Role	Cal	Aca	Sum	Foreign Org	Country	SS
(b)(6)	Y	(b)(6)	PHD	PD/PI	(b)(6)					NA
	N			Senior Research Associate						NA
	N			Technician						NA
	N			Technician						NA
(b)(6)	N		BS,PHD	Postdoctoral Scholar, Fellow, or Other Postdoctoral Position						NA
	N			Science Coordinator						NA
	N			Technician						NA

Glossary of acronyms:
S/K - Senior/Key
DOB - Date of Birth
Cal - Person Months (Calendar)
Aca - Person Months (Academic)
Sum - Person Months (Summer)
Foreign Org - Foreign Organization Affiliation
SS - Supplement Support
RE - Reentry Supplement
DI - Diversity Supplement
OT - Other
NA - Not Applicable

D.2 PERSONNEL UPDATES

D.2.a Level of Effort

Will there be, in the next budget period, either (1) a reduction of 25% or more in the level of effort from what was approved by the agency for the PD/PI(s) or other senior/key personnel designated in the Notice of Award, or (2) a reduction in the level of effort below the minimum amount of effort required by the Notice of Award?

No

D.2.b New Senior/Key Personnel

Are there, or will there be, new senior/key personnel?

No

D.2.c Changes in Other Support

Has there been a change in the active other support of senior/key personnel since the last reporting period?

Yes

File uploaded: (b)(6) Other Support March 2017.pdf

D.2.d New Other Significant Contributors

Are there, or will there be, new other significant contributors?

No

D.2.e Multi-PI (MPI) Leadership Plan

Will there be a change in the MPI Leadership Plan for the next budget period?

NA

Program Director/ Principal Investigator (Last, First): (b)(6)

OTHER SUPPORT – Direct Costs Current Year

McMahon, Andrew P.

ACTIVE

(b)(6)

D.2.c (b)(6) Other Support March 2017.pdf)

Program Director/ Principal Investigator (Last, First): (b)(6)

(b)(6)

E. OVERALL IMPACT

E.1 WHAT IS THE IMPACT ON THE DEVELOPMENT OF HUMAN RESOURCES?

Not Applicable

E.2 WHAT IS THE IMPACT ON PHYSICAL, INSTITUTIONAL, OR INFORMATION RESOURCES THAT FORM INFRASTRUCTURE?

Information made available to the scientific community through the GUDMAP website (www.gudmap.org).

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

Not Applicable

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?

NOTHING TO REPORT

F. OVERALL CHANGES

F.1 CHANGES IN APPROACH AND REASONS FOR CHANGE

Not Applicable

F.2 ACTUAL OR ANTICIPATED CHALLENGES OR DELAYS AND ACTIONS OR PLANS TO RESOLVE THEM

NOTHING TO REPORT

F.3 SIGNIFICANT CHANGES TO HUMAN SUBJECTS, VERTEBRATE ANIMALS, BIOHAZARDS, AND/OR SELECT AGENTS

F.3.a Human Subjects

No Change

F.3.b Vertebrate Animals

No Change

F.3.c Biohazards

No Change

F.3.d Select Agents

No Change

G. OVERALL SPECIAL REPORTING REQUIREMENTS

G.1 SPECIAL NOTICE OF AWARD TERMS AND FUNDING OPPORTUNITIES ANNOUNCEMENT REPORTING REQUIREMENTS

NOTHING TO REPORT

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

G.4.a Does the project involve human subjects?

No

G.4.b Inclusion Enrollment Data

Not Applicable

G.4.c ClinicalTrials.gov

Does this project include one or more applicable clinical trials that must be registered in ClinicalTrials.gov under FDAAA?

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Are there personnel on this project who are newly involved in the design or conduct of human subjects research?

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

Does this project involve human embryonic stem cells (only hESC lines listed as approved in the NIH Registry may be used in NIH funded research)?

Yes

hESC Registration number(s) from the NIH Registry:
0022

The explanation of a change in the use of hESCs

G.7 VERTEBRATE ANIMALS

Does this project involve vertebrate animals?

Yes

G.8 PROJECT/PERFORMANCE SITES

Organization Name:	DUNS	Congressional District	Address
Primary: University of Southern California	072933393	CA-034	1425 San Pablo Street (b)(6) Los Angeles CA 900339080
UNIVERSITY OF SOUTHERN CALIFORNIA	072933393		UNIVERSITY OF SOUTHERN CALIFORNIA DEPARTMENT OF CONTRACTS AND GRANTS LOS ANGELES CA 900323696

University of Southern California	072933393	CA-034	1425 San Pablo Street (b)(6) Los Angeles CA 900339080

G.9 FOREIGN COMPONENT

No foreign component

G.10 ESTIMATED UNOBLIGATED BALANCE

G.10.a Is it anticipated that an estimated unobligated balance (including prior year carryover) will be greater than 25% of the current year's total approved budget?

No

G.11 PROGRAM INCOME

Is program income anticipated during the next budget period?

No

G.12 F&A COSTS

Not Applicable

RESEARCH & RELATED BUDGET - SECTION A & B

ORGANIZATIONAL DUNS*: 072933393

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: UNIVERSITY OF SOUTHERN CALIFORNIA

Start Date*: 06-01-2017 **End Date*:** 05-31-2018

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1.		(b)(6)				PI	(b)(6)	(b)(6)			9,350.00	3,104.00	12,454.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name: **Total Senior/Key Person** **12,454.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
1	Post Doctoral Associates	(b)(6)			30,750.00	10,209.00	40,959.00
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
5	Sr. Res Ass., Techs, Science Coord.	(b)(6)			58,658.00	19,474.00	78,132.00
6	**Total Number Other Personnel**					**Total Other Personnel**	**119,091.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**131,545.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E

ORGANIZATIONAL DUNS*: 072933393

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: UNIVERSITY OF SOUTHERN CALIFORNIA

Start Date*: 06-01-2017 **End Date*:** 05-31-2018

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	**0.00**
Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	4,336.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**4,336.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		0.00
2. Stipends		0.00
3. Travel		0.00
4. Subsistence		0.00
5. Other:		
0 Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**0.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K

ORGANIZATIONAL DUNS*: 072933393

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: UNIVERSITY OF SOUTHERN CALIFORNIA

Start Date*: 06-01-2017 **End Date*:** 05-31-2018

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	32,495.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. Vivarium per Diem	49,220.00
9. FACS Core	4,000.00
10. Confocal Facility	13,000.00
Total Other Direct Costs	**98,715.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**234,596.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. MTDC	65.0	234,597.00	152,488.00
		Total Indirect Costs	**152,488.00**

Cognizant Federal Agency DHHS, (b)(6)
(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**387,084.00**

J. Fee	Funds Requested ($)*
	0.00

K. Budget Justification* File Name: (b)(6) 5351780792_1U01DK110792_Yr 2 Budget Justification.pdf
(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Budget Justification

Personnel

(b)(6) (PI): as PI of the proposal salary is requested reflecting the effort and Institutional Base Salary (b)(6) effort (b)(6)

(b)(6) (Science Coordinator): (b)(6) (b)(4) (b)(6) (b)(4) Salary is requested to reflect (b)(6) effort on the project. (b)(6)

(b)(6) (Research Associate): (b)(6) (b)(4) (b)(4) (b)(4) (b)(6) will be participating in all aspects of the proposal. Salary is requested to reflect (b)(6) effort on the project. (b)(6)

(b)(6) Senior Research Associate) (b)(6) (b)(4) (b)(4) reflect (b)(6) effort on the project. (b)(6)

(b)(6) (Histology Technician): (b)(6) will be (b)(4) (b)(4) Salary is requested to reflect (b)(6) contribution to the project. (b)(6) (b)(6)

(b)(6) (Lab Technician): (b)(6) (b)(4) (b)(4) Salary is requested to reflect (b)(6) contribution to the project. (b)(6)

(b)(6) (Lab Technician): (b)(6) (b)(4) (b)(4) Salary is requested to reflect (b)(6) contribution to the project. (b)(6) (b)(6)

Materials and Supplies

Costs reflect projected costs typical for project of this scale with multiple molecular and cellular approaches. In addition, we anticipate significant costs associated with antibody testing and tissue culture as a central aspect of the studies.

Travel

Travel costs are requested for the PI and key team members to attend annual consortium advisory meetings in Bethesda or elsewhere.

Other Costs

The project will require the maintenance and analysis of a large number of mouse strains as detailed in the research proposal. We anticipate this will require approximately 136 cages of isolator-caged mice within the barrier facility (b)(4) In addition, we will be performing extensive live imaging and anticipate costs associated with standard imaging center charges. FACS use will facilitate cell isolation for *in vitro* culture experiments.

Indirect Costs

Indirect Costs (F&A) calculated using the USC approved Federal sponsor rate of 65.0%.

Notice of Award

RESOURCE-RELATED COOPERATIVE AGREEMENT PROJECTS **Federal Award Date:** 09/12/2016

Department of Health and Human Services
National Institutes of Health
NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

Grant Number: 1U24DK110791-01
FAIN: U24DK110791

Principal Investigator(s):
(b)(6)

Project Title: University of Pittsburgh as the GUDMAP Tissue Hub and Collection Site

(b)(6)
University of Pittsburgh
(b)(6)
(b)(6)
Pittsburgh, PA 152132303

Award e-mailed to: (b)(6) @offres.pitt.edu

Period Of Performance:
Budget Period: 09/15/2016 – 05/31/2017
Project Period: 09/15/2016 – 05/31/2021

Dear Business Official:

The National Institutes of Health hereby awards a grant in the amount of $600,000 (see "Award Calculation" in Section I and "Terms and Conditions" in Section III) to UNIVERSITY OF PITTSBURGH AT PITTSBURGH in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 31 USC 6305 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award including the "Terms and Conditions" is acknowledged by the grantee when funds are drawn down or otherwise obtained from the grant payment system.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as "Research reported in this publication was supported by the National Institute Of Diabetes And Digestive And Kidney Diseases of the National Institutes of Health under Award Number U24DK110791. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health." Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Award recipients must promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under NIH awards will be free from bias resulting from an Investigator's Financial Conflict of Interest (FCOI), in accordance with the 2011 revised regulation at 42 CFR Part 50 Subpart F. The Institution shall submit all FCOI reports to the NIH through the eRA Commons FCOI Module. The regulation does not apply to Phase I Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) awards. Consult the NIH website http://grants.nih.gov/grants/policy/coi/ for a link to the regulation and additional important information.

If you have any questions about this award, please contact the individual(s) referenced in Section IV.

Sincerely yours,

(b)(6)

Grants Management Officer
NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

Additional information follows

SECTION I – AWARD DATA – 1U24DK110791-01

Award Calculation (U.S. Dollars)

Salaries and Wages	$225,631
Fringe Benefits	$68,514
Personnel Costs (Subtotal)	$294,145
Materials & Supplies	$47,891
Travel	$9,914
Other	$44,613
Federal Direct Costs	$396,563
Federal F&A Costs	$203,437
Approved Budget	$600,000
Total Amount of Federal Funds Obligated (Federal Share)	$600,000
TOTAL FEDERAL AWARD AMOUNT	$600,000
AMOUNT OF THIS ACTION (FEDERAL SHARE)	$600,000

SUMMARY TOTALS FOR ALL YEARS		
YR	**THIS AWARD**	**CUMULATIVE TOTALS**
1	$600,000	$600,000
2	$613,002	$613,002
3	$613,002	$613,002
4	$613,002	$613,002
5	$613,002	$613,002

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

Fiscal Information:

CFDA Name:	Diabetes, Digestive, and Kidney Diseases Extramural Research
CFDA Number:	93.847
EIN:	1250965591A1
Document Number:	UDK110791A
PMS Account Type:	P (Subaccount)
Fiscal Year:	2016

IC	CAN	2016	2017	2018	2019	2020
DK	8472288	$600,000	$613,002	$613,002	$613,002	$613,002

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

NIH Administrative Data:
PCC: KDH KDB / **OC**: 414L / **Released**: (b)(6) 09/11/2016
Award Processed: 09/12/2016 07:02:07 PM

SECTION II – PAYMENT/HOTLINE INFORMATION – 1U24DK110791-01

For payment and HHS Office of Inspector General Hotline information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

SECTION III – TERMS AND CONDITIONS – 1U24DK110791-01

This award is based on the application submitted to, and as approved by, NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

a. The grant program legislation and program regulation cited in this Notice of Award.
b. Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.
c. 45 CFR Part 75.

d. National Policy Requirements and all other requirements described in the NIH Grants Policy Statement, including addenda in effect as of the beginning date of the budget period.
e. Federal Award Performance Goals: As required by the periodic report in the RPPR or in the final progress report when applicable.
f. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(See NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm for certain references cited above.)

Research and Development (R&D): All awards issued by the National Institutes of Health (NIH) meet the definition of "Research and Development" at 45 CFR Part§ 75.2**.** As such, auditees should identify NIH awards as part of the R&D cluster on the Schedule of Expenditures of Federal Awards (SEFA). The auditor should test NIH awards for compliance as instructed in Part V, Clusters of Programs. NIH recognizes that some awards may have another classification for purposes of indirect costs. The auditor is not required to report the disconnect (i.e., the award is classified as R&D for Federal Audit Requirement purposes but non-research for indirect cost rate purposes), unless the auditee is charging indirect costs at a rate other than the rate(s) specified in the award document(s).

Carry over of an unobligated balance into the next budget period requires Grants Management Officer prior approval.

This award is subject to the requirements of 2 CFR Part 25 for institutions to receive a Dun & Bradstreet Universal Numbering System (DUNS) number and maintain an active registration in the System for Award Management (SAM). Should a consortium/subaward be issued under this award, a DUNS requirement must be included. See http://grants.nih.gov/grants/policy/awardconditions.htm for the full NIH award term implementing this requirement and other additional information.

This award has been assigned the Federal Award Identification Number (FAIN) U24DK110791. Recipients must document the assigned FAIN on each consortium/subaward issued under this award.

Based on the project period start date of this project, this award is likely subject to the Transparency Act subaward and executive compensation reporting requirement of 2 CFR Part 170. There are conditions that may exclude this award; see http://grants.nih.gov/grants/policy/awardconditions.htm for additional award applicability information.

In accordance with P.L. 110-161, compliance with the NIH Public Access Policy is now mandatory. For more information, see NOT-OD-08-033 and the Public Access website: http://publicaccess.nih.gov/.

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts with cumulative total value greater than $10,000,000 must report and maintain information in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made publicly available in the designated integrity and performance system (currently the Federal Awardee Performance and Integrity Information System (FAPIIS)). Full reporting requirements and procedures are found in Appendix XII to 45 CFR Part 75. This term does not apply to NIH fellowships.

Treatment of Program Income:
Other Research (Add/Deduct Option)

Notice: Under governing regulations, Federal funds administered by the Department of Health and Human Services shall not be expended for research involving human subjects, and individuals shall not be enrolled in such research, without prior approval by the Office of Human Research Protections (OHRP) of an assurance to comply with the requirements of 45 CFR 46 to protect human research subjects. This restriction applies to all collaborating sites without OHRP-approved assurances, whether domestic or foreign, and compliance must be ensured by the awardee.

Notice: Under governing policy, federal funds administered by the Public Health Service (PHS) shall not be expended for research involving live vertebrate animals without prior approval by the Office of Laboratory Animal Welfare (OLAW) of an assurance to comply with the PHS policy on humane care and use of laboratory animals. This restriction applies to all performance sites (e.g., collaborating institutions, subcontractors, subgrantees) without OLAW-approved assurances, whether domestic or foreign.

The present award is made without an OLAW-approved assurance and/or currently valid verification of IACUC approval for this project with the following restriction: Only activities that do not involve vertebrate animals may be conducted pending acceptance by the NIDDK of verification of IACUC approval. The verification of IACUC approval must be submitted not later than November 3, 2016 to the grants management specialist named below.

Failure to submit the verification of IACUC approval within the required timeframe or to otherwise comply with the above requirements can result in suspension and/or termination of this award, withholding of support, audit disallowances and/or other appropriate action.

The grantee is required to follow the model organism sharing plan included in the application and may not implement any changes in the plan without the written prior approval of the NIDDK.

In addition to the PI, the following individuals are named as key personnel:

(b)(6)

Written prior approval is required if any of the individual(s) named above withdraws from the project entirely, is absent from the project during any continuous period of 3 months or more, or reduces time devoted to the project by 25 percent or more from the level that was approved at the time of award.

This grant is in response to RFA/PA DK15-016. Acceptance of this award requires compliance with this solicitation. See the NIH Guide at http://grants.nih.gov/grants/guide/index.html for copy of the RFA/PA that includes administrative and programmatic requirements specific to this award.

Although the initial budget period for this award is 09/15/2016-05/31/2017, the award includes funds for 12 months of support. Future year budget periods will cycle on 06/01/2017. Allowable preaward costs may be charged to this award in accordance with the conditions outlined in the NIH Grants Policy Statement (revised November 2015) and with institutional requirements for prior approval.

In accordance with NIH Guide Notice NOT-OD-16-045, Notice of Salary Limitation on Grants, Cooperative Agreements, and Contracts, none of the funds in this award shall be used to pay the salary of an individual at a rate in excess of the applicable salary cap. Therefore this award and/or future years are adjusted accordingly, if applicable. See the salary cap summary and the time frames associated with salary caps at http://grants.nih.gov/grants/policy/salcap_summary.htm.

In order to meet current NIDDK objectives and based on the relative scientific merit ranking of this application, the budget for the initial period has been programmatically reduced. Although specific budget adjustments have been made, the Institution and Principal Investigator retain standard rebudgeting authorities for this mechanism of support.

See the budget information below for additional information.

Grantees can determine which progress reports are due through the website located at https://public.era.nih.gov/chl/public/search/index.jsp , and should periodically check the site, which is updated on or around the 30th of each month. Progress report due dates are also available in the eRA Commons Status system. In addition, automatic e-mail notifications are sent to the PD/PI prior to due date.

As of October 17, 2014, the National Institutes of Health (NIH) requires grantees to submit all type 5 progress reports using the eRA Research Performance Progress Report (RPPR) module. Annual progress reports submitted in any format other than the RPPR will not be processed by the NIH and will require resubmission through the RPPR module in accordance with NIH Guide Notice Number NOT-OD-15-014 released October 16, 2014.

The following special terms of award are in addition to, and not in lieu of, otherwise applicable U.S. Office of Management and Budget (OMB) administrative guidelines, U.S. Department of Health and Human Services (DHHS) grant administration regulations at 45 CFR Parts 74 and 92 (Part 92 is applicable when State and local Governments are eligible to apply), and other HHS, PHS, and NIH grant administration policies.
The administrative and funding instrument used for this program will be the cooperative agreement, an "assistance" mechanism (rather than an "acquisition" mechanism), in which substantial NIH programmatic involvement with the awardees is anticipated during the performance of the activities. Under the cooperative agreement, the NIH purpose is to support and stimulate the recipients' activities by involvement in and otherwise working jointly with the award recipients in a partnership role; it is not to assume direction, prime responsibility, or a dominant role in the activities. Consistent with this concept, the dominant role and prime responsibility resides with the awardees for the project as a whole, although specific tasks and activities may be shared among the awardees and the NIH as defined below.

The PD(s)/PI(s) will have the primary responsibility for:

- All aspects of the scientific activities, including defining the objectives and approaches, planning, conduct, analysis, and publication of results, interpretations, and conclusions of studies conducted under the terms and conditions of the cooperative agreement award.
- Collaborating with other investigators in the program for protocol development, sample, reagents and data sharing as appropriate, data quality control, and data organization
- Accountability towards the applicant organization officials and to the NIDDK for the performance and proper conduct of the research supported by the project in accordance with the terms and conditions of the award.
- Serving as a voting member of the Steering Committee and will attend the Planning Meeting and a Steering Committee meeting in the first year, two Steering Committee meetings a year in subsequent years and monthly teleconference calls.
- Accepting and implementing the goals, priorities, procedures, protocols, and policies agreed upon by the Steering Committee and subcommittees, and be responsible for close coordination and cooperation with the components of the GUDMAP consortium and with NIDDK staff.
- Adhering to PHS policy for the distribution of unique research resources produced with PHS funding as described under Special Requirements.
- Establishing written milestones for the project, in negotiation with NIDDK Project Staff prior to funding.
- Release all study design materials and procedure manuals into the public domain and/or make them available to other investigators, according to the approved plan for making data and materials available to the scientific community and the NIDDK, for the conduct of research at no charge other than the costs of reproduction and distribution, consistent with achieving the goals of this program initiative.
- Awardees will retain custody of and have primary rights to the data and software developed under these awards, subject to Government rights of access consistent with current DHHS, PHS, and NIH policies.

NIH staff will have substantial programmatic involvement that is above and beyond the normal stewardship role in awards, as described below:

- An NIH Project Scientist will have substantial programmatic involvement that is above and beyond the normal stewardship role in awards, as described below. However, the dominant role and prime responsibility for the project as a whole resides with the

awardees, although specific tasks and activities in carrying out the studies will be shared by awardees and the NIDDK.

- NIDDK will designate a Project Officer and a Grants Management Specialist to provide normal program stewardship and administrative oversight of the cooperative agreement.
- NIDDK will form an External Advisory Committee (EAC), comprised of the NIDDK Project Scientist and other NIH extramural staff with relevant scientific expertise or who manage research grant programs that relate scientifically to the goals of the GUDMAP projects, and outside advisors selected by the NIDDK. The EAC will meet annually with the GUDMAP Steering Committee to review and assess GUDMAP and to advise NIDDK of scientific developments and opportunities that may enhance the achievement of the GUDMAP goals.
- The NIDDK Project Scientist will attend and participate as a voting member in all meetings of the Steering Committee, and provide liaison between the Steering Committee and the External Advisory Committee.
- The NIDDK Project Scientist will help the Steering Committee develop and draft operating policies.
- The NIDDK Project Officer will review the scientific progress of the individual GUDMAP components, for compliance with operating policies developed by the Steering Committee, and may recommend to the NIDDK to withhold support, suspend, or terminate an award for lack of scientific progress or failure to adhere to policies established by the Steering Committee.
- An agency program official or IC program director will be responsible for the normal scientific and programmatic stewardship of the award and will be named in the award notice. The assigned Program Officer may also serve as an NIDDK Project Scientist.

Areas of Joint Responsibility include:

- Steering Committee - The NIDDK Project Scientist, PIs from the project funded through this FOA and RFA-DK-15-014, and RFA-DK-15-015 and voluntary representatives from the previously funded GUDMAP atlas projects funded under RFA-DK-11-001 will be responsible for forming a Steering Committee as defined below. An arbitration system, as detailed below, will be available to resolve disagreements among members of the Steering Committee. The Steering Committee will be the main governing board of the GUDMAP consortium. It will develop collaborative protocols, identify technological impediments to success and strategies to overcome them, develop shared software tools for disseminating information about the projects, and identify opportunities for sharing techniques and tools that might be developed in future GUDMAP atlas projects.
- The Steering Committee will be composed of the PIs from the project funded through this FOA, RFA-DK-15-014, and RFA-DK-15-015, representatives from the previously funded GUDMAP projects, and the NIDDK Project Scientist. The representatives and the PIs will each have one vote. The NIDDK Project Scientist for this project will have one vote. The Steering Committee will select a chairperson who will be someone other than an NIH staff member.
- The Steering Committee may, as it deems necessary, invite additional, non-voting scientific advisors to meetings at which research priorities and opportunities are discussed. The NIH reserves the right to augment the scientific or consumer expertise of the Steering Committee when necessary.
- There will be two Steering Committee meetings annually. The first meeting will be a Planning Meeting to be held in the Washington, DC area on **June 20-21, 2016**. At the Planning Meeting, the Steering Committee will be formed and a chairperson selected from among the members. At the Planning Meeting, the Steering Committee may: (a) draft a charter to detail policies and procedures, a process for monitoring compliance with the policies and procedures, and a process for recommending that the NIDDK Project Administrators act on evidence of non-compliance of any Consortium component with Steering Committee policies; (b) agree upon the terms of the charter; and (c) devise a plan for working with the GUDMAP database developers to provide ongoing input into database and website design.
- At the second and subsequent meetings, the Steering Committee will refine the GUDMAP scientific objectives and implementation as necessary, consistent with data produced by former and possible future GUDMAP atlas projects and from other laboratories.
- The Steering Committee will plan workshops, to which non-GUDMAP participants will also be invited, to inform the research community of the progress made toward development of the atlas, and to inform the research community of any technological

advances related to the implementation of the GUDMAP website/database. The NIDDK Project Scientist, the External Advisory Committee, and other NIH staff as appropriate will provide the Steering Committee with advice on participants for the workshops and symposia.

- The Steering Committee may establish subcommittees as it deems appropriate.
- Awardee members of the Steering Committee will be required to accept and implement policies approved by the Steering Committee.
- The EAC will meet annually with the GUDMAP Steering Committee to review and assess the progress of the GUDMAP consortium and to advise NIDDK of scientific developments and opportunities that may enhance the achievement of the GUDMAP goals.

Dispute Resolution

Any disagreements that may arise in scientific or programmatic matters (within the scope of the award) between award recipients and the NIH may be brought to Dispute Resolution. A Dispute Resolution Panel will have three members: a designee of the Steering Committee chosen without NIH staff voting, one NIH designee, and a third designee with expertise in the relevant area who is chosen by the other two; in the case of individual disagreement, the first member may be chosen by the individual awardee. This special dispute resolution procedure does not alter the awardee's right to appeal an adverse action that is otherwise appealable in accordance with PHS regulation 42 CFR Part 50, Subpart D and DHHS regulation 45 CFR Part 16.
- See more at: http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-15-016.html#sthash.UY9M5nfL.dpuf

STAFF CONTACTS

The Grants Management Specialist is responsible for the negotiation, award and administration of this project and for interpretation of Grants Administration policies and provisions. The Program Official is responsible for the scientific, programmatic and technical aspects of this project. These individuals work together in overall project administration. Prior approval requests (signed by an Authorized Organizational Representative) should be submitted in writing to the Grants Management Specialist. Requests may be made via e-mail.

Grants Management Specialist: (b)(6)
Email: (b)(6) @extra.niddk.nih.gov **Phone:** (b)(6) **Fax:** (b)(6)

Program Official: (b)(6)
Email: (b)(6) @niddk.nih.gov **Phone:** (b)(6)

SPREADSHEET SUMMARY
GRANT NUMBER: 1U24DK110791-01

INSTITUTION: UNIVERSITY OF PITTSBURGH AT PITTSBURGH

Budget	Year 1	Year 2	Year 3	Year 4	Year 5
Salaries and Wages	$225,631	$224,475	$223,034	$223,034	$223,034
Fringe Benefits	$68,514	$68,163	$67,726	$67,726	$67,726
Personnel Costs (Subtotal)	$294,145	$292,638	$290,760	$290,760	$290,760
Equipment				$1	$1
Materials & Supplies	$47,891	$47,646	$47,340	$47,340	$47,340
Travel	$9,914	$9,863	$9,800	$9,800	$9,800
Other	$44,613	$44,384	$44,003	$43,794	$43,794
TOTAL FEDERAL DC	$396,563	$394,531	$391,903	$391,695	$391,695
TOTAL FEDERAL F&A	$203,437	$218,471	$221,099	$221,307	$221,307
TOTAL COST	$600,000	$613,002	$613,002	$613,002	$613,002

Facilities and Administrative Costs	Year 1	Year 2	Year 3	Year 4	Year 5
F&A Cost Rate 1	54%	54%	55.5%	56.5%	56.5%
F&A Cost Base 1	$376,735	$32,878	$32,659	$391,694	$391,694
F&A Costs 1	$203,437	$17,754	$18,126	$221,307	$221,307

F&A Cost Rate 2		55.5%	56.5%		
F&A Cost Base 2		$361,653	$359,244		
F&A Costs 2		$200,717	$202,973		

PI: (b)(6)	Title: University of Pittsburgh as the GUDMAP Tissue Hub and Collection Site	
Received: 11/06/2015	FOA: DK15-016	Council: 05/2016
Competition ID: FORMS-C	FOA Title: GENITOURINARY DEVELOPMENT MOLECULAR ANATOMY PROJECT (GUDMAP) - HUMAN TISSUE CORE (U24)	
1 U24 DK110791-01	Dual:	Accession Number: 3880427
IPF: 2059802	Organization: UNIVERSITY OF PITTSBURGH AT PITTSBURGH	
Former Number:	Department: Pathology	
IRG/SRG: ZDK1 GRB-2 (M3)S	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: 400,000 Year 2: 409,050 Year 3: 421,354 Year 4: 427,924 Year 5: 437,770	Animals: N Humans: Y Clinical Trial: N Current HS Code: (b)(5) HESC: N	New Investigator: Early Stage Investigator:

Senior/Key Personnel:	*Organization:*	*Role Category:*
(b)(6)	University of Pittsburgh	Co-Investigator
	University of Pittsburgh	Co-Investigator
	University of Pittsburgh	PD/PI
	University of Pittsburgh	Co-Investigator
	University of Pittsburgh	Co-Investigator

OMB Number: 4040-0001
Expiration Date: 06/30/2016

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	State Application Identifier

1. TYPE OF SUBMISSION*
❍ Pre-application ❍ Application ● Changed/Corrected Application

4.a. Federal Identifier

b. Agency Routing Number

2. DATE SUBMITTED | **Application Identifier**

c. Previous Grants.gov Tracking Number
GRANT12034213

5. APPLICANT INFORMATION **Organizational DUNS*:** 004514360

Legal Name*: University of Pittsburgh
Department: Office of Research
Division:
Street1*: 123 University Place, B21
Street2:
City*: Pittsburgh
County: Allegheny
State*: PA: Pennsylvania
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 15213-2303

Person to be contacted on matters involving this application
Prefix: Mr. First Name*: (b)(6) Suffix:
Position/Title:
Street1*: 123 University Place, B21
Street2: (b)(6)
City*: Pittsburgh
County: Allegheny
State*: PA: Pennsylvania
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 15213-2303
Phone Number*: (b)(6) Fax Number (b)(6) Email: offres@offres.pitt.edu

6. EMPLOYER IDENTIFICATION NUMBER *(EIN) or (TIN)** 25-0965591

7. TYPE OF APPLICANT* X: Other (specify)

Other (Specify): private, non-profit, state-related educational ins

Small Business Organization Type ❍ Women Owned ❍ Socially and Economically Disadvantaged

8. TYPE OF APPLICATION*
● New ❍ Resubmission
❍ Renewal ❍ Continuation ❍ Revision

If Revision, mark appropriate box(es).
❍ A. Increase Award ❍ B. Decrease Award ❍ C. Increase Duration
❍ D. Decrease Duration ❍ E. Other *(specify)* :

Is this application being submitted to other agencies?* ❍Yes ●No What other Agencies?

9. NAME OF FEDERAL AGENCY*
National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER
TITLE:

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
University of Pittsburgh as the GUDMAP Tissue Hub and Collection Site

12. PROPOSED PROJECT
Start Date* 07/01/2016
Ending Date* 06/30/2021

13. CONGRESSIONAL DISTRICTS OF APPLICANT
PA-014

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: Dr. First Name*: (b)(6) Suffix: M.D.
Position/Title: (b)(6)
Organization Name*: University of Pittsburgh
Department: Pathology
Division:
Street1*: UPMC Shadyside
Street2: 5230 Centre Avenue, (b)(6)
City*: Pittsburgh
County: Allegheny
State*: PA: Pennsylvania
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 15213-2303
Phone Number*: (b)(6) Fax Number: Email*: (b)(6)@upmc.edu

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested*	$3,207,015.00
b. Total Non-Federal Funds*	$0.00
c. Total Federal & Non-Federal Funds*	$3,207,015.00
d. Estimated Program Income*	$0.00

16.IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?*

a. YES ○ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:
DATE:

b. NO ○ PROGRAM IS NOT COVERED BY E.O. 12372; OR
● PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

● I agree*

** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.*

18. SFLLL or OTHER EXPLANATORY DOCUMENTATION File Name:

19. AUTHORIZED REPRESENTATIVE

Prefix: Dr. First Name*: (b)(6) Suffix: Ph.D
Position/Title*: (b)(6)
Organization Name*: University of Pittsburgh
Department: Office of Research
Division:
Street1*: 123 University Place, B21
Street2:
City*: Pittsburgh
County: Allegheny
State*: PA: Pennsylvania
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 15213-2303
Phone Number*: (b)(6) Fax Number: (b)(6) Email*: offres@offres.pitt.edu

Signature of Authorized Representative* (b)(6)

Date Signed* 11/06/2015

20. PRE-APPLICATION File Name:

21. COVER LETTER ATTACHMENT File Name:1235-Cover letter.pdf

424 R&R and PHS-398 Specific Table Of Contents

OMB Number: 4040-0010
Expiration Date: 06/30/2016

Project/Performance Site Location(s)

Project/Performance Site Primary Location

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	University of Pittsburgh
Duns Number:	0045143600000
Street1*:	UPMC Shadyside
Street2:	5230 Centre Avenue
City*:	Pittsburgh
County:	Allegheny
State*:	PA: Pennsylvania
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	15232-0000
Project/Performance Site Congressional District*:	PA-014

Project/Performance Site Location 1

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	University of Pittsburgh
DUNS Number:	0045143600000
Street1*:	Children's Hospital of UPMC
Street2:	4401 Penn Avenue
City*:	Pittsburgh
County:	Allegheny
State*:	PA: Pennsylvania
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	15224-0000
Project/Performance Site Congressional District*:	PA-014

Project/Performance Site Location 2

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	University of Pittsburgh
DUNS Number:	0045143600000
Street1*:	(b)(4)
Street2:	
City*:	
County:	
State*:	
Province:	
Country*:	
Zip / Postal Code*:	
Project/Performance Site Congressional District*:	PA-014

	File Name
Additional Location(s)	

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED Other Project Information

1. Are Human Subjects Involved?* ● **Yes** ○ **No**

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? ○ Yes ● No

If YES, check appropriate exemption number: _ 1 _ 2 _ 3 _ 4 _ 5 _ 6

If NO, is the IRB review Pending? ● **Yes** ○ **No**

IRB Approval Date:

Human Subject Assurance Number 00006790

2. Are Vertebrate Animals Used?* ○ **Yes** ● **No**

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ○ Yes ○ No

IACUC Approval Date:

Animal Welfare Assurance Number

3. Is proprietary/privileged information included in the application?* ○ **Yes** ● **No**

4.a. Does this project have an actual or potential impact - positive or negative - on the environment?* ○ **Yes** ● **No**

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ○ Yes ○ No

4.d. If yes, please explain:

5. Is the research performance site designated, or eligible to be designated, as a historic place?* ○ **Yes** ● **No**

5.a. If yes, please explain:

6. Does this project involve activities outside the United States or partnership with international collaborators?* ○ **Yes** ● **No**

6.a. If yes, identify countries:

6.b. Optional Explanation:

	Filename
7. Project Summary/Abstract*	1236-Abstract Final 20151025.pdf
8. Project Narrative*	1237-Project Narrative.pdf
9. Bibliography & References Cited	1238-References Cited_Final.pdf
10.Facilities & Other Resources	1239-Facilities FINAL GUDMAP 20151030.pdf
11.Equipment	1240-Equipment FINAL GUDMAP 20151030.pdf

Funding Opportunity Number: RFA-DK-15-016. Received Date: 2015-11-06T15:43:10.000-05:00

ABSTRACT

Congenital diseases of the genitourinary tract (kidneys, bladder, ureter, urethra etc.) are a leading cause of organ failure carrying with it an increased risk of death, and are a growing public health burden. At present, the only therapies are dialysis (for the kidneys) and organ transplantation. With the demand for transplants far exceeding supply there is an imminent need for alternate therapies. A comprehensive understanding of how the genitourinary tract develops *in utero* is necessary to effectively develop novel therapies to replace or repair injured tissue. The **GenitoUrinary Development Molecular Anatomy Project (GUDMAP)** has been successful at providing a high-resolution map of gene expression in the mouse GenitoUrinary system. However, a similar description has not been available for the human genitourinary system, nor has it been possible to develop optimized experimental techniques to grow, expand and differentiate human genitourinary progenitor cells *in vitro*. These research efforts by the developmental biology community have been hampered by the lack of a central hub for the procurement, quality control and distribution of human genitourinary samples. The Health Sciences Tissue Bank (HSTB) at the University of Pittsburgh has been involved in human tissue procurement for over 18 years, with a long standing history of collecting, maintaining and disbursing quality samples to research scientists, both in house and outside the University of Pittsburgh. HSTB is embedded within the Department of Pathology of the University of Pittsburgh Health Systems; thus providing rapid access to very high quality tissue and biological specimens. HSTB has established consenting protocols in line with the best practices recommendations from the NIH, a strong informatics backbone to facilitate specimen procurement and annotation, and has in place a robust quality control and quality assurance programs. The HSTB biorepository is fully accredited by the College of American Pathologists (CAP). HSTB has an established program accruing fetal tissues. The fetal tissue IRB has been in place since 2005. HSTB has the infrastructure for dissecting specimens and collecting different tissue types. In this calendar year, we have disbursed over 300 fresh samples collected from 77 cases. The collections can be significantly ramped up as material could have been accrued from as many as 725 cases last year. We have preliminary data showing that we can isolate the human urogenital system (kidneys, ureters and bladders) from various developmental ages (6-24 weeks). We have produced publication quality images of these genitourinary organs (including kidneys and bladder) and have also been able to isolate and expand cells from various genitourinary organs. Further, we have shipped high quality tissue to various GUDMAP investigators and they have verified the quality of the tissue sent. *We propose to act as both the GUDMAP Tissue Hub and Tissue Gathering site to build upon the pre-existing specialized collecting abilities of HSTB and provide high quality genitourinary samples to members of the scientific community including those within GUDMAP.*

Project Narrative:

An understanding of human genitourinary development is critical to tackling the growing number of developmental diseases affecting these tissues. This grant proposes to leverage the significant infrastructure of the University of Pittsburgh to provide high quality fetal tissue to the GUDMAP atlas projects.

Health Sciences Tissue Bank Facilities/Equipment Description

The Health Sciences Tissue Bank (HSTB) provides essential support for University of Pittsburgh research programs needing biological materials from patients seen at UPMC. The main objectives of the HSTB are to provide a mechanism to simplify and streamline the process of research tissue accrual and disbursement, and to provide efficient research pathology support services including histology, immunohistochemistry and paraffin tissue microarrays. The Health Sciences Tissue Bank is part of the University of Pittsburgh Core Research Facilities. Although the tissue bank is under the auspices of The University, we also have a strong working relationship with UPMC and the Department of Pathology. The HSTB has three College of American Pathology (CAP) certified laboratories in the flagship UPMC hospitals: (b)(4) (b)(4) as well as a collection site in the community hospital (b)(4) In addition, the HSTB extensively interacts with Oncology and Pathology Informatics and has computer and server facilities located in these collaborative facilities. The facilities available to the tissue resource at each of these institutions are detailed below:

Shadyside Hospital (SYS)

Health Sciences Tissue Bank Shadyside Laboratory Space:

The Health Sciences Tissue Bank (HSTB) administrative office is located a short distance from the (b)(4); (b)(6) (b)(4); (b)(6) (b)(4); (b)(6) The HSTB laboratory and freezer room space occupies 3300 square feet. This space includes the tissue banking lab space, research histology lab space, freezer rooms and storage rooms. The space is divided into six rooms. The largest room, measuring 30'x20', is for tissue processing, slide retrieval and storage. This laboratory is equipped with a cryobath, liquid nitrogen tank and dry ice for varied methods of snap freezing tissue, a Thermo cryostat used to cut frozen sections for quality review by a pathologist. Centrifuges, Cytospin, calibrated pipettes, microscopes, and sterile supplies are available for tissue procurement and dissection. The lab space has a refrigerator to store media and other necessary reagents as well as a -80°C freezer for short term sample storage. There are 9 working stations in the lab area all equipped with desktop computers, barcode scanners and hooked up to a network printer. There is a storage area for paraffin embedded tissue blocks and slides. Locked filing cabinets are located in the space for secure storage of documents and files. These facilities provide staff with all the necessary materials to procure quality tissue for tissue collection and disbursement.

The smaller laboratory area, measuring 30'x10' is for research histology. This lab space has the unique equipment necessary for formalin fixed paraffin embedded (FFPE) tissue processing and staining, along with the specific equipment needed for paraffin tissue microarray (TMA) construction. For paraffin processing, a ThermoShandon Excelsior tissue processor and Sakura Tissue Tek embedding center are used. There are 3 Microm microtomes, 2 are equipped with histocollimators. They can be setup for routine sectioning, thick sectioning microtomy and laser capture microdissection (LCM) slides or other protocol specific requests. There is 1 automated stainer for H&E staining and 2 automated Dako stainers used for immunohistochemical (IHC) staining along with calibrated pipettes for serial dilution and titration protocols, which are used to stain tissue based on study design. The tissue microarray portion of the lab contains 2 Beecher Tissue Microarrayers with coring capabilities from 0.6 to 2.0mm. The histology lab also contains its own ThermoShandon cryostat allowing for the capability of providing frozen section slides. Included in the lab is a 2°-8°C walk-in cooler and -20°C freezer for reagent storage. Other available supplies include water baths, glassware, 2 incubator ovens, a fume hood for cover slipping and other tools needed to perform daily tasks. The histology space includes 3 active work stations with desktop computers hooked up to a network printer. One of the work stations has a Slidemate slide writer locally connected to one of the computers used for automated slide labeling.

There are two designated freezer areas. One contains 12 Thermo -80C freezers, while the other room is set up specifically for vapor phase liquid nitrogen freezers, containing 6 vessels. This space has piped liquid nitrogen from the hospital facility. Both freezer rooms also contain additional secure storage space. There are two hallways, measuring 30'x6' and 25'x8', used for filing cabinets for glass slides, paraffin blocks and supplies.

Health Sciences Tissue Bank Shadyside Office Space:

(b)(6) and the tissue banking staff have offices within the (b)(4); (b)(6) area, which are in near proximity to the (b)(4) . The Director, (b)(6) has a 500 sq. ft. office suite which contains a desk space with a desktop computer and multiheaded microscope. This space also contains a conference table with seating for 8. Outside of his suite, there is an anteroom with desk space for his administrative assistant. The Assistant Director has a 110 sq. ft. office within the HSTB at UPMC

Shadyside, along with an 80 sq. ft. shared office space for the Project and Quality Managers. The Research Histology Supervisor has a 130 sq. ft. lab space on the histology side of the main laboratory set up. All office spaces contain desktop computers with dual monitors mapped to network printers, scanners, telephones, locked filing cabinets, and other office supplies necessary for administrative operations. The rooms are also equipped with a dry-erase whiteboard for teaching assistance and microscopes as needed.

(b)(4); (b)(6) This area is approximately 450 sq. ft and includes the main gross room and the frozen section area. It functions as the central processing and sectioning lab for gross pathology at (b)(4); (b)(6) It has 5 grossing stations that have fume hoods for processing non-sterile specimens. Each of the fume hoods is equipped with PCs linked to the hospital mainframe system, sinks, and a DictaPhone Voice Processor for dictation of gross descriptions.
This facility is a fully functional surgical pathology gross room, and contains equipment necessary for this purpose. Such equipment includes: Leica CM1800 CryoStat, H&E staining station, ButcherBoy band saw for sectioning of bone, Cabinet X-Ray System Faxitron Series HP, Polarstar No-frost refrigerator, Revco -70 C upright freezer, Flammable cabinet, Cryobath CB-60 isopentane cryopreservation unit, Aculab GS-2001 Standard Digital Scale, and dissecting equipment, chemicals, glassware, and storage shelves for such purposes. This room also has a two-head American optical microscope for frozen section interpretation.

Health Sciences Tissue Bank - Imaging Services: Imaging services are offered through the Health Sciences Tissue Bank (HSTB). The digital imaging core facility offers clinical and research services. The imaging core has imaging equipment for generating, annotating, interpreting, storing and analyzing digital images. This facility is located at UPMC Shadyside in the Hillman Cancer Pavilion and has about 200 sq. ft. of space for the imaging laboratory. The imaging facility provides pathologist oversight, technical support staff and space for imaging studies, validation, training and conferencing. Images can be securely hosted and made available to investigators for remote viewing or saved locally for investigators on a DVD, USB flash drive or external hard drive.
Equipment: Imaging devices include Nikon digital cameras for macroscopic pathology and Spot insight cameras for microscopic imaging. For virtual microscopy at 20x, 40x and 60x magnification a variety of whole slide scanners (Omnyx, Aperio and Hamamatsu Nanozoomer) are available. The Nanozoomer has z-stack (multiple plane) capability.
Image analysis: The imaging facility offers image algorithm development and image analysis. The Visiopharm platform is primarily used for this work, which allows cellular structures and biomarkers in tissue samples to be detected and quantified, automated alignment of serial tissue sections, and tissue microarray (TMA) image analysis. Quantitative image analysis of immunohistochemistry can also be performed on images using Aperio's nuclear, positive pixel count or membrane algorithms.

(b)(4); (b)(6)

Health Sciences Tissue Bank (b)(4); (b)(6) Laboratory Space:
The HSTB laboratory and freezer room space occupies 1800 sq. ft in (b)(4); (b)(6) This space includes the tissue banking laboratory and three freezer rooms. The lab space is 100 sq. ft. and is equipped for tissue processing, slide retrieval and storage. This laboratory contains a cryobath and dry ice for varied methods of snap freezing tissue, a Thermo cryostat used to cut frozen sections for quality review by a pathologist. Centrifuges, cryobath, calibrated pipettes, microscopes, and sterile supplies are available for tissue procurement and dissection. The lab space has a refrigerator to store media and other necessary reagents as well as an adjacent 100 sq. ft. freezer room with a -80°C freezer for short term sample storage. There are 4 working stations in the lab area all equipped with desktop computers, barcode scanners and hooked up to a network printer. There is a storage area for paraffin embedded tissue blocks and slides. Locked filing cabinets are located in the space for secure storage of documents and files.
The Presbyterian site has three freezer rooms in (b)(4); (b)(6) one located on the (b)(4) and two located (b)(4) measuring 600 and 300 sq. ft. Combined, the freezer rooms house 14 -80°C freezers and 1 liquid nitrogen storage vessel. The largest of the three rooms located (b)(4) also has 1 desktop computer. The (b)(4); (b)(6) site also has administrative office space located down the hall from the laboratory. The office is 80 sq. ft. and contains a desktop computer and locked filing cabinets. These facilities provide staff with all the necessary materials to procure quality tissue for tissue collection and disbursement.

UPMC (b)(4); (b)(6) Pathology Gross Room:

This area is approximately 1000 sq. ft. in area and includes the main gross room, the imaging room and the frozen section room. The main gross room lab is approximately 750 sq. ft. in area. It functions as the central processing and sectioning lab for gross pathology at (b)(4); (b)(6) There is an additional frozen section room located on the (b)(4) . This frozen section room is equipped with current state-of-the-art informatics and electronics for communication with the operating rooms. This frozen section room measures approximately 400 sq. ft. in area. It has two cryostats and three cutting stations. It also contains two computers connected to the network. The frozen section room has digital video feed to and from the operating rooms. This also allows for instantaneous discussions with the surgeons as well immediate “show and tell” for them. This room serves as the center for procurement of fresh tissue samples for research.

(b)(4); (b)(6)

(b)(4); (b)(6)

(b)(4); (b)(6)

(b)(4); (b)(6)

(b)(4); (b)(6)

(b)(4); (b)(6)

Children's Hospital of Pittsburgh Facilities and Other Resources:

Children's Hospital Laboratory:

(b)(6) has a 450 sq. ft. laboratory (half a bay) on the (b)(4) (b)(4) (b)(6) laboratory is equipped for sophisticated molecular and developmental biological experimentation. The pediatric nephrology division has shared facilities that includes a biosafety hood, - 20°C and -70°C freezers, cell culture incubators, Hypoxia chamber for cell and organ culture, a microtome, 2 dissecting microscopes, an upright fluorescent microscope, a digital camera, electrophoresis and power supplies, 3 thermocyclers, a high quality water purification system, a pH meter, an analytical balance and hybridization ovens. Ample bench top space, desk space and computer access is available. (b)(6) has an office on the (b)(4) that is 140 sq. ft. near (b)(6) laboratory.

(b)(6) laboratory encompasses approximately 900 square feet of laboratory space, adjacent to (b)(6), facilitating access to shared divisional equipment. (b)(6) has an

(b)(4) that is 140 sq. ft. near (b)(6) laboratory.

Animals:
N/A

Computers:
(b)(6) office and laboratory are equipped with iMac desktop computers (1 in the office and 2 in the laboratories) and ample hard drive space. These are connected to an intranet server with additional hard drive space. All computers are connected to the Internet.
(b)(6) office and laboratory are equipped with iMac desktop computers (1 in the office and 3 in the laboratories) and ample hard drive space. These are connected to an intranet server with additional hard drive space. All computers are connected to the Internet.

Clinical:
N/A

Office:
(b)(6) has an office on the (b)(4) that is 140 sq. ft. near (b)(6) laboratory. All staff in the (b)(6) lab has their own individual desk space.
(b)(6) has an office on the (b)(4) that is 140 sq. ft. near (b)(6) laboratory. All staff in the (b)(6) lab has their own individual desk space.

Other:
(b)(4) These cores both consist of a sorter (FACSAriaII) and an analyzer (LSRII), as well as significant expert technical support. This will be available for the project.

Pathology Core:
The Pathology Core is located (b)(4) The Histology core will provide tissue processing, sectioning, general staining, immunohistochemistry, and in situ hybridization. This will be available for the project.

Cell Imaging Core:
The Cell Imaging Core, located (b)(4) has confocal microscopy and live cell imaging as well as technical support. This will be available for the project.

Pittsburgh Center for Kidney Research:
This center facilitates multidisciplinary research related to kidney physiology, cell biology and pathophysiology. The cores include: Core A Cellular Physiology; Core B Single Nephron and Organ Physiology; Core C Urinary Tract Epithelial Imaging; and Core D Use of Model Organisms to Elucidate Novel Aspects of Kidney Function.

Equipment:

Validation laboratories (b)(6)

(b)(6) have a fully equipped laboratory for molecular biology, and flow hoods for cell culture.

Equipment in the lab includes:

- 1 Biosafety hood (Kewaunee)
- 2 Cell culture hoods (Filtech)
- 5 freezers (3 -20 and 2 -80) (Thermo)
- 2 Cell culture incubators (Thermo)
- 1 tissue processor (Leica)
- 1 embedding station (Leica)
- 1 microtome (Thermo)
- 1 Floatation bath (Boekel)
- 3 dissecting microscopes (Leica)
- 1 upright fluorescent microscope (Leica)
- 2 digital cameras (Axio)
- 1 3D reconstructive Imaging equipment (MBF, Zeiss)
- 3 Hybridization ovens (Labnet)
- 3 electrophoresis and power supplies (Fisher)
- 3 thermocyclers (Biorad)
- 1 high quality water purification system (Millipore)
- 1 pH meter (Fisher)
- 1 analytical balance (Denver Instruments)
- 3 hybridization ovens (Fisher)
- 3 water baths (Fisher)

Health Sciences Tissue Bank Laboratories:

(b)(4); (b)(5)

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: Dr. First Name*: (b)(6) Suffix: M.D.

Position/Title*: (b)(6)
Organization Name*: University of Pittsburgh
Department: Pathology
Division:
Street1*: UPMC Shadyside
Street2: 5230 Centre Avenue, (b)(6)
City*: Pittsburgh
County: Allegheny
State*: PA: Pennsylvania
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 15213-2303

Phone Number*: (b)(6) Fax Number: E-Mail*: (b)(6) @upmc.edu

Credential, e.g., agency login: (b)(6)

Project Role*: PD/PI Other Project Role Category:

Degree Type: MD Degree Year: 1989

	File Name
Attach Biographical Sketch*:	1243-Biosketch-(b)(6) 20150825.pdf
Attach Current & Pending Support:	

Funding Opportunity Number: RFA-DK-15-016 . Received Date: 2015-11-06T15:43:10.000-05:00

PROFILE - Senior/Key Person

Prefix: Dr. First Name*: (b)(6) Suffix: M.D.

Position/Title*: (b)(6)
Organization Name*: University of Pittsburgh
Department: Pediatrics
Division: (b)(6)
Street1*:
Street2:
City*: Pittsburgh
County: Allegheny
State*: PA: Pennsylvania
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 15224-0000

Phone Number*: (b)(6) Fax Number: E-Mail*: (b)(6) @chp.edu

Credential, e.g., agency login: (b)(6)

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: MD Degree Year: 2001

File Name

Attach Biographical Sketch*: 1244(b)(6) biosketch- new.pdf

Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: Dr. First Name*: (b)(6) Suffix: M.D.

Position/Title*: (b)(6)
Organization Name*: University of Pittsburgh
Department: Pathology
Division:
Street1*: UPMC Shadyside Hospital (b)(6)
Street2: 5150 Centre Avenue
City*: Pittsburgh
County: Allegheny
State*: PA: Pennsylvania
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 15232-0000

Phone Number*: (b)(6) Fax Number (b)(6) E-Mail* (b)(6) @upmc.edu

Credential, e.g., agency login (b)(6)

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: MD Degree Year: 1996

File Name

Attach Biographical Sketch*: 1245(b)(6) NIH Biosketch.pdf

Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: Dr. First Name*: (b)(6) Suffix: M.D.

Position/Title*: (b)(6)
Organization Name*: University of Pittsburgh
Department: Pathology
Division:
Street1*: (b)(6)
Street2:
City*: Pittsburgh
County: Allegheny
State*: PA: Pennsylvania
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 15213-0000

Phone Number*: (b)(6) Fax Number: E-Mail*: (b)(6)@upmc.edu

Credential, e.g., agency login: (b)(6)

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: MD Degree Year: 1988

Attach Biographical Sketch*: File Name 124(b)(6) Biosketch 102315 Fetal urologic tissue bank.pdf

Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: Dr. First Name*: (b)(6) Suffix: Ph.D

Position/Title*: (b)(6)
Organization Name*: University of Pittsburgh
Department: Pediatrics
Division: (b)(6)
Street1*:
Street2:
City*: Pittsburgh
County: Allegheny
State*: PA: Pennsylvania
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 15213-0000

Phone Number*: (b)(6) Fax Number: (b)(6) E-Mail*: (b)(6)@chp.edu

Credential, e.g., agency login: (b)(6)

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: PhD Degree Year: 2007

Attach Biographical Sketch*: File Name 1247-(b)(6) NIH Biosketch-GUDMAP.pdf

Attach Current & Pending Support:

OMB No. 0925-0001/0002 (Rev. 08/12 Approved Through 8/31/2015)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

(b)(6)

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 1

ORGANIZATIONAL DUNS*: 0045143600000

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: University of Pittsburgh

Start Date*: 07-01-2016 **End Date*:** 06-30-2017 **Budget Period: 1**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .	Dr.	(b)(6)			M.D.	PD/PI	(b)(6)				36,660.00	8,358.00	45,018.00
2 .	Dr.				M.D.	Co-investigator					9,000.00	2,052.00	11,052.00
3 .	Dr.				M.D.	Co-investigator					9,000.00	2,052.00	11,052.00
4 .	Dr.				M.D.	Co-investigator					25,881.00	5,901.00	31,782.00
5 .	Dr.				PhD	Co-investigator					18,540.00	4,227.00	22,767.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **121,671.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	HSTB Manager	(b)(6)			4,159.00	1,506.00	5,665.00
1	Project Coordinator				20,563.00	7,444.00	28,007.00
3	Research Techincian				75,407.00	27,297.00	102,704.00
1	QA Coordinator				13,028.00	4,716.00	17,744.00
1	IT Coordinator				7,783.00	2,817.00	10,600.00
1	Data Coordinator				7,565.00	2,738.00	10,303.00
8	**Total Number Other Personnel**					**Total Other Personnel**	**175,023.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**296,694.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 1

ORGANIZATIONAL DUNS*: 0045143600000
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: University of Pittsburgh

Start Date*: 07-01-2016 **End Date*:** 06-30-2017 **Budget Period: 1**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	
Additional Equipment: File Name:	

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	10,000.00
2. Foreign Travel Costs	
Total Travel Cost	**10,000.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Tracking Number: GRANT12034939 Funding Opportunity Number: RFA-DK-15-016 . Received Date: 2015-11-06T15:43:10.000-05:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 1

ORGANIZATIONAL DUNS*: 0045143600000
Budget Type*: ● Project ○ Subaward/Consortium
Organization: University of Pittsburgh

Start Date*: 07-01-2016 **End Date*:** 06-30-2017 **Budget Period: 1**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	48,306.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . HSTB Services	20,000.00
9 . Project Management Tool, BIOS	25,000.00
Total Other Direct Costs	**93,306.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**400,000.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	54.00	380,000.00	205,200.00
		Total Indirect Costs	**205,200.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) U.S. Department of Health and Human Services (b)(6) (b)(6)

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**605,200.00**

J. Fee	Funds Requested ($)*

K. Budget Justification* File Name: 1234-(b)(6) budget justification 10.30.2015.pdf
(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 2

ORGANIZATIONAL DUNS*: 0045143600000

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: University of Pittsburgh

Start Date*: 07-01-2017 **End Date*:** 06-30-2018 **Budget Period: 2**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .	Dr.	(b)(6)			M.D.	PD/PI		(b)(6)			36,660.00	8,358.00	45,018.00
2 .	Dr.				M.D.	Co-investigator					9,270.00	2,114.00	11,384.00
3 .	Dr.				M.D.	Co-investigator					9,270.00	2,114.00	11,384.00
4 .	Dr.				M.D.	Co-investigator					26,658.00	6,078.00	32,736.00
5 .	Dr.				PhD	Co-investigator					19,096.00	4,354.00	23,450.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **123,972.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	HSTB Manager	(b)(6)			4,263.00	1,543.00	5,806.00
1	Project Coordinator				21,077.00	7,630.00	28,707.00
3	Research Techincian				77,492.00	28,052.00	105,544.00
1	QA Coordinator				13,353.00	4,834.00	18,187.00
1	IT Coordinator				7,978.00	2,888.00	10,866.00
1	Data Coordinator				7,792.00	2,821.00	10,613.00
8	**Total Number Other Personnel**					**Total Other Personnel**	**179,723.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**303,695.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 2

ORGANIZATIONAL DUNS*: 0045143600000
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: University of Pittsburgh

Start Date*: 07-01-2017 **End Date*:** 06-30-2018 **Budget Period: 2**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	10,000.00
2. Foreign Travel Costs	
Total Travel Cost	**10,000.00**

E. Participant/Trainee Support Costs	**Funds Requested ($)***
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees **Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Tracking Number: GRANT12034939 Funding Opportunity Number: RFA-DK-15-016 . Received Date: 2015-11-06T15:43:10.000-05:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 2

ORGANIZATIONAL DUNS*: 0045143600000
Budget Type*: ● Project ○ Subaward/Consortium
Organization: University of Pittsburgh

Start Date*: 07-01-2017 **End Date*:** 06-30-2018 **Budget Period: 2**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	49,755.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . HSTB Services	20,600.00
9 . Project Management Tool, BIOS	25,000.00
Total Other Direct Costs	**95,355.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**409,050.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	55.50	388,448.00	215,589.00
		Total Indirect Costs	**215,589.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): U.S. Department of Health and Human Services, (b)(6) (b)(6)

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**624,639.00**

J. Fee	Funds Requested ($)*

K. Budget Justification* File Name: 1234-Fetal budget justification 10.30.2015.pdf
(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Tracking Number: GRANT12034939 Funding Opportunity Number: RFA-DK-15-016 . Received Date: 2015-11-06T15:43:10.000-05:00

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 3

ORGANIZATIONAL DUNS*: 0045143600000

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: University of Pittsburgh

Start Date*: 07-01-2018 **End Date*:** 06-30-2019 **Budget Period: 3**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .	Dr.	(b)(6)			M.D.	PD/PI		(b)(6)			36,660.00	8,358.00	45,018.00
2 .	Dr.				M.D.	Co-investigator					9,548.00	2,177.00	11,725.00
3 .	Dr.				M.D.	Co-investigator					9,548.00	2,177.00	11,725.00
4 .	Dr.				M.D.	Co-investigator					27,458.00	6,260.00	33,718.00
5 .	Dr.				PhD	Co-investigator					19,669.00	4,485.00	24,154.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **126,340.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	HSTB Manager	(b)(6)			4,370.00	1,582.00	5,952.00
1	Project Coordinator				21,604.00	7,821.00	29,425.00
3	Research Techincian				79,635.00	28,828.00	108,463.00
1	QA Coordinator				13,687.00	4,955.00	18,642.00
1	IT Coordinator				8,177.00	2,960.00	11,137.00
1	Data Coordinator				8,025.00	2,905.00	10,930.00
8	**Total Number Other Personnel**					**Total Other Personnel**	**184,549.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**310,889.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 3

ORGANIZATIONAL DUNS*: 0045143600000
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: University of Pittsburgh

Start Date*: 07-01-2018 **End Date*:** 06-30-2019 **Budget Period: 3**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	
Additional Equipment: File Name:	

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	10,000.00
2. Foreign Travel Costs	3,000.00
Total Travel Cost	**13,000.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Tracking Number: GRANT12034939 Funding Opportunity Number: RFA-DK-15-016 . Received Date: 2015-11-06T15:43:10.000-05:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 3

ORGANIZATIONAL DUNS*: 0045143600000
Budget Type*: ● Project ○ Subaward/Consortium
Organization: University of Pittsburgh

Start Date*: 07-01-2018 **End Date*:** 06-30-2019 **Budget Period: 3**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	51,247.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . HSTB Services	21,218.00
9 . Project Management Tool, BIOS	25,000.00
Total Other Direct Costs	**97,465.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**421,354.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	56.50	400,136.00	226,077.00
		Total Indirect Costs	**226,077.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): U.S. Department of Health and Human Services, (b)(6) (b)(6)

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**647,431.00**

J. Fee	Funds Requested ($)*

K. Budget Justification* File Name: 1234-Fetal budget justification 10.30.2015.pdf
(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 4

ORGANIZATIONAL DUNS*: 0045143600000

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: University of Pittsburgh

Start Date*: 07-01-2019 **End Date*:** 06-30-2020 **Budget Period: 4**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .	Dr.	(b)(6)			M.D.	PD/PI		(b)(6)			36,660.00	8,358.00	45,018.00
2 .	Dr.				M.D.	Co-investigator					9,835.00	2,242.00	12,077.00
3 .	Dr.				M.D.	Co-investigator					9,835.00	2,242.00	12,077.00
4 .	Dr.				M.D.	Co-investigator					28,281.00	6,448.00	34,729.00
5 .	Dr.				PhD	Co-investigator					20,259.00	4,619.00	24,878.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **128,779.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical	(b)(6)					
1	HSTB Manager				4,479.00	1,621.00	6,100.00
1	Project Coordinator				22,144.00	8,016.00	30,160.00
3	Research Techincian				81,838.00	29,625.00	111,463.00
1	QA Coordinator				14,029.00	5,079.00	19,108.00
1	IT Coordinator				8,381.00	3,034.00	11,415.00
1	Data Coordinator				8,266.00	2,992.00	11,258.00
8	**Total Number Other Personnel**					**Total Other Personnel**	**189,504.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**318,283.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 4

ORGANIZATIONAL DUNS*: 0045143600000
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: University of Pittsburgh

Start Date*: 07-01-2019 **End Date*:** 06-30-2020 **Budget Period:** 4

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	10,000.00
2. Foreign Travel Costs	
Total Travel Cost	**10,000.00**

E. Participant/Trainee Support Costs	**Funds Requested ($)***
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees **Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 4

ORGANIZATIONAL DUNS*: 0045143600000
Budget Type*: ● Project ○ Subaward/Consortium
Organization: University of Pittsburgh

Start Date*: 07-01-2019 **End Date*:** 06-30-2020 **Budget Period:** 4

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	52,786.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . HSTB Services	21,855.00
9 . Project Management Tool, BIOS	25,000.00
Total Other Direct Costs	**99,641.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**427,924.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	56.50	406,071.00	229,430.00
		Total Indirect Costs	**229,430.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): U.S. Department of Health and Human Services, (b)(6) (b)(6)

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**657,354.00**

J. Fee	Funds Requested ($)*

K. Budget Justification* File Name: 1234-Fetal budget justification 10.30.2015.pdf
(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Tracking Number: GRANT12034939 Funding Opportunity Number: RFA-DK-15-016 . Received Date: 2015-11-06T15:43:10.000-05:00

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 5

ORGANIZATIONAL DUNS*: 0045143600000

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: University of Pittsburgh

Start Date*: 07-01-2020 **End Date*:** 06-30-2021 **Budget Period: 5**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .	Dr.	(b)(6)			M.D.	PD/PI		(b)(6)			36,660.00	8,358.00	45,018.00
2 .	Dr.				M.D.	Co-investigator					10,130.00	2,310.00	12,440.00
3 .	Dr.				M.D.	Co-investigator					10,130.00	2,310.00	12,440.00
4 .	Dr.				M.D.	Co-investigator					29,130.00	6,642.00	35,772.00
5 .	Dr.				PhD	Co-investigator					20,867.00	4,758.00	25,625.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **131,295.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	HSTB Manager	(b)(6)			4,591.00	1,662.00	6,253.00
1	Project Coordinator				22,697.00	8,216.00	30,913.00
3	Research Techincian				84,103.00	30,445.00	114,548.00
1	QA Coordinator				14,380.00	5,206.00	19,586.00
1	IT Coordinator				8,591.00	3,110.00	11,701.00
1	Data Coordinator				8,514.00	3,082.00	11,596.00
8	**Total Number Other Personnel**					**Total Other Personnel**	**194,597.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**325,892.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 5

ORGANIZATIONAL DUNS*: 0045143600000
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: University of Pittsburgh

Start Date*: 07-01-2020 **End Date*:** 06-30-2021 **Budget Period: 5**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	
Additional Equipment: File Name:	

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	10,000.00
2. Foreign Travel Costs	
Total Travel Cost	**10,000.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 5

ORGANIZATIONAL DUNS*: 0045143600000
Budget Type*: ● Project ○ Subaward/Consortium
Organization: University of Pittsburgh

Start Date*: 07-01-2020 **End Date*:** 06-30-2021 **Budget Period: 5**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	54,368.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . HSTB Services	22,510.00
9 . Project Management Tool, BIOS	25,000.00
Total Other Direct Costs	**101,878.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**437,770.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	56.50	415,259.00	234,621.00
		Total Indirect Costs	**234,621.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): U.S. Department of Health and Human Services, (b)(6) (b)(6)

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**672,391.00**

J. Fee	Funds Requested ($)*

K. Budget Justification* File Name: 1234-Fetal budget justification 10.30.2015.pdf
(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

BUDGET JUSTIFICATION

Personnel

(b)(6) of the Health Sciences Tissue Bank (HSTB) of the University of Pittsburgh and a practicing pathologist with subspecialty training in Genitourinary Pathology. He will be responsible for the oversight of the project. This will include interfacing and working with internal collaborators to ensure accrual and annotation of the appropriate specimens. He will also interact with the external collaborators and clients to ensure appropriate specimen aggregation and disbursement. He will work closely with NIDDK to ensure successful execution of the project, meeting the mission and goals of the Tissue Core.

(b)(6) Co-I, Effort = (b)(6) is the (b)(6) (b)(6) He also serves as the (b)(6) He provides direction and advice related to the different Information systems and tools used by HSTB. He is also the director of the Imaging core; a subsidiary of HSTB. The imaging core will perform whole slide image acquisition and provide access to these images for the Tissue Core clients.

(b)(6) Co-I, Effort = (b)(6) is the (b)(6) (b)(6) He will be responsible for evaluating appropriate surgical pathology and autopsy specimens and overseeing collection of the biological materials for the Tissue Core. He will work closely with (b)(6) (b)(6) to perform routine and specialized histological assessment of the appropriate specimens.

(b)(6) Co-I, Effort = (b)(6) is a clinician scientist (b)(6) (b)(6) with a flourishing research program related to kidney development. She has a thorough understanding of genitourinary development and is ideally suited to act as co-coordinator of the validation lab for this project.

(b)(6) Co-I, Effort = (b)(6) is a kidney developmental biologist with over (b)(6) studying the genitourinary tract. Furthermore, he is also a classically trained human anatomist and embryologist which make him ideally suited to act as a coordinator of the validation lab of the proposed tissue hub and collection site.

(b)(6) **:** Effort = (b)(6) This (b)(6) will be responsible coordination management of day to day operations. She supervises HSTB staff members and will manage the overall efforts of the HSTB and set operational standards related to the HSTB scope of work. She will assure proper communication and resolution conflicts and issues.

(b)(6) **:** Effort = (b)(6) This (b)(6) will be responsible for project intake, tracking and recording keeping. She will coordinate the GUDMAP investigator requests to the GUDMAP-Human Tissue Repository including documenting the needs of the investigator, assuring regulatory compliance, coordinating with tissue and data collection staff members and assuring proper completion and shipping of requests. (b)(6) is also a cytotechnologist and smaller portion of her effort will be applied to oversight and performance of this function.

TBN (Technician CHP validation lab): Effort = 12.0 Calendar months (100%). This grant will fund 100% of the technicians salary. This technician will perform all the required validation of the specimens including: histology, immunohistochemistry, in situ hybridization, cell isolation and real time PCR.

(b)(6) Effort = (b)(6) This HSTB tissue bank technician and will perform the day-to-day tasks associated with the collection of specimens. This includes maintaining a working knowledge of all SOPs related to the ongoing collections that are requested by the GUDMAP investigators. She will coordinate with the clinical departments within (b)(4); (b)(6) interface with the Pathology and other hospital staff members as required to obtain the requested specimens and enter data related to each case in the BIOS.

(b)(6) Effort = (b)(6) This (b)(6) will perform the day-to-day tasks associated with the collection of specimens. This includes maintaining a working knowledge of all SOPs related to the ongoing collections that are requested by the GUDMAP investigators. She will coordinate with the clinical departments within (b)(4); (b)(6) interface with the Pathology and other hospital staff members as required to obtain the requested specimens and enter data related to each case in the BIOS.

(b)(6) This (b)(6) will be responsible for the quality program. He will manage all aspects of quality management including record keeping, training of staff members to standard operating procedures (SOPs), data entry practices and audits, and quality related events. He will coordinate the overall record keeping and management of the quality metrics from the tissue collection and data entry processes with the quality measurements performed through the Department of Pediatrics team.

(b)(6) Effort = (b)(6) This (b)(6) specialist will be responsible for overall management of the Biospecimen Inventory and Operations System with regard to this project. He will manage the specimen search process, control the data entry lexicon as needed, and provide reports of collection activity for investigators who request samples and as needed for other purposes. He will maintain the data integrity and make corrections and amendments based on the quality control activities. In the case that new fields and library elements are required he will manage that process in conjunction with the Project Manager and Quality Manager. He will be required to produce final sample pick lists as specimens are disbursed.

(b)(6) Effort = (b)(6) The (b)(6) will be responsible for aggregating information from the different information systems on the specimens offered as part of the Tissue Core. This will include pathology information as well as more specialized information (like cytogenetics); if applicable. The data coordinator will work with the Project manager on cohort identification for the different requests. In addition the data coordinator will also be responsible for providing data to the clients of the Tissue Core.

Supplies

HSTB Consumable Laboratory Supplies: (b)(4) annually. Or about (b)(4) monthly will be used for sample collections, integrity, maintenance, and transport including sample and shipping containers, dry ice, and other basic supplies. (b)(4)

International Institute for the Advancement of Medicine (IIAM): (b)(4) annually. IIAM will be used to source specimens from later developmental ages (24-42 weeks) that are not available through internal sources. IIAM has indicated that they are able to provide samples for approximately (b)(4) per year in this category at a cost of (b)(4)

Validation Laboratory Consumable Laboratory Supplies: (b)(4) annually. Or about (b)(4) monthly will be required to purchase reagents for staining, immunohistochemistry and in situ reagents as well as cell, culture medium and consumable plastics related to these processes. These processes will be performed in response to the needs of the GUDMAP investigators.

Travel

Pathology: The Project PI and a co-investigator will need to travel to GUDMAP consortia meetings, to be held twice a year. A total of $4,000 is allocated for this travel in year 1.

Validation Laboratories: The Project co-investigators will need to travel to consortia meetings, to be held twice a year. (b)(6) will also attend the American Society of Nephrology meeting where GUDMAP typically has a booth. A total of $6,000 is allocated for this travel in year 1.

(b)(6) will also attend the International Meeting on Development Nephrology to be held in 2018, where GUDMAP will hold workshops. In year 3, $3,000 is allocated for this travel.

Other Expenses

Tissue embedding/processing, storage, and disbursement: (b)(4) year 1 with 3% escalation each year in years 2-5. These are billable services based on the fiscal parameters in place within the University of Pittsburgh for the HSTB. Tissue embedding and processing will be required at all levels for quality management and to provide product to GUDMAP investigators and (b)(4) is requested annually. Storage costs are based on the partial cost of a freezer with a 10 year life span plus projected maintenance and certification costs; (b)(4) is requested annually. The cost for disbursement of samples to GUDMAP investigators will be charged to the account award for this project. We estimate that approximately 30 disbursements will be made at a billable cost of (b)(4) each for a total annual cost of (b)(4)

Website maintenance, project management tool, BIOS, image acquisition: $25,000 annually. Resources will be required to maintain and update our internally developed inventory management system (BIOS). The project management tool is internally developed and is the mechanism for starting and following the progress of the request from the client. The clients will be provided access to the contents of the resource via a Sharepoint link that will be password protected. Whole slide image acquisition will be done to offer clients access to high quality images of the specimens in the resource. These images will be from routine and specialized histologic and immunohistochemical/ in-situ protocols. We also have capabilities for image analysis and will offer, if required. We estimate these endeavors will require a total annual support of $25,000.

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals ($)	
Section A, Senior/Key Person		632,057.00
Section B, Other Personnel		923,396.00
Total Number Other Personnel	40	
Total Salary, Wages and Fringe Benefits (A+B)		1,555,453.00
Section C, Equipment		
Section D, Travel		53,000.00
1. Domestic	50,000.00	
2. Foreign	3,000.00	
Section E, Participant/Trainee Support Costs		
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other		
6. Number of Participants/Trainees		
Section F, Other Direct Costs		487,645.00
1. Materials and Supplies	256,462.00	
2. Publication Costs		
3. Consultant Services		
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs		
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		
8. Other 1	106,183.00	
9. Other 2	125,000.00	
10. Other 3		
Section G, Direct Costs (A thru F)		2,096,098.00
Section H, Indirect Costs		1,110,917.00
Section I, Total Direct and Indirect Costs (G + H)		3,207,015.00
Section J, Fee		

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OMB Number: 0925-0001

1. Project Director / Principal Investigator (PD/PI)

Prefix:
First Name*:
Middle Name:
Last Name*:
Suffix:

(b)(6)

2. Human Subjects

Clinical Trial? ● No ○ Yes

Agency-Defined Phase III Clinical Trial?* ○ No ○ Yes

3. Permission Statement*

If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and e-mail address of the official signing for the applicant organization, to organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)?

● Yes ○ No

4. Program Income*

Is program income anticipated during the periods for which the grant support is requested? ○ Yes ● No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

Budget Period*	Anticipated Amount ($)*	Source(s)*

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5. Human Embryonic Stem Cells

Does the proposed project involve human embryonic stem cells?* ● No ○ Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://grants.nih.gov/stem_cells/registry/current.htm. Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used:

Cell Line(s): Specific stem cell line cannot be referenced at this time. One from the registry will be used.

6. Inventions and Patents (For renewal applications only)

Inventions and Patents*: ○ Yes ○ No

If the answer is "Yes" then please answer the following:

Previously Reported*: ○ Yes ○ No

7. Change of Investigator / Change of Institution Questions

❑ Change of principal investigator / program director

Name of former principal investigator / program director:

Prefix:

First Name*:

Middle Name:

Last Name*:

Suffix:

❑ Change of Grantee Institution

Name of former institution*:

PHS 398 Research Plan

Please attach applicable sections of the research plan, below.

OMB Number: 0925-0001

1. Introduction to Application (for RESUBMISSION or REVISION only)	
2. Specific Aims	1241-Specific Aims_Final.pdf
3. Research Strategy*	1242-FINAL Research Strategy.pdf
4. Progress Report Publication List	
Human Subjects Sections	
5. Protection of Human Subjects	1248-Final Human subjects 20151024.pdf
6. Inclusion of Women and Minorities	1249-Inclusion of Women and Minorities.pdf
7. Inclusion of Children	1250-Inclusion of Children.pdf
Other Research Plan Sections	
8. Vertebrate Animals	
9. Select Agent Research	
10. Multiple PD/PI Leadership Plan	
11. Consortium/Contractual Arrangements	
12. Letters of Support	1251-All LOS.pdf
13. Resource Sharing Plan(s)	1252-ResourceSharing.pdf
Appendix (if applicable)	
14. Appendix	

SPECIFIC AIMS

Congenital malformations of the genitourinary tract carry with them significant morbidity and increased risk of mortality for individual patients, and is a growing public health burden. At present, there are limited therapies available to ameliorate the progressive loss of genitourinary tissue. A comprehensive understanding of how the genitourinary organs (including kidney and urinary tract) develop *in utero* is necessary to effectively develop novel therapies to replace or repair injured tissue. The **GenitoUrinary Development Molecular Anatomy Project (GUDMAP)** has been extraordinarily successful at providing a high-resolution map of gene expression in the murine genitourinary system [1-8]. However, a similar description has not been available for the developing human genitourinary system, nor has it been possible to develop optimized experimental techniques to grow, expand and differentiate human genitourinary progenitor cells *in vitro*. These research efforts by the developmental community have been hampered by the lack of a central hub for the procurement, and distribution of high quality human genitourinary samples.

The Health Sciences Tissue Bank (HSTB) at the University of Pittsburgh has been involved in research human tissue procurement for over 18 years: collecting, maintaining and disbursing quality samples to research scientists, both in (b)(4). HSTB is embedded within the Department of Pathology of the University of Pittsburgh Health Systems; thus providing rapid access to very high quality tissue and biological specimens. HSTB has established consenting protocols in line with the best practices recommendations from the NIH, a strong informatics backbone to facilitate specimen procurement and annotation, and has in place robust quality control and quality assurance programs. The HSTB biorepository is fully accredited by the College of American Pathologists (CAP). HSTB has an established program accruing fetal tissues that has been IRB approved since 2005. In this calendar year, we have disbursed over (b)(4) samples collected from (b)(4). The collections can be significantly ramped up as material could have been accrued from as many as (b)(4) last year.

We have preliminary data that we can isolate human genitourinary tissues (kidneys, ureters and bladders) from various developmental ages (6-24 weeks). We have produced publication quality histological images of the developing urogenital organs (including kidneys and bladder), and have immunostained kidneys for endothelium, nephron progenitors and early-differentiated nephron structures and bladders for the urothelium and muscle layers. We have utilized Dynabeads® to separate distinct cellular subpopulations in the kidney including: nephron progenitors, ureteric epithelium, podocytes and endothelium, and have confirmed that we can produce high quality material that is appropriate for RNA sequencing. *We propose to act as both the GUDMAP Tissue Hub and Tissue Gathering site to build upon the pre-existing HSTB and provide top quality genitourinary samples to members of the scientific community including those within GUDMAP*.

Aim 1: To generate an inventory of genitourinary tissue throughout normal human development

The main goal of this aim is to develop a pipeline for the acquisition, quality control and distribution of human genitourinary samples obtained throughout development (6-42 weeks gestation). We currently have access to 6-24 week samples through the HSTB. However, for later gestational stages (25-42 weeks gestation) we have partnered with the International institute for the Advancement of Medicine. This will provide access to a novel resource for neonatal donation. We aim to collect and store a minimum of (b)(4) per developmental week. Each of these samples will have histology, immunohistochemistry and *in situ* hybridization performed to assess tissue quality, protein and RNA integrity. Furthermore, we will obtain maternal blood, urine and amniotic fluid; based on the clinical situation and ability to procure. Based on our current experience, we get these biological materials in most cases. Anonymized demographic information of each specimen will also be provided.

Aim 2: To provide fresh genitourinary tissue and biological research specimens

This aim will generate an ongoing resource to distribute fresh developmental human genitourinary samples from various stages (6-42 weeks) to the GUDMAP Atlas projects. The samples will be procured by a pathologist and inspected for mechanical damage. Samples will be collected from all qualified cases. The samples will then be subdivided based on the demand for fresh/frozen aliquots; the validation laboratory for quality control will keep a portion of each sample. The tissue samples will be immediately sent out for live cell use or immediately separated into distinct cellular populations before shipping based on researcher demands. Permissible annotating information; including demographics of each specimen, will also be provided.

A. BACKGROUND AND SIGNIFICANCE

1. The University of Pittsburgh Health Science Tissue Bank (HSTB) is an established fetal tissue core

Biological research specimen collection at the University of Pittsburgh is centralized through the Health Sciences Tissue Bank (HSTB). The workflow and expertise that is already in place will be leveraged to generate the GUDMAP Tissue Hub and we will also act as the primary tissue collection site. The HSTB has over 18 years of experience of prospectively procuring tissues and biological materials for researchers. The HSTB has a tissue procurement site at (b)(4); (b)(6) (b)(4) which is part of a multi-hospital chain, consisting of (b)(4) (b)(4) We have been collecting fetal tissue for over 10 years with an established IRB ((b)(6) (b)(6) co-I). Currently the HSTB has numerous researchers acquiring fetal tissue for various projects from 6-24 weeks of gestation. The tissue collections include liver, heart, gonads, legs, brain, genitourinary, and placenta. (b)(6) (co-I) has been utilizing the HSTB to procure genitourinary tissues including kidneys, ureters and bladders.

2. The HSTB has a strict consenting protocol

We have an established consenting protocol in line with the best practices recommendations from the NIH. All patients who present to obstetrics and family planning who wish to undergo an elective abortion, or have experienced a spontaneous abortion, are asked by a registered nurse (not involved with the procurement) to give consent for tissue procurement and banking. There is a 24-hour waiting period after the consent process and the initial registered nurse is not involved with the tissue procurement. This consent form also gives permission for tracking of patient progression, gathering of patient demographics and collection of clinically relevant information to be included in the database as well as an option for the donation of maternal blood, urine and amniotic fluid. The consent form related to research on tissue from an elective abortion (less than 24 weeks gestation) has been designed with extensive input from clinical colleagues and the Institutional Review Board of the University of Pittsburgh to ensure compliance with all Pennsylvania state and federal laws.

3. The proposed GUDMAP Tissue Hub (HUB) and collection site has significant infrastructure

The proposed HUB will leverage the resources of the current HSTB, which has a physical footprint in 4 hospitals of UPMC, which includes space and technical staff. The current organization consists of 16 staff members, which includes: a Medical Director (b)(6) PI), an Assistant Director (b)(6) , a Project Manager (b)(6) , Quality Assurance Manager (b)(6) , lead technicians, supervisors, and technical staff. In addition the HUB will include a fetal pathologist (b)(6) co-I), a pediatric clinician (b)(6) co-I) and a classically trained human anatomist (b)(6) co-I). (b)(6) will spearhead this initiative. He is a clinician scientist with intimate knowledge of tissue banks [9-16] and the genitourinary system [17-19]. (b)(6) is a perinatal pathologist who has extensive knowledge and experience related to identification and quality control of fetal specimens [20-22]. Both (b)(6) are developmental biologists with successful research programs related to development of the genitourinary system [23-28]. This team is uniquely qualified to run, quality control and distribute samples to the successful GUDMAP Atlas projects. The HSTB has approximately 1000 sq. ft. of space at each of the flagship hospitals. This reflects significant institutional commitment and support to this research support facility (**see letters from** (b)(6) (b)(6) We have a strong Informatics backbone with our flagship and community hospitals linked through a common laboratory information system. In addition we have a variety of web-based tools to streamline the biological specimen procurement activities and extensively annotate the accrued specimens.

4. The proposed HUB and collection site has protocols for rigorous quality control

To keep up to date with the needs of the ever-growing area of tissue banking, the University of Pittsburgh is an institutional member of the International Society for Biological and Environmental Repositories (ISBER; http://www.isber.org). This is the organization responsible for establishing and disseminating best practices for biorepositories. ISBER works very closely with the National Cancer Institute (NCI) and the NCI's Biorepositories and Biospecimen Research Branch. A unique attribute of ISBER is that it represents repository organizations, users, as well as companies that develop the myriad collection of items and services that sustain repositories. In 2005, the organization published the "best practices for repositories" (ISBER, 2005) [29], a document containing a thorough and comprehensive treatise on repository management and

operations. This was followed by another set of standards developed by the NCI in 2007 (National Cancer Institute best practices for biospecimen resources: http://biospecimens.cancer.gov/global/pdfs/nci_best_practices_060507.pdf). The HSTB repository has maintained these documents as reference material and follows these practices in its daily operations. These practices would be continued, extrapolated, refined and implemented for the HUB efforts.

5. Ischemia time is minimized
We record the warm ischemic time on our samples and take steps to keep it at a minimum to ensure the highest quality biological specimens [30, 31]. We get feedback from our users and utilize this feedback to tailor our collection processes on a case-by-case basis to maximize the needs of investigators. All warm ischemic times are recorded within Biospecimen Inventory and Operations System (BIOS).

6. The proposed HUB has an established track record of being highly collaborative
The HSTB has been a core facility for the University of Pittsburgh Cancer Center for the past decade, providing biological specimens and research pathology support. We receive some funding from the NCI as a Shared Resource as part of the Cancer Center Support Grant (CCSG) for the University of Pittsburgh Cancer Institute. This is the 27th year of funding for CCSG (Core PI: (b)(6) P30 CA047904). In this capacity, HSTB works closely with a multitude of investigators and handles a variety of biospecimen requests both locally and nationally.

7. HSTB has a track record of very effective engagement in National and International initiatives
A. The Cancer Genome Atlas (TCGA): This is a collaboration between the National Cancer Institute (NCI) and National Human Genome Research Institute (NHGRI). TCGA generated large datasets of genomic changes in major types and subtypes of cancer. TCGA accrued matched tumor and normal tissue specimens from 11,000 patients; from 33 cancer types and subtypes [32], including 10 rare cancers. The University of Pittsburgh was the second largest contributor to the TCGA Project, with over 800 qualified cases.

B. The Clinical Proteomic Tumor Analysis Consortium (CPTAC): This is a comprehensive and coordinated effort to accelerate the understanding of the molecular basis of cancer through the application of robust, quantitative, proteomic technologies and workflows. HSTB was part of the initial pilot and has been selected as a collection site for the ongoing expanded phase targeting 2000 cases spanning 10 tumor types.

C. The Cancer Human Biobank (caHUB**):** This is a biorepository and biospecimens derived program that carried out specialized biospecimens and data procurements to support biospecimens science activities. HSTB participated in the caHUB initiative focused on biopreservation variability [33, 34]. HSTB was the largest contributor to this initiative and provided samples and data from approximately 6000 cases; covering four tumor types.

D. SPORE Initiative: HSTB is the biospecimen and research Pathology services resource for our four funded SPORE initiatives: 1. lung, 2. head and neck, 3. skin, and 4. Gynecologic cancers [10, 15]. We have provided samples and data to many investigators outside of the University of Pittsburgh, as part of SPORE driven multi-institutional efforts.

8. Identification of late gestation procurement sites
We have not previously collected tissues from cases later than 24 weeks gestation. We are in the process of altering our IRB and autopsy consent forms to permit the collection of tissues from these cases and allow for deposition of these tissues in our tissue bank. We have developed a relationship with the International Institute for the Advancement of Medicine (IIAM) (iiam.org) who already provide neonatal tissue samples to the NIH initiative LungMap (LungMap.org). The IIAM contains a national tissue bank that will allow for the acquisition of genitourinary tissue from 25-42 weeks of gestation. This tissue bank receives on average 20 neonatal cases a year (**see letter of support from IIAM**). The neonatal tissue will undergo stringent quality assurance and quality control by HSTB, similar to the quality assurance and control (QA/QC) performed for our in house fetal tissue, before being banked or distributed to the requesting, qualified GUDMAP atlas projects.

B. INNOVATION

This application is innovative on multiple levels including: 1. Team approach, 2. Established collaborative system, 3. High quality collection and validation, 4. Data management and project management tools.

1. Team approach

As mentioned in the significance section we have brought together a unique set of individuals with diverse backgrounds to facilitate the establishment of the HUB and collection site. We have leveraged the already existing tissue and data collection expertise of HSTB at the University of Pittsburgh. To this we will add significant clinical, pathological and anatomical expertise in the genitourinary tract for a novel and diverse research team well equipped to perform all the actions necessary of the HUB.

2. Established collaborative system

Currently, HSTB provides high quality tissue samples to over 100 researchers. This is a novel resource embedded within the Department of Pathology that works closely with individual researchers (b)(4) (b)(4) to satisfy the specific research needs of each laboratory. The proposed HUB and collection site at the University of Pittsburgh will utilize a similar collaborative approach with the successful GUDMAP Atlas projects.

3. High quality collection and validation protocol

HSTB is accredited by the College of American Pathologists (CAP) and certified under the Biorepository Accreditation Program (BAP). As part of BAP, “peer” inspectors perform on-site inspection using CAP accreditation checklists. This is a critical and comprehensive assessment of quality practices covering all aspects of biorepository operations (collecting, processing, storing, disbursing and data annotation of biospecimens). The HUB at the University of Pittsburgh also has specific, pathological, clinical and anatomical expertise that will seamlessly work as part of this Tissue Hub, to ensure the highest quality of specimens for all investigators.

4. Data management and project management tools

A. HSTB has developed in-house an inventory management system (BIOS) that will be utilized for tracking the stored specimens. This inventory management system is linked to Medipac; this clinical patient management interface imports demographic data eliminating manual entry; a source of errors. BIOS also interfaces with the Pathology LIS, CoPath; allowing access to Pathology reports.

B. HSTB also has a project management tool through which requests are initiated via a web interface. The project management tool portal shows the progress of the request and has been very useful to introduce transparency in the functioning of HSTB.

C. We also plan to provide GUDMAP investigators access to data related to the number of cases and pertinent details of the case (gestational age, tissue types, relevant QA/QC information). This access will be through secure password protected mechanisms using software like Sharepoint.

C. APPROACH

1. Preliminary Work and Current Status of the University of Pittsburgh Health Sciences Tissue Bank

This proposal includes five different aspects of work. This portion of the proposal is organized to describe our preliminary work and current status in each of the following areas:

1.1. Accrual of tissues and biological specimens (kidney evaluation team, bladder evaluation team)
1.2. Data Annotation
1.3. Packaging and Shipping
1.4. Consenting and IRB related issues
1.5. Material Transfer Agreement (MTA) issues

1.1. Accrual of tissues and biological specimens

Due to the uniqueness of this tissue type, all of the fetal specimens (excluding the neonatal which will be through IIAM) will be derived from (b)(4); (b)(6) which performs on average (b)(4) (b)(4) (**Table 1**).

Table 1: Number of fetal cases seen at (b)(4); (b)(6)

Fetal age			No. Of cases available/year
First trimester (6-12 weeks)	**Second trimester (13-24 weeks)**	**Autopsy**	
(b)(4)			

The current version of the consent form provides opportunity for the patient to also allow donation of maternal blood and urine to the HSTB. Although all of the tissue will be collected from one hospital site, all of the 18 UPMC hospitals are linked by a common laboratory information system. This vast system allows access to information on the maternal medical record and de-identified information related to the demographics will be available to the successful GUDMAP Atlas projects.

Procedures for Collecting, Processing and Distributing Specimens: All fetal tissue is collected through a collaborative process including Family Planning, Obstetrics and Pathology. All patients are consented for the procedure and tissue donation separately by the Family Planning and Obstetrics staff. Furthermore, patients are consented 24-hours in advance, allowing notice of potential cases for the following day. Once a patient has agreed to donate fetal tissues for research purposes, the HSTB is alerted and subsequently Pathology is involved. The HSTB acts as a courier and delivers the material to Pathology for gross examination and dissection. After pickup from the procedure area, the tissue-banking technician brings the specimen to the surgical pathology gross room area. The clinical pathology staff assigned to that bench performs immediate gross pathology assessment. The pathologist (b)(6) co-I) is involved at this stage in the clinical evaluation and subsequent harvesting of the specimen to ensure quality control at the level of gross evaluation. All specimens are grossly evaluated for mechanical disruption. After appropriate materials have been obtained for histologic evaluation for clinical diagnosis, the genitourinary tissue will then be rapidly triaged for GUDMAP Atlas projects. Pathology has snap freezing capabilities as well as the appropriate materials to preserve specimens via other required methods. In addition, the tissue banking space is in close proximity to the gross room. The samples will then be taken to the validation laboratories (b)(6) for further assessment of the tissue prior to distribution; this transfer system is already established based on the existing collaboration.

We have extensive experience and the requisite staff to ensure adherence to the yet to be defined GUDMAP Atlas projects criteria as proven by successful contributions made to TCGA, caHUB and CPTAC. HSTB has in place the infrastructure to provide adequate support for all the elements needed for the GUDMAP project. The Tissue Resource was the only core facility rated "outstanding" in the NCI review of the Cancer Center in 2010 and again in 2015, with an overall impact score of 20 (core PI: (b)(6) P30 CA047904). We have the infrastructure in place as well as the experience to procure and process the required tissue and biological materials for the various GUDMAP projects. In addition the HSTB has extensive experience in running and maintaining a viable CAP accredited tissue resource. The current facilities consist of 45 ultra-low mechanical freezers and 7 liquid nitrogen storage vessels. The HSTB has adequate space for the long-term storage of specimens collected for the GUDMAP project.

The HSTB has an online request tool in place to streamline investigator driven research projects. This online tool allows researchers to submit all contact information, project specific requirements and necessary regulatory documents to the project manager of HSTB. We are in the process of working with our information technology department to generate a secure link for GUDMAP investigators. Once the Project Manager has reviewed and approved the request, the project is assigned to a staff member for appropriate actions. This electronic request site creates a centralized hub where HSTB staff and the requesting investigator can all access the project, provide appropriate documentation, see relevant information and communicate via project updates and email.

HSTB fetal tissue collection: The Fetal Tissue IRB has been in existence since 2005. Since 2010, the numbers of consents and collections has been steadily increasing (**Table 2**) and we are in an excellent position to expand our services to include the needs of the GUDMAP Atlas projects. Accrual of tissues less than 16 weeks only began in the middle of 2015, and we have already collected over 20 cases. Based on the demand of the Atlas projects we can ramp up the accrual for these early cases, since consent efforts to date are based on current needs and most women were not asked to donate.

Table 2: Number of cases, active projects and disbursements per year for fetal tissues

Year	No. of cases	No. of active projects	No. of disbursements
2010	(b)(4)		
2011			
2012			
2013			
2014			
2015			

The anticipated volumes for this project are detailed below (**Table 3**). The projected accrual is less than 15% of our actual clinical volumes. We have been conservative to ensure that we have the capacity to meet projected targets.

Table 3: Anticipated fetal collections for GUDMAP per year

Fetal Age				No. of cases/yr
6-12 weeks	12-18 weeks	18-24 weeks	25-42 weeks	
(b)(4)				

The success rate for obtaining kidney and bladder specimens from our cases 16-24 weeks gestation is typically very high (>90%). We have not consistently looked for ureters; however with our team of sub-specialty experts we will be able to troubleshoot, and successfully implement, the dissection of any genitourinary tissue specimens needed by the GUDMAP Atlas projects.

Furthermore, we are also in the process of expanding our IRB protocol to collect neonatal biological samples from later gestational sudden deaths (between 25-42 weeks). To ensure ability to collect specimens from later gestational ages, we have partnered with the International Institute for the Advancement of Medicine (IIAM) (**see letter from** (b)(6)). We envisage collecting tissue specimens from all eligible cases. In addition maternal biofluids may be collected, as per needs of the GUDMAP projects.

The specimens will undergo a thorough histological assessment by an expert pathologist ((b)(6) co-I) and anatomist (b)(6) , co-I), before being provided for a GUDMAP Atlas project. Additionally, other quality assurance techniques including immunohistochemistry, *in situ* hybridization and RNA isolation can be performed by the validation team (b)(6) ; as per GUDMAP project needs.

Standard Operating Procedures (SOPs): The SOPs of the HSTB contain extensive details related to Collection/ Handling/ Storage/ Data Entry, Quality Management Plan, disbursement of biological specimens and Education and Training of Technical staff. HSTB is a CAP-certified facility. The proposed HUB collection processes would follow similar SOPs. In addition, the GUDMAP collection would have a quality assurance and control (QA/QC) and validation plan reflective of the specific requirements of GUDMAP; including detailed histologic assessment. Immunohistochemistry, *in situ* hybridization and RNA isolation will be performed as part of the quality assessment and validation, based on the specific needs of the GUDMAP projects.

Data and Safety Monitoring Plan: The HSTB has in place a data and safety monitoring plan for all subjects enrolled in tissue and biological specimen donation. The data and safety monitoring plan is part of the annual submission to the IRB. Similar data and safety monitoring plans function in the clinical trials involvement. The activities of the HSTB, with respect to biological specimen aggregation, as well as data annotation, are in full compliance with United States Federal statues, regulations, and ordinances. We also monitor any changes in rules and regulations concerning tissue and biological specimen aggregation and data degradation. The Institutional Review Board of the University of Pittsburgh insures complete compliance with these procedures and policies.

The highlights of the plan are as follows:

1. The data is stored on password-protected computers.
2. The data is provided to investigators only after the identifiers have been removed. The data is NEVER provided with any identifiers. A linkage code is used. The Tissue Bank retains the key to the code.
3. The biological materials are provided to research studies that are IRB approved or are utilizing the Tissue Bank IRB approved protocol that allows disbursement of biological materials that have been de-identified. No materials are ever given to studies that are not IRB approved.
4. The PI evaluates the data every quarter to assess the specimen volume and variety of accrual.
5. Adverse events, if any, need to be documented and immediately provided to the IRB. The principle adverse events that can be associated with a facility like HSTB pertain to data security. No adverse events have occurred in this facility to date.

1.2. Data Annotation

Annotation of biospecimens: We have developed a variety of informatics tools with institutional support and commitment. This is an endeavor that has taken five plus years of committed informatics support from a variety of sources (NCI, National Center for Research Resources and Department of Defense). These bioinformatics tools will be critical for the GUDMAP Atlas projects as they will allow data entry, facilitate storage, querying for specific needs, retrieval and data annotation for GUDMAP projects, in a legal, ethical and HIPAA compliant

manner, consistent with best practices.

The current systems involved in the annotation of biospecimens at the University of Pittsburgh are as follows:
A. Inventory system and Bar-coding: At the University of Pittsburgh we have developed and implemented a web-based inventory system called **BIOS (Biospecimen Inventory and Operations System).** BIOS is a multi-facility web application designed to facilitate the tracking, banking, and distribution of tissue bank specimens. It unifies the efforts of tissue collection, patient's consent status, billing and data aggregation in one module. BIOS facilitates the logging of received samples/specimens collected, association of specimens with IRB protocols, researcher searching of stored specimens, and dispersal of specimens. Currently, BIOS interfaces with the ePatient system, which is a constantly updated feed of all patient information from UPMC facilities. BIOS uses ePatient to retain certain demographic information about the patients associated with each specimen as well as to retrieve/store CoPath reports associated with surgical visits. Demographic and CoPath report data are visible in the BIOS system upon request from users. BIOS provides a central repository for the tissue bankers for tracking and distribution of biospecimens and for robust querying and reporting of biospecimens and associated data to fulfill the requirements of researchers. By combining the flexible query interface of BIOS with the ability to export the result of queries, custom reports can be prepared. We have a dedicated person who has been extensively trained; he can create a variety of reports such as summaries of bank-wide operations during a specified period or daily work lists for a particular banker etc.
BIOS's web application layer is secured through SSL (Secure Sockets Layer) and the use of groups for restricting user access. All new user requests are vetted by UPMC information technology security. Security is further refined based on user role. Facility managers are able to designate a user's role in the system (IT, admin, technician, researcher, pathologist, researcher annotate, researcher request, microarray technician, and read-only). A system security plan is on file with the UPMC System Security team and is reviewed on an annual basis. The BIOS application is scanned by the UPMC System Security team on an annual basis using tools that predict and isolate risks to the security of the system. The Enterprise Provider Solutions Clinical Programs team of UPMC maintains the BIOS application. All new requests for enhancements, bug fixes, or implementations go through this dedicated resource. Similarly this group also serves as a 24-hours a day, 7 days a week help desk for any BIOS related support issues. The BIOS system has been successfully implemented at our institute and is currently being used for the day-to-day operations of a system-wide tissue bank. We have worked on making BIOS accessible and user-friendly for our researchers. **We will provide a similar and appropriate; secure interface for access and sharing information with the GUDMAP Atlas projects; most likely using a Sharepoint type mechanism.**

B. The Pathology Laboratory Information System: Our institute uses CoPath, a Cerner (Kansas City, MO) product. It supports technical workflow, resulting and patient reporting, charge entry and transmission, management reporting, and QA/QC activities for Anatomic Pathology and related labs (14) throughout the UPMC system. This system also includes PICSPlus (v2.5), an integrated module for Anatomical Pathology imaging, and Synoptic Reporting, a feature for capture and reporting of discrete diagnostic elements. These integrated products will be harnessed and utilized to search for specific tissue samples within the proposed HUB and will be linked with high quality images of histology, immunohistochemistry and *in situ* hybridization as well as commenting on RNA quality. We have also implemented state of the art 2-D bar coding in the gross room and histology, making the storage, archival and retrieval of paraffin specimens more robust and efficient. **The reporting and imaging functions are very important for the GUDMAP project; providing clinical annotation as well as high-resolution images.**

C. Electronic Medical Records: A large percentage of our medical records are now in an electronic form. We have developed in-house software capable of mining these records for key text words. The data can then be identified and ported into electronic databases for research use in a de-identified manner. We will provide required appropriate annotating information for the specimens provided for GUDMAP Atlas projects.

D. Web based Tissue Requesting tool: The HSTB currently utilizes a web based project request tool. This tool will have a tailored drop down window specific for the GUDMAP Atlas projects and provide them with secure access to the database. The tool has the ability to manage IRB, MTA and other project related documentation. It automates communication between the HSTB and the tissue utilization committees, the researchers and the HSTB technical staff. This tool drives the fast turnaround time, utilization and other project management metrics.

E. Transferring clinical and epidemiologic data to coordination center and outside collaborators: HSTB has been a part of institutional efforts to transfer clinical and epidemiological data to coordination centers for all outside collaborators. HSTB was an integral part of the cooperative prostate cancer tissue resource (CPCTR) an NCI funded resource that was in existence from 1999-2006. As part of this effort de-identified clinical data was provided to the NCI. The University Of Pittsburgh Department Of Biomedical Informatics and the Division of Pathology Informatics both have extensive experience in terms of transmission of data. Additional capabilities for data transmission have been incorporated as part of the Shared Pathology Informatics Network (SPIN) initiative. Our recent broad engagement with TCGA and caHUB has resulted in transfer of data on over 1700 cases. This is done using the website designated by the NCI/SAIC (Open-Clinica) and Comprehensive Data Resource (CDR). We have extensive experience and the infrastructure to seamlessly transfer de-identified information as part of this project. **This will be extremely important to provide this demographic information to the GUDMAP investigators.**

F. Honest broker infrastructure: The honest broker is an individual/organization/system that acts for or on the behalf of the tissue/databank. The role of the honest broker is to collect and provide health information to research investigators in such a manner that it would not be reasonably possible for the investigators or other individuals to identify the patients directly or indirectly. The honest broker provides a firewall between clinical and research activities. Clinical information is stripped of HIPAA denoted personal health identifiers. Research material may have linkage codes, precluding the identification of patients to researchers. University of Pittsburgh has implemented a novel, IRB-approved mechanism to address honest broker functions to meet the specimen and data needs of researchers. The HSTB stores biologic specimens. The clinical data repositories store clinical information and are handled by various clinical staff from different departments; in the case of GUDMAP this will be Pathology and Gynecology and Obstetrics. Pathology and Oncology Informatics have designed software tools for querying availability of specimens, extracting data, and de-identifying specimens and annotating data for clinical and translational research. These entities partnered and submitted a joint IRB proposal to create an institutional honest broker facility. This provides a large group of honest brokers, ensuring availability for projects without any conflict of interest. This honest broker system currently consists of approximately 41 honest brokers (including 15 from HSTB), two supervisors and four medical faculty members. This infrastructure will be harnessed for the HUB at the University of Pittsburgh. The honest broker system is described in detail in a publication from our group [12]. **This system also provides a very robust system for data aggregation across a variety of different platforms and to the various Atlas projects of GUDMAP.**

G. Anticipated workflow for tissue and data transfer related to GUDMAP Atlas projects: The specimens will be anonymized with patient identifiers stripped from the specimens. The specimens will be annotated with appropriate annotating data. The specimens will be tagged using randomly generated numbers (either provided by NIDDK or generated in-house). The linkage codes are maintained by HSTB in a secure environment. This is a standard approach for biological specimens and data transfer from HSTB to investigators. The data annotation will be provided to the GUDMAP Atlas projects in a HIPAA compliant manner, consistent with the IRB requirements of the University of Pittsburgh. The Honest Broker system plays a critical role in this whole process (as described above). Thus allowing for the information to be provided to each other with identified information as they go through the different steps related to tissue and data accrual, storage, retrieval and disbursement. These are all established practices in routine use within the HSTB.

H. Whole Slide Imaging (WSI): The HSTB has imaging equipment for generating, annotating, interpreting, storing and analyzing digital images. This service is provided with pathologist oversight and appropriate technical support staff. As part of the HUB, we will provide GUDMAP investigators with whole slide images of the various histologic and fluorescence stains performed on the tissues as part of QA/QC. This will help investigators select appropriate specimens and create efficiencies. The WSI capabilities could also be leveraged for sharing of images between projects; enhancing interactions and collaborations.

1.3. Packaging and Shipping: Fetal genitourinary tissues required for research must always be in a condition that will maintain the integrity of the specimen [30, 31, 35]. This also applies to the transport of specimens from one site to another. During transportation, different specimens require maintenance at specific temperatures and this can be achieved by using appropriate packaging material such as dry ice, or gel packs. To maintain temperature at or below -150^{0}C, a liquid nitrogen dry shipper will be used. The HSTB repository has been involved in transporting specimens to and from the repository and has SOPs in place to ensure that tissue integrity is maintained at all times during such activities. The procedures provide details about packaging to

maintain the cold chain (wet ice/dry ice conditions) and other conditions (such as room temperature) for specific tissue types. Currently, there are regulations governing the transportation of potentially infectious materials (US Transportation Regulations- 49 Code of Federal Regulations [CFR]) such as the International Aviation Organization (ICAO) and the International Air Transport Association (IATA) for international transport regulations and information on classifying biospecimens for shipment. Failure to comply with these stipulated rules and regulations could result in delay or refusal of shipment and consequently biospecimen deterioration. All HSTB staff, through University Environmental Health and Safety, are IATA trained and all shipping practices are compliant with IATA regulations which is currently widely accepted as the standard for repository personnel by the NIH. As part of the TCGA and caHUB engagements, we have extensive experience using cryoports shipped to us by the Biospecimen Core Resource (BCR). **Our current level of training for the technical staff ensures awareness related to shipping and packaging related issues and we will utilize this knowledge to ship high quality tissues to the GUDMAP Atlas projects.**

1.4. Consenting and IRB related issues: The HSTB of the University of Pittsburgh has been very cognizant of issues pertaining to the legal and ethical aspects of tissue banking. We are particularly aware of the sensitivity related to human fetal and neonatal tissue that we currently collect and will make available to the GUDMAP Atlas projects. The HSTB and the IRB committee of the University of Pittsburgh have designed a consent form in relation to fetal collection. This form is modeled on the form proposed by the NIH. Since the project needs are no different from internal biospecimen/data needs, we do not anticipate any IRB issues/concerns. This is further emphasized by our longstanding relationship with TCGA and caHUB, which have similar data and biospecimen needs.

1.5. Material Transfer Agreement (MTA) issues: The University of Pittsburgh has experience in drafting and execution of MTAs. Specifically we have experience working with the NCI and the Science Applications International Corporation (SAIC/Leidos). There have been a lot of mutual discussions and work pertaining to MTA language, predominantly as a result of the involvement of HSTB in the Cancer Genome Atlas and caHUB. This experience will be invaluable in the relationship related to this GUDMAP project, if the University of Pittsburgh is invited to participate. The current experience has served to clear the path for future relationships. **To facilitate the transfer of biospecimens to GUDMAP Atlas researchers, a blanket MTA will be set up to encompass all the GUDMAP projects.**

Plan to interface with GUDMAP Atlas projects: As the proposed tissue hub and collection site for the GUDMAP Atlas projects we will interface regularly with all the Atlas projects to ensure that the needs of the individual projects are met. In the beginning this will involve individual phone conference calls with the specific projects, as well as regular coordination committee calls that the NIDDK might schedule. We will have regular calls with the project PIs and sites once the biomaterial and data transfers start occurring. We will work very closely with the projects and with NIDDK to ensure appropriate specimen types and data are provided; as well as perform appropriate quality assessments. We have a track record of being very flexible to ensure researcher satisfaction. We will participate in the monthly conference calls and will also meet in person twice a year at the GUDMAP Atlas project meetings to get updated on all the ground breaking science and personally interact with the PIs and staff from the various projects to create a collaborative environment for high-quality work. In addition, we will attend the annual American Society of Nephrology meeting and the International Workshop on Developmental Nephrology where GUDMAP has a workshop, this is held every 3 years. We have existing relationships with GUDMAP members; and have sought advice to optimize our processes as well as share material; as needed. Kindly see **letters of support from** (b)(6)

(b)(6)

AIM 1: To generate an inventory of genitourinary tissue throughout normal human development

1. General approach and rationale: HSTB has a long-standing relationship with the research community producing high quality tissue, including fetal human tissue, under the strictest consenting procedures. Although there exists significant data related to the molecular characterization of mouse genitourinary development [23-28], the information related to human development is vastly understudied. We propose that we have the knowledge, infrastructure and expertise to acquire, quality control and bank specimens, both snap frozen and paraffin embedded, for use by GUDMAP Atlas projects.

2. Preliminary data:

A. Histology of human fetal kidneys: We have collected embryonic tissues from 6-24 weeks of gestation as previously discussed. Our representative histological data reveals the high quality of the tissue that we are able to collect with well-preserved renal architecture (**Figure 1**). Depicted here is a 21 week old fetal human kidney showing the nephrogenic zone including the developing nephron progenitors, nephron structures (renal vesicles, comma and S-shaped bodies and developing glomeruli) and branching ureteric epithelium. We have had these images evaluated by the Kidney evaluation team including the project pathologist (b)(6) co-I), anatomist (b)(6) co-I) and GUDMAP member (b)(6) **letter of support**).

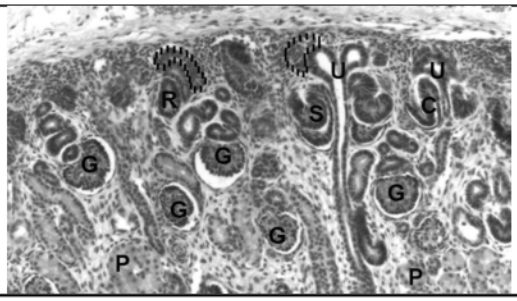

Figure 1: Histological image of human fetal kidney at 21 weeks. This is a representative histological image of the nephrogenic zone from a 21 week-old human fetal kidney. Depicted are many of the developing kidney structures including nephron progenitors (dashed lines), renal vesicles (R), comma (C) and S-shaped bodies (S), glomeruli (G), proximal tubules (P), ureteric epithelium (U).

B. Immunohistochemistry showing the developing renal vasculature: We wanted to determine whether the antigens were preserved and if we could visualize the various vascular components of the developing kidney. We utilized a CD31 antibody (stains all mature endothelial cells). A 19-week-old developing human kidney was utilized; it showed the dense vascular network that exists throughout the nephrogenic zone including the glomerular and peritubular capillary networks (**Figure 2A**). We also demonstrated the highly preserved nature of the intricate glomerular and peritubular capillaries (**Figure 2B**) and large caliber vessels (**Figure 2C**).

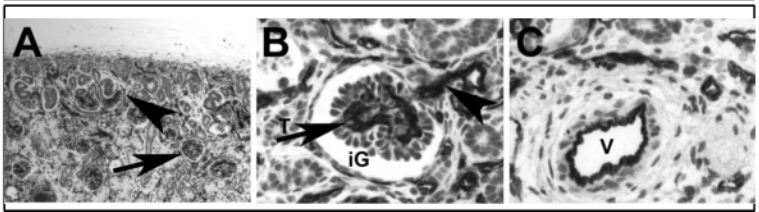

Figure 2: Human fetal kidney at 19 weeks of age stained for endothelium. A. Low power image of the renal cortex stained for CD31 (endothelium) showing numerous immature glomeruli (arrow) with glomerular capillaries (brown), and peritubular capillaries (brown) surrounding the dense renal tubules indicated by the arrowhead. **B.** An immature glomerulus (iG) with the dense capillary loops (arrow) and the accompanying urinary pole (arrowhead) next to a renal tubule (T) associated with peritubular capillaries. **C.** Larger caliber renal vessel (V).

C. Immunofluorescence of the kidney showing the nephron progenitors and early derivatives: We also wanted to determine whether we could use non-amplified immunofluorescence to visualize nephron progenitors and early nephron derivatives. Six2 is a known marker of the nephron progenitors; NCAM is a marker of both the nephron progenitors and the early-differentiated nephron structures [36, 37]. A representative image of a 17-week-old human fetal kidney shows the nephron progenitors stained with Six2 and NCAM (**Figure 3A-C**); the early nephron derivatives are positive for NCAM and have downregulation of Six2 (**Figure 3A-C**). The kidney evaluation team confirmed the staining pattern.

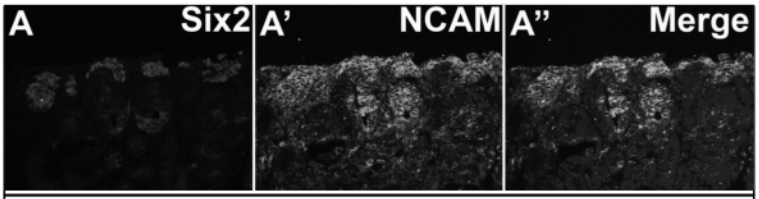

Figure 3: Human fetal kidney at 17 weeks of age stained for nephron progenitors and early derivatives. The nephron progenitors are positive for Six2 (A and A'', red) and NCAM (A' and A'', green). Conversely, the differentiated nephron structures down regulated Six2 but maintained NCAM expression. Dapi = blue

D. Histology of human fetal bladders: We wanted to harvest other urogenital organs to confirm that we could produce high quality tissue samples from other developing genitourinary organs. We focused on the bladder as the urothelium of the bladder is notoriously difficult to fix and stain with high quality due to damage that occurs directly after harvesting. In our first set of samples, we saw a similar urothelial damage phenotype due to post harvesting damage. We consulted (b)(6) (GUDMAP) and (b)(6) (GUDMAP) who advised that immediately post-harvesting the bladders should be bisected and immediately immersed in fixative. This approach has been very successful; please see representative images from a 21-week human fetal bladder, with a continuous urothelium and well-preserved lamina propria (**Figure 4A**) and muscle (**Figure 4B**). These images were evaluated by the Bladder evaluation team including (b)(6) (b)(6) as well as GUDMAP members (b)(6) (**letter of support)** and (b)(6) (**letter of support)**.

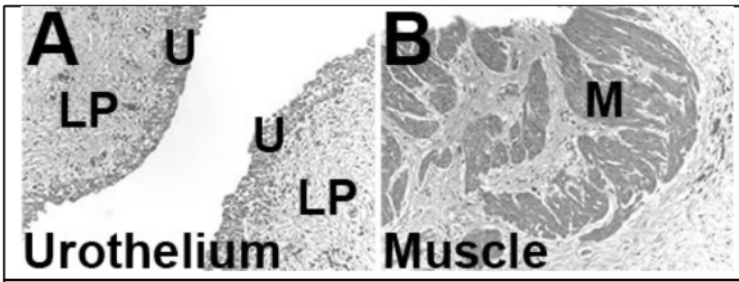

Figure 4: Histological images of human 21-week-old fetal bladders. A. Representative image showing the urothelium (U) and lamina propria (LP). **B.** Image of the bladder muscle (M).

e. Immunostaining of developing bladder urothelium and muscle: As with the kidney tissue we wanted to confirm that the bladder tissue had preserved antigens. We stained for urothelial (Uroplakin 3a and Cadherin 20) and muscle markers (αSMA) [38]. We observed well-preserved urothelium (**Figure 5A-B**), lamina propria (data not shown) and muscle layers (**Figure 5C**). The bladder evaluation team confirmed these findings.

Figure 5: Human fetal bladder at 21 weeks stained for urothelium and muscle. A-B. The urothelium stained for the umbrella (Uroplakin 3a, Upk3a) and superficial (Cadherin, Ck20) cells. **C.** Bladder muscle stained for αSMA (red). Dapi =blue.

3. Experimental Approach:

A. Assessing genitourinary histology: When the genitourinary tissues are received, we will process a third of the tissue into paraffin for histological examination. Sections will be cut at 4μm and stained with hematoxylin and eosin to evaluate basic morphology. Our pathologist and anatomist will evaluate tissue quality. High-resolution images will then be taken and these images will be uploaded and be available for GUDMAP projects and the scientific community. Our target goal is to have available a minimum of 5 cases (tissues and if possible other biologics) per week of gestational age for ages 6-42 weeks.

B. Evaluation of tissue specific antibodies: A subsequent third of the tissue will be embedded into TissueTek optimum cutting temperature (OCT) for immunofluorescence (IF). Based on the needs of GUDMAP projects, we will section at 6μm and perform IF to confirm the presence of antigens. These stained slides will be reviewed to assess for antigen preservation. Similarly, these high-resolution images will be uploaded and made available to the successful Atlas projects and the scientific community.

C. *In situ* hybridization to assess mRNA integrity: The remaining third of the tissue will be embedded into TissueTek optimum cutting temperature (OCT) for *in situ* hybridization (ISH). Based on the needs of GUDMAP projects, we will section at 6μm and perform ISH to confirm preservation of mRNA. These stained slides will be reviewed to assess mRNA degradation. Similarly, these high-resolution images will be uploaded and made available to the successful Atlas projects and the scientific community.

4. Anticipated Results, Pitfalls and Alternatives: We anticipate being able to provide high quality tissue to the successful GUDMAP projects by a combination of the HUB branch of the HSTB and the IIAM (for the later gestation time points). As an alternative for these later gestational time points, we are in the process of updating our IRB protocol at the University of Pittsburgh to include consenting for tissues from neonates of later gestational ages that have undergone sudden death. This would likely produce improved specimen quality and turnaround time since we can immediately harvest the tissue and provide these to the GUDMAP Atlas projects. Furthermore, if in the unlikely event that we are unable to acquire enough tissue from our in house tissue hub and collection site, we will utilize other tissue banks that are known to supply embryonic

tissue including IIAM. We will work closely with the GUDMAP Atlas projects to collect, process and store tissue as per the specific directions of the projects thus ensuring the highest quality of materials. We take great pride in providing to our investigators the highest quality of materials specifically tailored to their scientific needs.

AIM 2: To provide fresh genitourinary tissue and biological research specimens

1. General approach and rationale: As part of Aim 1, we will establish a standard operating procedure to generate a tissue bank of human fetal and neonatal genitourinary tissue, based on the needs of the GUDMAP projects. However, it will also be critical to provide fresh tissues for cell-based experiments to the various projects. Subsequently, in this aim we will work with the individual GUDMAP Atlas projects to collect and send out fresh high quality tissue for cell based experiments.

2. Preliminary data:

A. Isolation of fresh kidney compartments: As mentioned earlier, the HSTB is a well-established tissue core that has a long history of producing high quality fresh tissues for various researchers. The HSTB also has a significant track record of producing high quality fetal tissue and sending this to local researchers (including Dr. (b)(6) for cell based experiments. (b)(6) has developed a unique protocol to isolate various tissue compartments from these developing genitourinary tissues. Here we show that we have isolated from developing kidney proximal tubules, podocytes, ureteric epithelium and nephron progenitors (**Figure 6A**). The nephron progenitors were isolated using an optimized Dynabeads® protocol from the (b)(6) laboratory and grown in the defined expansion media [6]. The human fetal nephron progenitors can also be expanded in culture (**Figure 6B**).

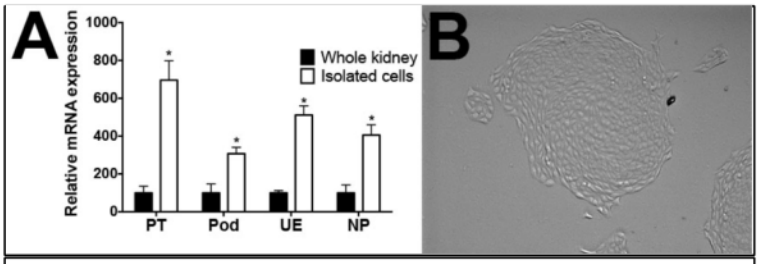

Figure 6: Freshly isolated kidney compartments. A. This histogram represents the isolated kidney compartments and enrichment of proximal tubules (PT), podocytes (Pod), ureteric epithelium (UE) and nephron progenitors (NP). **B.** Representative image of expanded nephron progenitors in culture.

B. Generate high quality RNA from Dynabeads® sorted nephron progenitors: We wanted to determine whether we could generate high quality RNA from these isolated kidney compartments. For these experiments we focused on the nephron progenitors and isolated cells with Dynabeads®. We isolated total RNA with the Qiagen miRNeasy kit, which also includes small RNAs, as these are likely to be of interest to GUDMAP Atlas projects. Here we show a bioanalyzer gel image (**Figure 7A**) and corresponding representative RNA plot depicting the small RNAs and 18S/28S ratio of the mRNAs (**Figure 7B**).

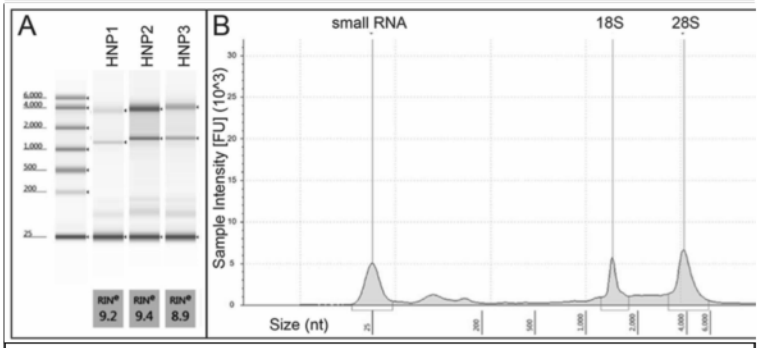

Figure 7: High quality RNA isolated from human fetal nephron progenitors. A. Bioanalyzer plot of 3 separate nephron progenitor (HNP1-3) isolations showing the high quality RNA as shown by the RIN values. **B.** Representitive plot showing the small RNAs and 18S to 28S peaks of mRNAs for the isolated nephron progenitors.

C. Human fetal kidneys can be shipped, nephron progenitors isolated and expanded in culture: We have shown from our preliminary data that we can isolate and culture distinct cell populations from the developing kidney tissues. However, it is critical that we are able to send high quality tissue to outside investigators and maintain tissue viability; and provide samples from which cells can be isolated and grown. To this end we have worked with (b)(6) (**see letter**) and shipped kidneys to his laboratory for cellular isolation and expansion in culture. His laboratory used their standard protocol to isolate nephron progenitors from the human kidney samples. These were then plated and the cells grown under the

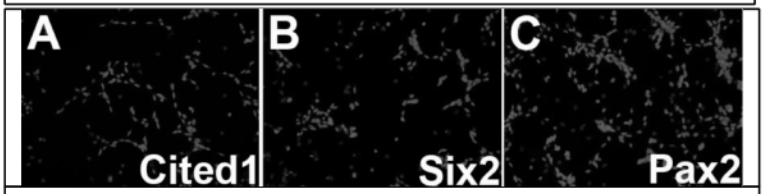

Figure 8: Nephron progenitor expansion *in vitro*. A-C. Isolated nephron progenitors maintain expression of the nephron progenitor markers (red) Cited1 (A), Six2 (B) and Pax2 (B). Dapi = blue.

expansion conditions [6]. They were able to expand the nephron progenitors and maintain nephron progenitor markers (**Figure 8**) without causing nephron progenitor differentiation (data not shown).

3. Experimental Approach:

A. Collection of fresh tissue for immediate shipment: In our preliminary data we show that we can collect genitourinary organs and produce high quality histological images and cell culture material both in house and via shipment to GUDMAP laboratories. In this aim, we will develop a collaborative relationship with the successful GUDMAP projects to provide high quality fresh samples based on individual needs. The tissue will be dissected by (b)(6) and a designated technician, and inspected for mechanical damage. The tissue will then be sent to the validation laboratories for further analysis before shipment. A small piece of the tissue will be used for histological evaluation to confirm tissue integrity. **The remaining tissue will be sent directly to the GUDMAP Atlas project investigators, arriving within 24 hours of acquisition**. The ages and number of samples that are required will be determined via interactions between the HUB and the individual Atlas projects (the current HSTB approach for all projects). We will work with each investigator to ensure they receive the highest quality fresh samples and will adjust collection, based on individual project requirements and feedback.

B. Isolation of distinct cell populations for shipment: We have developed in house techniques for the isolation of distinct cellular populations. Based on consultation with the Atlas projects we will determine the specific needs and cellular compartments that are needed to complete the projects and will isolate these cell types using Dynabeads®. In brief, we will utilize the Dynabeads® FlowComp™ Flexi kit (Invitrogen). This kit contains Dynabeads® that are conjugated to streptavidin. We will then biotinylate with the specific antibody needed to separate the required cell type. We will incubate isolated cells from the required tissues with the specific biotinylated antibody; then incubate these cells with bound antibodies with the streptavidin conjugated Dynabeads®. These will then be placed into a magnet to separate the cells. We will utilize a release buffer to remove the beads from the cells; by placing the cells back into the magnet to remove the beads. We will then verify the purity of these cells prior to shipment to the individual atlas projects.

C. Provide Laser capture and microdissection (LCM) services**:** HSTB provides LCM for specific projects. We have experience using the Leica LMD6000 LCM platform. If a specific GUDMAP project requires micro-dissected samples, the HUB will be glad to work with the PI of that project to provide this service.

4. Anticipated Results, Pitfalls and Alternatives: In this aim we anticipate being able to harvest and distribute high quality tissue and cells from the various fetal organ tissues to the successful Atlas projects. A pathologist and anatomist will evaluate all the tissues before shipment. We will validate each sample by taking a small piece for histology. We do not anticipate any major problems related to the acquisition and distribution of the tissues. Some tissues might need different processing to maintain tissue integrity; e.g. with the bladder urothelium. In these instances we will work with the individual projects to maximize the quality of the material they require. However, if we are unable to meet the demands of the various Atlas projects via the volume of our tissue hub and collection site, we will utilize additional identified tissue collection sites such as IIAM. Secondly, we will harvest isolated cell populations from the various developing genitourinary tissues based on the needs of the Atlas projects. We have extensive experience with this isolation technique and do not anticipate difficulties with this isolation. If we have problems with particular antibodies to bind to cell populations, we will work with the individual Atlas projects to optimize the isolation process for the cell type of interest.

D. Plans for banked tissue beyond grant period: A premise of this proposal is that the University of Pittsburgh HUB would collect and store specimens in addition to those immediately required by the GUDMAP investigators. This includes duplicate and consortium priority specimens; HSTB would retain custody of these residual specimens. In order to sustain the availability of residual specimens after the award period, the costs for ongoing storage, record keeping, and the effort required to disburse the specimens and associated data would be invoiced to the requesting investigator. The utility of sustaining such a valuable resource would depend on charging reasonably affordable rates. HSTB would need to cover the costs to maintain storage of residual specimens and provide sufficient and timely follow-up to requests. Therefore this plan presupposes that some cost to maintain this resource could fall to the HSTB. In addition to residual specimens, GUDMAP investigators may want to request prospective collection after the award period; we would make efforts to fulfill such requests assuming regulatory and financial agreements can be completed.

Human Subjects

1. The protection of human subjects from research risks

All the work that is outlined in this proposal is covered under an Institutional Review Board (IRB) (IRB # 0702050) from the University of Pittsburgh IRB committee and is adherent with all the state and federal laws. Furthermore, the University of Pittsburgh's DHHS Human Subjects Assurance Number is 00006790.

Obtaining tissues from patients undergoing procedures: These are patients who have signed the tissue banking consent form, which is a form separate from the procedure consent form. This tissue banking consent form allows these tissues and biological materials to be banked and stored with appropriate patient identifiers. The signed consent form also gives the Tissue Bank the ability to extract additional information and data from the currently existing medical record archives. The consent form also permits the additional collection of blood and urine, if agreed upon by the patient. The signed consent form also provides the Tissue Bank the ability to obtain follow-up data.

This research consent process is separate from the procedure related consent processes, which are done by the clinician performing the procedure. The separation of the research consent process from the clinical procedure related consent process allows the patient to focus more clearly and definitively on the consent for research. In addition, the research consent can be revoked at any time until the tissue has been disbursed and utilized. To minimize the possibility of coercion or undue influence, no monetary or other considerations will be provided as an inducement to participation. There is also a 24-hour period between the time of consent and the procedure to allow the patient sufficient time to consider and reconsider their decision. Similarly, the consenting research subject will not be allowed to direct the tissue to any specific researcher. The researchers will have no contact with the subjects.

Characteristics of the Subject Population: This proposal aims to provide a tissue resource encompassing all women of childbearing ages. The sole site of collection will be the (b)(4); (b)(6) that has a robust program for fetal genitourinary tissue specimen collection.

Plans for Recruitment of Subjects and Consent Procedures: The patient must sign the consent form for the procedure that will be used to obtain the tissue (i.e., dilation and curettage, dilation and evacuation, labor induction) or have signed consent for care before she can be approached to sign the fetal tissue research consent. For women having an elective abortion, this rule complies with the Pennsylvania Abortion Control Act. The patient may not designate the recipient of the tissue or organ in consenting to its use for research. The person obtaining consent for fetal tissue procurement must be a clinician involved in the care of the patient to comply with HIPAA. The person obtaining consent for fetal tissue procurement cannot be the surgeon or care provider overseeing the medical evacuation of the uterus nor the person who obtained consent for the elective abortion. For women having an elective abortion, this rule complies with the Pennsylvania Abortion Control Act. The attending physician retains the responsibility for determining the procedure to be used for termination of the pregnancy or treatment of a spontaneous abortion.

Data and safety monitoring plan: The Health Science Tissue Bank has in place a data and safety monitoring plan for all subjects enrolled in tissue and biological specimen donation. The data and safety monitoring plan is part of the annual submission to the IRB. Similar data and safety monitoring plans function in the clinical trials involvement. The activities of the Health Sciences Tissue Bank, with respect to biological specimen aggregation, as well as data annotation, are in full compliance with United States Federal statues, regulations, and ordinances. We also monitor any changes in rules and regulations concerning tissue and biological specimen aggregation and data degradation. The Institutional Review Board of the University of Pittsburgh insures complete compliance with these procedures and policies.

The highlights of the plan are as follows:

1. The data is stored on password-protected computers.
2. The data is provided to investigators only after the identifiers have been removed. The data is NEVER provided with any identifiers. A linkage code is used. The Tissue Bank retains the key to the code.
3. The biological materials are provided to research studies that are IRB approved or are utilizing the Tissue Bank IRB approved protocol that allows disbursement of biological materials that have been de-identified. No materials are ever given to studies that are not IRB approved.
4. The PI evaluates the data every quarter to assess the volume of accrual and the variety of specimens accrued.

5. Adverse events, if any, need to be documented and immediately provided to the IRB. The principle adverse events that can be associated with a facility like HSTB pertain to data security. No adverse events have occurred in this facility till date.

2. Inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity

Gender: Our research proposal aims to provide genitourinary tissue for research related to the GUDMAP atlas projects. The program will collect both male and female tissue depending on the needs of the successful atlas projects.

Race: Pittsburgh is a racially mixed metropolis and this is reflected in the patient population seen at (b)(4); (b)(6) (b)(4); (b)(6) will provide an appropriate racial mix to the tissue specimens procured.

Children: Not Applicable.

Age: The age distribution of patients included in this proposal is representative of the demographics of this region and information related to the age will be provided to the researchers. The fetal tissues collected from (b)(4); (b)(6) will be in the gestational age range of 6-24 weeks. We have an agreement in place with the International institute for the Advancement of Medicine. This agreement will provide us access to neonatal samples who were delivered in the gestational age range of 25-42 weeks. This will provide access to a novel resource for neonatal donation.

Women and female minorities will be included in this project. All federal, state, and local regulations will be followed in the consenting process and collection of the fetal tissues. In particular, we will adhere to 45 CFR 46 Subpart B 46.204.

OMB Number: 0925-0002

Planned Enrollment Report

Study Title: Research on tissue from an elective or spontaneous abortion < 24 weeks gestation

Domestic/Foreign: Domestic

Comments: About half the tissues will be collected under this IRB approved project. Tissues from 25-42 gestational weeks will be obtained from IIAM and will include collections from throughout the US.

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	**0**
Asian	50	0	0	0	**50**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	100	0	10	0	**110**
White	200	0	20	0	**220**
More than One Race	0	0	20	0	**20**
Total	**350**	**0**	**50**	**0**	**400**

Study 1 of 1

Funding Opportunity Number: RFA-DK-15-016. Received Date: 2015-11-06T15:43:10.000-05:00

Children will not be included in this project as the aims are to collect fetal tissues.

Please note that the letters of support are listed alphabetically first by University of Pittsburgh faculty/UPMC and then by External Collaborators.

Resource Sharing

This application proposes to establish the GUDMAP human fetal tissue hub and collection site at the University of Pittsburgh. This will be achieved by leveraging the already highly collaborative and successful Health Sciences Tissue Bank. We have a proven track record of collaborative relations with researchers within the University of Pittsburgh and externally through the various national projects we are involved in. All specimens collected by HSTB are de-identified and distributed to the investigators by an honest broker system to protect the identity of the patients. Demographic and other appropriate annotating information will be available and provided for the various specimens. During the validation process we will generate high quality images to verify the tissue quality and usefulness for the successful projects. These images will be made freely available and shared with the greater scientific community through the GUDMAP website. We also plan to provide GUDMAP investigators access to data related to the number of cases and pertinent details of the case (gestational age, tissue types and relevant QA/QC information). This access will be through secure password protected mechanisms using software like Sharepoint. The tissues collected under this project are not patentable and therefore IP rights will not be exercised.

Notice of Award

RESEARCH PROJECT COOPERATIVE AGREEMENT **Federal Award Date:** 06/30/2017

Department of Health and Human Services
National Institutes of Health

NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

Grant Number: 1U01DK110792-01 REVISED
FAIN: U01DK110792

Principal Investigator(s):
(b)(6)

Project Title: Four-dimensional Modeling of Mouse and Human Nephrogenesis.

(b)(6)

Award e-mailed to: uscaward@usc.edu

Period Of Performance:
Budget Period: 09/15/2016 – 05/31/2017
Project Period: 09/15/2016 – 05/31/2021

Dear Business Official:

The National Institutes of Health hereby revises this award (see "Award Calculation" in Section I and "Terms and Conditions" in Section III) to UNIVERSITY OF SOUTHERN CALIFORNIA in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 31 USC 6305 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award including the "Terms and Conditions" is acknowledged by the grantee when funds are drawn down or otherwise obtained from the grant payment system.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as "Research reported in this publication was supported by the National Institute Of Diabetes And Digestive And Kidney Diseases of the National Institutes of Health under Award Number U01DK110792. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health." Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Award recipients must promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under NIH awards will be free from bias resulting from an Investigator's Financial Conflict of Interest (FCOI), in accordance with the 2011 revised regulation at 42 CFR Part 50 Subpart F. The Institution shall submit all FCOI reports to the NIH through the eRA Commons FCOI Module. The regulation does not apply to Phase I Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) awards. Consult the NIH website http://grants.nih.gov/grants/policy/coi/ for a link to the regulation and additional important information.

If you have any questions about this award, please contact the individual(s) referenced in Section IV.

Sincerely yours,

(b)(6)

Grants Management Officer
NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

Additional information follows

SECTION I – AWARD DATA – 1U01DK110792-01 REVISED

Award Calculation (U.S. Dollars)

Salaries and Wages	$91,402
Fringe Benefits	$25,909
Personnel Costs (Subtotal)	$117,311
Materials & Supplies	$37,513
Travel	$4,168
Other	$47,162
Equipment or Facility Rental/User Fees	$18,756
Participant Tuition/Fees/Health Insurance	$979
Federal Direct Costs	$225,889
Federal F&A Costs	$146,192
Approved Budget	$372,081
Total Amount of Federal Funds Obligated (Federal Share)	$372,081
TOTAL FEDERAL AWARD AMOUNT	$372,081
AMOUNT OF THIS ACTION (FEDERAL SHARE)	$0

SUMMARY TOTALS FOR ALL YEARS		
YR	**THIS AWARD**	**CUMULATIVE TOTALS**
1	$372,081	$372,081
2	$387,084	$387,084
3	$387,084	$387,084
4	$387,084	$387,084
5	$387,084	$387,084

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

Fiscal Information:

CFDA Name:	Diabetes, Digestive, and Kidney Diseases Extramural Research
CFDA Number:	93.847
EIN:	1951642394A1
Document Number:	UDK110792A
PMS Account Type:	P (Subaccount)
Fiscal Year:	2016

IC	CAN	2016	2017	2018	2019	2020
DK	8472278	$372,081	$387,084	$387,084	$387,084	$387,084

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

NIH Administrative Data:
PCC: KDH KDB / **OC**: 414L / **Released:** (b)(6) 06/30/2017
Award Processed: 06/30/2017 07:01:24 PM

SECTION II – PAYMENT/HOTLINE INFORMATION – 1U01DK110792-01 REVISED

For payment and HHS Office of Inspector General Hotline information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

SECTION III – TERMS AND CONDITIONS – 1U01DK110792-01 REVISED

This award is based on the application submitted to, and as approved by, NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

a. The grant program legislation and program regulation cited in this Notice of Award.
b. Conditions on activities and expenditure of funds in other statutory requirements, such as

those included in appropriations acts.
c. 45 CFR Part 75.
d. National Policy Requirements and all other requirements described in the NIH Grants Policy Statement, including addenda in effect as of the beginning date of the budget period.
e. Federal Award Performance Goals: As required by the periodic report in the RPPR or in the final progress report when applicable.
f. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(See NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm for certain references cited above.)

Research and Development (R&D): All awards issued by the National Institutes of Health (NIH) meet the definition of "Research and Development" at 45 CFR Part§ 75.2**.** As such, auditees should identify NIH awards as part of the R&D cluster on the Schedule of Expenditures of Federal Awards (SEFA). The auditor should test NIH awards for compliance as instructed in Part V, Clusters of Programs. NIH recognizes that some awards may have another classification for purposes of indirect costs. The auditor is not required to report the disconnect (i.e., the award is classified as R&D for Federal Audit Requirement purposes but non-research for indirect cost rate purposes), unless the auditee is charging indirect costs at a rate other than the rate(s) specified in the award document(s).

This institution is a signatory to the Federal Demonstration Partnership (FDP) Phase VI Agreement which requires active institutional participation in new or ongoing FDP demonstrations and pilots.

Carry over of an unobligated balance into the next budget period requires Grants Management Officer prior approval.

This award is subject to the requirements of 2 CFR Part 25 for institutions to receive a Dun & Bradstreet Universal Numbering System (DUNS) number and maintain an active registration in the System for Award Management (SAM). Should a consortium/subaward be issued under this award, a DUNS requirement must be included. See http://grants.nih.gov/grants/policy/awardconditions.htm for the full NIH award term implementing this requirement and other additional information.

This award has been assigned the Federal Award Identification Number (FAIN) U01DK110792. Recipients must document the assigned FAIN on each consortium/subaward issued under this award.

Based on the project period start date of this project, this award is likely subject to the Transparency Act subaward and executive compensation reporting requirement of 2 CFR Part 170. There are conditions that may exclude this award; see http://grants.nih.gov/grants/policy/awardconditions.htm for additional award applicability information.

In accordance with P.L. 110-161, compliance with the NIH Public Access Policy is now mandatory. For more information, see NOT-OD-08-033 and the Public Access website: http://publicaccess.nih.gov/.

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts with cumulative total value greater than $10,000,000 must report and maintain information in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made publicly available in the designated integrity and performance system (currently the Federal Awardee Performance and Integrity Information System (FAPIIS)). Full reporting requirements

and procedures are found in Appendix XII to 45 CFR Part 75. This term does not apply to NIH fellowships.
Treatment of Program Income:
Other Research (Add/Deduct Option)

SECTION IV – DK Special Terms and Conditions – 1U01DK110792-01 REVISED

REVISION #1

This award is being revised to rescind the animal subjects restriction placed on the notice of grant award dated 09/09/2016. NIDDK received the IACUC approval on 05/26/2016.

Al terms and conditions listed below still apply.

Notice: Under governing policy, federal funds administered by the Public Health Service (PHS) shall not be expended for research involving live vertebrate animals without prior approval by the Office of Laboratory Animal Welfare (OLAW) of an assurance to comply with the PHS policy on humane care and use of laboratory animals. This restriction applies to all performance sites (e.g., collaborating institutions, subcontractors, subgrantees) without OLAW-approved assurances, whether domestic or foreign.

The grantee is required to follow the model organism sharing plan included in the application and may not implement any changes in the plan without the written prior approval of the NIDDK.

Notice: Under governing regulations, Federal funds administered by the Department of Health and Human Services shall not be expended for research involving human subjects, and individuals shall not be enrolled in such research, without prior approval by the Office of Human Research Protections (OHRP) of an assurance to comply with the requirements of 45 CFR 46 to protect human research subjects. This restriction applies to all collaborating sites without OHRP-approved assurances, whether domestic or foreign, and compliance must be ensured by the awardee.

This award involves the use of human embryonic stem cells (hESCs). The grantee may use only those hESCs that appear on the NIH Human Embryonic Stem Cell Registry as eligible for NIH funding (http://grants.nih.gov/stem_cells/registry/current.htm) and in accord with any restrictions placed on the use of those lines.

This grant is in response to RFA/PA DK15-014. Acceptance of this award requires compliance with this solicitation. See the NIH Guide at http://grants.nih.gov/grants/guide/index.html for copy of the RFA/PA that includes administrative and programmatic requirements specific to this award.

In accordance with the NIH Guide Notice NOT-OD-02-017 entitled, "Graduate Student Compensation" released December 10, 2001, total direct costs (salary, fringe benefits and tuition remission) for graduate students are provided at a level not to exceed the NIH maximum allowable amount (zero level of the Ruth L. Kirschstein National Research Service Award stipend in effect at the time of the competing award). Support recommended for future years has been adjusted accordingly, if applicable.

Although the initial budget period for this award is 09/15/2016-05/31/2017, the award includes funds for 12 months of support. Future year budget periods will cycle on 06/01/2017. Allowable preaward costs may be charged to this award in accordance with the conditions outlined in the NIH Grants Policy Statement (revised November 2015) and with institutional requirements for prior approval.

In accordance with NIH Guide Notice NOT-OD-16-045, Notice of Salary Limitation on Grants, Cooperative Agreements, and Contracts, none of the funds in this award shall be used to pay the salary of an individual at a rate in excess of the applicable salary cap. Therefore this award and/or future years are adjusted accordingly, if applicable. See the salary cap summary and the time frames associated with salary caps at http://grants.nih.gov/grants/policy/salcap_summary.htm.

In order to meet current NIDDK objectives and based on the relative scientific merit ranking of this application, the budget for the initial period has been programmatically reduced. Although

specific budget adjustments have been made, the Institution and Principal Investigator retain standard rebudgeting authorities for this mechanism of support.

See the budget information below for additional information.

Grantees can determine which progress reports are due through the website located at https://public.era.nih.gov/chl/public/search/index.jsp , and should periodically check the site, which is updated on or around the 30th of each month. Progress report due dates are also available in the eRA Commons Status system. In addition, automatic e-mail notifications are sent to the PD/PI prior to due date.

As of October 17, 2014, the National Institutes of Health (NIH) requires grantees to submit all type 5 progress reports using the eRA Research Performance Progress Report (RPPR) module. Annual progress reports submitted in any format other than the RPPR will not be processed by the NIH and will require resubmission through the RPPR module in accordance with NIH Guide Notice Number NOT-OD-15-014 released October 16, 2014.

The following special terms of award are in addition to, and not in lieu of, otherwise applicable U.S. Office of Management and Budget (OMB) administrative guidelines, U.S. Department of Health and Human Services (DHHS) grant administration regulations at 45 CFR Parts 74 and 92 (Part 92 is applicable when State and local Governments are eligible to apply), and other HHS, PHS, and NIH grant administration policies.
The administrative and funding instrument used for this program will be the cooperative agreement, an "assistance" mechanism (rather than an "acquisition" mechanism), in which substantial NIH programmatic involvement with the awardees is anticipated during the performance of the activities. Under the cooperative agreement, the NIH purpose is to support and stimulate the recipients' activities by involvement in and otherwise working jointly with the award recipients in a partnership role; it is not to assume direction, prime responsibility, or a dominant role in the activities. Consistent with this concept, the dominant role and prime responsibility resides with the awardees for the project as a whole, although specific tasks and activities may be shared among the awardees and the NIH as defined below.

The PD(s)/PI(s) will have the primary responsibility for:

- All aspects of the scientific activities, including defining the objectives and approaches, planning, conduct, analysis, and publication of results, interpretations, and conclusions of studies conducted under the terms and conditions of the cooperative agreement award.
- Collaborating with other investigators in the program for protocol development, sample, reagents and data sharing as appropriate, data quality control, and data organization
- Accountability towards the applicant organization officials and to the NIDDK for the performance and proper conduct of the research supported by the project in accordance with the terms and conditions of the award.
- Serving as a voting member of the Steering Committee and will attend the Planning Meeting and a Steering Committee meeting in the first year, two Steering Committee meetings a year in subsequent years and monthly teleconference calls.
- Accepting and implementing the goals, priorities, procedures, protocols, and policies agreed upon by the Steering Committee and subcommittees, and be responsible for close coordination and cooperation with the components of the GUDMAP consortium and with NIH staff.
- Adhering to PHS policy for the distribution of unique research resources produced with PHS funding as described under Special Requirements.
- Establishing written milestones for the project, in negotiation with NIDDK Project Staff prior to funding.
- Release all study design materials and procedure manuals into the public domain and/or make them available to other investigators, according to the approved plan for making data and materials available to the scientific community and the NIDDK, for the conduct of research at no charge other than the costs of reproduction and distribution, consistent with achieving the goals of this program initiative.
- Awardees will retain custody of and have primary rights to the data and software developed under these awards, subject to Government rights of access consistent with current DHHS, PHS, and NIH policies.

NIH staff will have substantial programmatic involvement that is above and beyond the normal stewardship role in awards, as described below:

- An NIH Project Scientist will have substantial programmatic involvement that is above and beyond the normal stewardship role in awards, as described below. However, the dominant role and prime responsibility for the project as a whole resides with the awardees, although specific tasks and activities in carrying out the studies will be shared by awardees and the NIDDK.
- NIDDK will designate a Project Officer and a Grants Management Specialist to provide normal program stewardship and administrative oversight of the cooperative agreement.
- NIDDK will form an External Advisory Committee (EAC), comprised of the NIDDK Project Scientist and other NIH extramural staff with relevant scientific expertise or who manage research grant programs that relate scientifically to the goals of the GUDMAP projects, and outside advisors selected by the NIDDK. The EAC will meet annually with the GUDMAP Steering Committee to review and assess GUDMAP and to advise NIDDK of scientific developments and opportunities that may enhance the achievement of the GUDMAP goals.
- The NIDDK Project Scientist will attend and participate as a voting member in all meetings of the Steering Committee, and provide liaison between the Steering Committee and the External Advisory Committee.
- The NIDDK Project Scientist will help the Steering Committee develop and draft operating policies.
- The NIDDK Project Officer will review the scientific progress of the individual GUDMAP components, for compliance with operating policies developed by the Steering Committee, and may recommend to the NIDDK to withhold support, suspend, or terminate an award for lack of scientific progress or failure to adhere to policies established by the Steering Committee.
- An agency program official or IC program director will be responsible for the normal scientific and programmatic stewardship of the award and will be named in the award notice. The assigned Program Officer may also serve as an NIH Project Scientist.

Areas of Joint Responsibility include:

- Steering Committee - The NIH Project Scientist, PIs from the project funded through this FOA and RFA-DK-15-015, and RFA-DK-15-016 and voluntary representatives from the previously funded GUDMAP atlas projects funded under RFA-DK-11-001 will be responsible for forming a Steering Committee as defined below. An arbitration system, as detailed below, will be available to resolve disagreements among members of the Steering Committee. The Steering Committee will be the main governing board of the GUDMAP consortium. It will develop collaborative protocols, identify technological impediments to success and strategies to overcome them, develop shared software tools for disseminating information about the projects, and identify opportunities for sharing techniques and tools that might be developed in future GUDMAP atlas projects.
- The Steering Committee will be composed of the PIs from the project funded through this FOA, RFA-DK-15-015, and RFA-DK-15-016, representatives from the previously funded GUDMAP projects, and the NIDDK Project Scientist. The representatives and the PIs will each have one vote. The NIDDK Project Scientist for this project will have one vote. The Steering Committee will select a chairperson who will be someone other than an NIH staff member.
- The Steering Committee may, as it deems necessary, invite additional, non-voting scientific advisors to meetings at which research priorities and opportunities are discussed. The NIH reserves the right to augment the scientific or consumer expertise of the Steering Committee when necessary.
- There will be two Steering Committee meetings annually. The first meeting will be a Planning Meeting to be held in the Washington, DC area on June 20-21, 2016. At the Planning Meeting, the Steering Committee will be formed and a chairperson selected from among the members. At the Planning Meeting, the Steering Committee may: (a) draft a charter to detail policies and procedures, a process for monitoring compliance with the policies and procedures, and a process for recommending that the NIH Project Administrators act on evidence of non-compliance of any Consortium component with Steering Committee policies; (b) agree upon the terms of the charter; and (c) devise a plan for working with the GUDMAP database developers to provide ongoing input into database and website design.
- At the second and subsequent meetings, the Steering Committee will refine the GUDMAP scientific objectives and implementation as necessary, consistent with data produced by former and possible future GUDMAP atlas projects and from other laboratories.

- The Steering Committee will plan workshops, to which non-GUDMAP participants will also be invited, to inform the research community of the progress made toward development of the atlas, and to inform the research community of any technological advances related to the implementation of the GUDMAP website/database. The NIDDK Project Scientist, the External Advisory Committee, and other NIH staff as appropriate will provide the Steering Committee with advice on participants for the workshops and symposia.
- The Steering Committee may establish subcommittees as it deems appropriate.
- Awardee members of the Steering Committee will be required to accept and implement policies approved by the Steering Committee.
- The EAC will meet annually with the GUDMAP Steering Committee to review and assess the progress of the GUDMAP consortium and to advise NIDDK of scientific developments and opportunities that may enhance the achievement of the GUDMAP goals.

Dispute Resolution
Any disagreements that may arise in scientific or programmatic matters (within the scope of the award) between award recipients and the NIH may be brought to Dispute Resolution. A Dispute Resolution Panel will have three members: a designee of the Steering Committee chosen without NIH staff voting, one NIH designee, and a third designee with expertise in the relevant area who is chosen by the other two; in the case of individual disagreement, the first member may be chosen by the individual awardee. This special dispute resolution procedure does not alter the awardee's right to appeal an adverse action that is otherwise appealable in accordance with PHS regulation 42 CFR Part 50, Subpart D and DHHS regulation 45 CFR Part 16.

STAFF CONTACTS

The Grants Management Specialist is responsible for the negotiation, award and administration of this project and for interpretation of Grants Administration policies and provisions. The Program Official is responsible for the scientific, programmatic and technical aspects of this project. These individuals work together in overall project administration. Prior approval requests (signed by an Authorized Organizational Representative) should be submitted in writing to the Grants Management Specialist. Requests may be made via e-mail.

Grants Management Specialist: (b)(6)
Email: (b)(6) @extra.niddk.nih.gov **Phone:** (b)(6) **Fax:** (b)(6)

Program Official: (b)(6)
Email: (b)(6) @niddk.nih.gov **Phone:** (b)(6)

SPREADSHEET SUMMARY
GRANT NUMBER: 1U01DK110792-01 REVISED

INSTITUTION: UNIVERSITY OF SOUTHERN CALIFORNIA

Budget	Year 1	Year 2	Year 3	Year 4	Year 5
Salaries and Wages	$91,402	$95,087	$95,087	$95,087	$95,087
Fringe Benefits	$25,909	$26,954	$26,954	$26,954	$26,954
Personnel Costs (Subtotal)	$117,311	$122,041	$122,041	$122,041	$122,041
Materials & Supplies	$37,513	$39,025	$39,025	$39,025	$39,025
Travel	$4,168	$4,336	$4,336	$4,336	$4,336
Other	$47,162	$49,064	$49,064	$49,064	$49,064
Equipment or Facility Rental/User Fees	$18,756	$19,513	$19,513	$19,513	$19,513
Participant Tuition/Fees/Health Insurance	$979	$1,019	$1,019	$1,019	$1,019
TOTAL FEDERAL DC	$225,889	$234,998	$234,998	$234,998	$234,998
TOTAL FEDERAL F&A	$146,192	$152,086	$152,086	$152,086	$152,086
TOTAL COST	$372,081	$387,084	$387,084	$387,084	$387,084

Facilities and Administrative	Year 1	Year 2	Year 3	Year 4	Year 5

Costs					
F&A Cost Rate 1	65%	65%	65%	65%	65%
F&A Cost Base 1	$224,910	$233,979	$233,979	$233,979	$233,979
F&A Costs 1	$146,192	$152,086	$152,086	$152,086	$152,086

PI: (b)(6)	Title: Four-dimensional Modeling of Mouse and Human Nephrogenesis.	
Received: 11/06/2015	FOA: DK15-014	Council: 05/2016
Competition ID: FORMS-C	FOA Title: GENITOURINARY DEVELOPMENT MOLECULAR ANATOMY PROJECT (GUDMAP) - ATLAS PROJECTS (U01)	
1 U01 DK110792-01	Dual:	Accession Number: 3880462
IPF: 7636101	Organization: UNIVERSITY OF SOUTHERN CALIFORNIA	
Former Number:	Department: Stem Cell Biology	
IRG/SRG: ZDK1 GRB-2 (M3)S	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: 247,939 Year 2: 252,897 Year 3: 257,955 Year 4: 263,113 Year 5: 268,376	Animals: Y Humans: N Clinical Trial: N Current HS Code: (b)(5) HESC: Y Special Topics: Human Embryonic Stem Cells	New Investigator: Early Stage Investigator:
Senior/Key Personnel:	*Organization:*	*Role Category:*
(b)(6)	University of Southern California	PD/PI

OMB Number: 4040-0001
Expiration Date: 06/30/2016

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	State Application Identifier

1. TYPE OF SUBMISSION*

❍ Pre-application ● Application ❍ Changed/Corrected Application

4.a. Federal Identifier
DK094526

b. Agency Routing Number

2. DATE SUBMITTED
2015-11-06

Application Identifier

c. Previous Grants.gov Tracking Number

5. APPLICANT INFORMATION

Organizational DUNS*: 072933393

Legal Name*: University of Southern California
Department: Contracts and Grants
Division:
Street1*: 2001 N. Soto Street
Street2: Suite 205
City*: Los Angeles
County: Los Angeles
State*: CA: California
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 90089-9235

Person to be contacted on matters involving this application
Prefix: (b)(6) Suffix:
Position/Title: (b)(6)
Street1*: 2001 N. Soto Street
Street2: (b)(6)
City*: Los Angeles
County: Los Angeles
State*: CA: California
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 90089-9235
Phone Number*: (b)(6) Email: (b)(6)@usc.edu

6. EMPLOYER IDENTIFICATION NUMBER *(EIN) or (TIN)** 95-1642394

7. TYPE OF APPLICANT* O: Private Institution of Higher Education

Other (Specify):
Small Business Organization Type ❍ Women Owned ❍ Socially and Economically Disadvantaged

8. TYPE OF APPLICATION*

● New ❍ Resubmission
❍ Renewal ❍ Continuation ❍ Revision

If Revision, mark appropriate box(es).
❍ A. Increase Award ❍ B. Decrease Award ❍ C. Increase Duration
❍ D. Decrease Duration ❍ E. Other *(specify)* :

Is this application being submitted to other agencies?* ❍Yes ●No What other Agencies?

9. NAME OF FEDERAL AGENCY*
National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER
TITLE:

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
Four-dimensional Modeling of Mouse and Human Nephrogenesis.

12. PROPOSED PROJECT
Start Date*: 07/01/2016
Ending Date*: 06/30/2021

13. CONGRESSIONAL DISTRICTS OF APPLICANT
CA-034

Contact PD/PI: (b)(6)

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: (b)(6) Suffix:

Position/Title: (b)(6)

Organization Name*: University of Southern California

Department: Stem Cell Biology

Division: Keck School of Medicine

Street1*: 1425 San Pablo Street

Street2: (b)(6)

City*: Los Angeles

County: Los Angeles

State*: CA: California

Province:

Country*: USA: UNITED STATES

ZIP / Postal Code*: 90033-9080

Phone Number*: (b)(6) Fax Number: (b)(6) Email*: (b)(6) @med.usc.edu

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested*	$2,128,962.00
b. Total Non-Federal Funds*	$0.00
c. Total Federal & Non-Federal Funds*	$2,128,962.00
d. Estimated Program Income*	$0.00

16.IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?*

a. YES ○ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:

DATE:

b. NO ● PROGRAM IS NOT COVERED BY E.O. 12372; OR

○ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

● I agree*

** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.*

18. SFLLL or OTHER EXPLANATORY DOCUMENTATION File Name:

19. AUTHORIZED REPRESENTATIVE

Prefix: (b)(6) Suffix:

Position/Title*: (b)(6)

Organization Name*: University of Southern California

Department: Contracts and Grants

Division:

Street1*: 2001 N. Soto Street

Street2: (b)(6)

City*: Los Angeles

County: Los Angeles

State*: CA: California

Province:

Country*: USA: UNITED STATES

ZIP / Postal Code*: 90089-9235

Phone Number*: (b)(6) Fax Number: (b)(6) Email*: (b)(6) @usc.edu

Signature of Authorized Representative*

(b)(6)

Date Signed*

11/06/2015

20. PRE-APPLICATION File Name:

21. COVER LETTER ATTACHMENT File Name:

Contact PD/PI: (b)(6)

424 R&R and PHS-398 Specific Table Of Contents

OMB Number: 4040-0010
Expiration Date: 06/30/2016

Project/Performance Site Location(s)

Project/Performance Site Primary Location

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	University of Southern California
Duns Number:	0729333930000
Street1*:	1425 San Pablo Street
Street2:	(b)(6)
City*:	Los Angeles
County:	Los Angeles
State*:	CA: California
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	90033-9080
Project/Performance Site Congressional District*:	CA-034

File Name

Additional Location(s)

Funding Opportunity Number: RFA-DK-15-014. Received Date: 2015-11-06T17:13:20.000-05:00

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED Other Project Information

1. Are Human Subjects Involved?* ○ **Yes** ● **No**

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? ○ Yes ○ No

If YES, check appropriate exemption number: _ 1 _ 2 _ 3 _ 4 _ 5 _ 6

If NO, is the IRB review Pending? ○ **Yes** ○ **No**

IRB Approval Date:

Human Subject Assurance Number

2. Are Vertebrate Animals Used?* ● **Yes** ○ **No**

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ● Yes ○ No

IACUC Approval Date:

Animal Welfare Assurance Number A3518-01

3. Is proprietary/privileged information included in the application?* ○ **Yes** ● **No**

4.a. Does this project have an actual or potential impact - positive or negative - on the environment?* ○ **Yes** ● **No**

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ○ Yes ○ No

4.d. If yes, please explain:

5. Is the research performance site designated, or eligible to be designated, as a historic place?* ○ **Yes** ● **No**

5.a. If yes, please explain:

6. Does this project involve activities outside the United States or partnership with international collaborators?* ○ **Yes** ● **No**

6.a. If yes, identify countries:

6.b. Optional Explanation:

	Filename
7. Project Summary/Abstract*	1235-9.(b)(6)GUDMAP-U01 Project Summary 11-15.pdf
8. Project Narrative*	1236-(b)(6)GUDMAP-U01 Project Narrative 11-15.pdf
9. Bibliography & References Cited	1237-(b)(6)GUDMAP-U01 References 11-15.pdf
10.Facilities & Other Resources	1238-(b)(6)GUDMAP-U01 FacilitiesandResources 11-15.pdf
11.Equipment	
12. Other Attachments	1239-12.(b)(6)GUDMAP U01 Support Biosketches.pdf

Funding Opportunity Number: RFA-DK-15-014. Received Date: 2015-11-06T17:13:20.000-05:00

Project Summary/Abstract

The Genito-Urinary Developmental Molecular Anatomy Project (GUDMAP) has generated information and research tools to enhance our understanding of the development of urogenital system, both informing and stimulating research into urogenital development, and associated disorders and disease. Our proposed studies focus on the developing kidney complementing existing data available through the GUDMAP website. The functional unit of the kidney is the nephron — hence, our focus on obtaining a thorough understanding of mammalian nephrogenesis. The current GUDMAP view of this process is largely two-dimensional and mouse focused. We will harness recent advances in both static and live dynamic cell imaging, the access to human kidney specimens and the development of pluripotent stem cell (PSC) culture-seeded nephrogenesis to extend our understanding of both mouse and human nephrogenesis. In **Aim 1,** we will develop high-resolution 3D views of mouse and human nephrogenesis through selective imaging approaches comparing mouse and human nephrogenesis to develop comparative 3D molecular atlases of nephron patterning and nephron morphogenesis. In **Aim 2**, we will take advantage of improvements in imaging and organ culture, and a bank of genetically modified mouse strains, to perform time lapse imaging of the nephron progenitor niche, and the formation, morphogenesis and patterning of the mouse nephron. Dynamic imaging studies will be applied to pluripotent stem cell (PSC)-derived models of human nephrogenesis. Together, these studies will significantly enrich the GUDMAP resource generating comparative 4D views of nephron development in the mouse and human kidney. Given the recent advances in the directed differentiation of PSCs into nephron-like structures, the studies will provide a benchmark for normal nephrogenesis that will guide the emerging field of regenerative kidney biology.

Project Narrative

Regenerative approaches to treat kidney disease are predicated on a good understanding of the developmental mechanisms that build a functional kidney. The proposal sets out to develop comparative, views of the nephron forming processes in space and over time in the mouse and human kidney. These studies will provide an important resource for kidney researchers and a benchmark for efforts to engineer functional kidney structures.

Facilities and Resources

Space

(b)(4); (b)(6)

(b)(6) Over 90 research and clinical faculty across USC are connected with the center through the USC Stem Cell program that (b)(6) established at USC to unite its many strengths across all campuses including the Children's Hospital of Los Angeles.

Core Facilities (b)(4)

Stem Cell Core: molecular biology lab with Q-PCR, laser dissection equipment, and shared lab space. Supports development of human pluripotent stem cell lines, lot tested bioreagents, biobanking, histology, and karyotyping. Includes culture equipment, e.g., hoods, incubators, fluorescent live cell imaging microscopes. **Flow-Cytometry Core:** five different instruments allowing sorting of tagged cells into subgroups, multiple fluorochrome use supported (Special Order Research Product (SORP) FACSAria I, FACSAria II, MoFlo Astrios, Special Order Research Product (SORP) LSRII, and Beckman Coulter Cyan ADP. **I Imaging Core:** contains the following systems: 510 Meta multiphoton, 14 channel multispectral confocal microscope, Zeiss LSM 5 Exciter (LSM 5(1)) & Zeiss LSM 5 Pascal (LSM5(2)) Axio imager.M1 upright confocal microscope with a UV Diode laser, an Argon and HeNe lasers, Zeiss Axio imager.Z1 upright compound microscope, Zeiss Axiovert 200 inverted compound microscope, in house built Optical Projection Tomography (OPT), Leica SP8-X confocal on a DMI-8 inverted microscope with white light laser (470-670nm), UV diode laser (405nm) and an Argon laser (458, 488, 514, 594nm) and Digital Light Sheet (DLS) module. The SP8-X has the following objectives: 5x, 10x, 20x oil, 40x oil and 63x oil; Zeiss LSM 780NLO confocal on a AxioObserver.Z1 inverted stand, with a UV laser (405nm), Argon laser (458, 488,514,594nm) and HeNe lasers (561, 633nm) and the following objectives: 5x, 10x, 20x 0.8, 40x LD water and 40x oil. Zeiss Axioscan, and Zeiss Axiozoom with Apotome structured illumination. The Zeiss LSM 780NLO is equipped with an environmental chamber for live imaging. An Ibid stage top incubator is used for live imaging on the SP8-X. The OPT device has xeon white light source, 5 excitation filters and 4 emission filters covering the most commonly used fluorochromes used in the lab. The OPT is being used to capture 3D morphology of developing kidney anatomy. Note the last three machines where purchased by (b)(6) with funds from CIRM and USC. The Zeiss Axioscan is the workhorse system for generating high-resolution tiled images (file up 15gbytes) that (b)(6) has being using in the human GUDMAP. Each connects to state-of-the-art digital imaging and software analysis systems, with in house Imaris data analysis capability. (b)(4) houses a variety of robotic devices for automated high throughput pipetting of in house chemical and viral libraries (ViaFlo 96 Liquid Handler), high content imaging devices including the Cellomics Arrayscan VTi High Content Screener and the Molecular Dynamics ImageXpress Micro System, Molecular Devices Spectra MaxM5. The center has tissue culture facilities and a Nikon Biostation CT. Most recently, the (b)(4) (b)(4) performs genome engineering on ESC and iPSC lines to generate/correct disease causing mutations and to generate reporter cell lines to identify specific cell types in *in vitro* and *in vivo* assays. These facilities are complemented by an excellent, pathogen free **vivarium space** for the holding/breeding of mouse strains that incorporates surgical and embryo manipulation suites for research related surgery and transgenic mouse production within the basement of the BCC building. The (b)(6) group has access to 1,400 cages that house nearly 200 distinct strains of mice, the majority of which are genetically engineered strains generated within (b)(6) research programs. The laboratory also has two microinjection stations that enable genomic through cytoplasmic/pronuclear injection of mouse zygotes with DNA/RNA/protein or blastocyst injection and chimera production with genetically modified ES cells.

(b)(6)

Core Facilities (adjacent buildings)

Core facilities in the attached (b)(4) and across the street at the (b)(4) (b)(4) include: the **transgenic animal core**, **DNA sequencing, microarray/genomics** and **flow cytometry**. The (b)(4) provides several high-throughput Illumina platforms for Genotyping of DNA/RNA samples ((HiSeq/NextSeq/MySeq); an Illumina Beadlab system enables production level DNA methylation/SNP genotyping/gene expression analysis. Two Tecan Genesis workstations provide robotic capability and laboratory Information Management System (LIMS) and GenomeStudio data analysis software analytical capability. Not listed are a broad-range of facilities at the (b)(4) (b)(4) notably those around bioengineering, bioinformatics, printing and fabrication.

Imaging Microscopy services

Cell and Tissue Imaging Core Facility (b)(4) provides assistance and instrumentation for cell and tissue imaging including specimen preparation, thin sectioning, embedding procedures, cryosectioning, photography, digital photomicroscopy and photomicrography and computer aided graphics.

Data Analysis and Management

The (b)(4) is a team of statisticians, epidemiologists, database developers, programmers, project coordinators and data managers who integrate statistical, epidemiological and computing resources and offer them to investigators conducting clinical, biomedical and translational research.

Benefit of environment to research

(b)(4); (b)(6)

(b)(6)

(b)(4); (b)(6)

Contact PD/PI (b)(6)

OMB No. 0925-0001/0002 (Rev. 08/12 Approved Through 8/31/2015)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

(b)(6)

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Withheld pursuant to exemption

(b)(6)

of the Freedom of Information and Privacy Act

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of the Freedom of Information and Privacy Act

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 1

ORGANIZATIONAL DUNS*: 0729333930000

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: University of Southern California

Start Date*: 07-01-2016 **End Date*:** 06-30-2017 **Budget Period: 1**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1.		(b)(6)				PD/PI	(b)(6)				9,165.00	2,850.00	12,015.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **12,015.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
1	Graduate Students	(b)(6)			12,800.00	0.00	12,800.00
	Undergraduate Students						
	Secretarial/Clerical						
1	Project Administrator				9,000.00	2,799.00	11,799.00
2	Research Associate (PhD)				46,184.00	14,363.00	60,547.00
1	Laboratory Technician				18,000.00	5,598.00	23,598.00
1	Histology Technician				7,593.00	2,362.00	9,955.00
6	**Total Number Other Personnel**					**Total Other Personnel**	**118,699.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**130,714.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 1

ORGANIZATIONAL DUNS*: 0729333930000
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: University of Southern California

Start Date*: 07-01-2016 **End Date*:** 06-30-2017 **Budget Period: 1**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	
Additional Equipment: File Name:	

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	4,500.00
2. Foreign Travel Costs	
Total Travel Cost	**4,500.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		1,057.00
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**1,057.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Tracking Number: GRANT12035015 Funding Opportunity Number: RFA-DK-15-014 . Received Date: 2015-11-06T17:13:20.000-05:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 1

ORGANIZATIONAL DUNS*: 0729333930000
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: University of Southern California

Start Date*: 07-01-2016 **End Date*:** 06-30-2017 **Budget Period: 1**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	40,500.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	20,250.00
7. Alterations and Renovations	
8 . Mouse Per Diem Costs- 150 cages @$0.93/cage/day	50,918.00
Total Other Direct Costs	**111,668.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**247,939.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	65.00	247,939.00	161,160.00
		Total Indirect Costs	**161,160.00**

Cognizant Federal Agency DHHS, (b)(6)
(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**409,099.00**

J. Fee	Funds Requested ($)*

K. Budget Justification* File Name: 1234-(b)(6)GUDMAP-U01
Budget Justification Final2 11-15.pdf
(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Tracking Number: GRANT12035015 Funding Opportunity Number: RFA-DK-15-014 . Received Date: 2015-11-06T17:13:20.000-05:00

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 2

ORGANIZATIONAL DUNS*: 0729333930000

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: University of Southern California

Start Date*: 07-01-2017 **End Date*:** 06-30-2018 **Budget Period: 2**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1		(b)(6)				PD/PI	(b)(6)				9,348.00	2,907.00	12,255.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **12,255.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
1	Graduate Students	(b)(6)			13,056.00	0.00	13,056.00
	Undergraduate Students						
	Secretarial/Clerical						
1	Project Administrator				9,180.00	2,855.00	12,035.00
2	Research Associate (PhD)				47,107.00	14,651.00	61,758.00
1	Laboratory Technician				18,360.00	5,710.00	24,070.00
1	Histology Technician				7,745.00	2,409.00	10,154.00
6	**Total Number Other Personnel**					**Total Other Personnel**	**121,073.00**

Total Salary, Wages and Fringe Benefits (A+B) **133,328.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 2

ORGANIZATIONAL DUNS*: 0729333930000
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: University of Southern California

Start Date*: 07-01-2017 **End Date*:** 06-30-2018 **Budget Period: 2**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	
Additional Equipment: File Name:	

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	4,590.00
2. Foreign Travel Costs	
Total Travel Cost	**4,590.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		1,078.00
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**1,078.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Tracking Number: GRANT12035015 Funding Opportunity Number: RFA-DK-15-014 . Received Date: 2015-11-06T17:13:20.000-05:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 2

ORGANIZATIONAL DUNS*: 0729333930000
Budget Type*: ● Project ○ Subaward/Consortium
Organization: University of Southern California

Start Date*: 07-01-2017 **End Date*:** 06-30-2018 **Budget Period:** 2

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	41,310.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	20,655.00
7. Alterations and Renovations	
8 . Mouse Per Diem Costs- 150 cages @$0.93/cage/day	51,936.00
Total Other Direct Costs	**113,901.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**252,897.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	65.00	252,897.00	164,383.00
		Total Indirect Costs	**164,383.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, (b)(6)

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**417,280.00**

J. Fee	Funds Requested ($)*

K. Budget Justification* File Name: 1234(b)(6) GUDMAP-U01 Budget Justification Final2 11-15.pdf
(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Tracking Number: GRANT12035015 Funding Opportunity Number: RFA-DK-15-014 . Received Date: 2015-11-06T17:13:20.000-05:00

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 3

ORGANIZATIONAL DUNS*: 0729333930000

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: University of Southern California

Start Date*: 07-01-2018 **End Date*:** 06-30-2019 **Budget Period: 3**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1.		(b)(6)				PD/PI	(b)(6)				9,535.00	2,965.00	12,500.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **12,500.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
1	Graduate Students	(b)(6)			13,317.00	0.00	13,317.00
	Undergraduate Students						
	Secretarial/Clerical						
1	Project Administrator				9,364.00	2,912.00	12,276.00
2	Research Associate (PhD)				48,049.00	14,943.00	62,992.00
1	Laboratory Technician				18,727.00	5,824.00	24,551.00
1	Histology Technician				7,900.00	2,457.00	10,357.00
6	**Total Number Other Personnel**					**Total Other Personnel**	**123,493.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**135,993.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 3

ORGANIZATIONAL DUNS*: 0729333930000
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: University of Southern California

Start Date*: 07-01-2018 **End Date*:** 06-30-2019 **Budget Period: 3**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	
Additional Equipment: File Name:	

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	4,682.00
2. Foreign Travel Costs	
Total Travel Cost	**4,682.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		1,099.00
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**1,099.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 3

ORGANIZATIONAL DUNS*: 0729333930000
Budget Type*: ● Project ○ Subaward/Consortium
Organization: University of Southern California

Start Date*: 07-01-2018 **End Date*:** 06-30-2019 **Budget Period: 3**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	42,137.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	21,069.00
7. Alterations and Renovations	
8 . Mouse Per Diem Costs- 150 cages @$0.93/cage/day	52,975.00
Total Other Direct Costs	**116,181.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**257,955.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	65.00	257,955.00	167,671.00
		Total Indirect Costs	**167,671.00**

Cognizant Federal Agency DHHS, (b)(6)
(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**425,626.00**

J. Fee	Funds Requested ($)*

K. Budget Justification* File Name: 1234 (b)(6) GUDMAP-U01 Budget Justification Final2 11-15.pdf
(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 4

ORGANIZATIONAL DUNS*: 0729333930000

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: University of Southern California

Start Date*: 07-01-2019 **End Date*:** 06-30-2020 **Budget Period: 4**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1.		(b)(6)				PD/PI	(b)(6)				9,726.00	3,025.00	12,751.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **12,751.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates	(b)(6)					
1	Graduate Students				13,583.00	0.00	13,583.00
	Undergraduate Students						
	Secretarial/Clerical						
1	Project Administrator				9,551.00	2,970.00	12,521.00
2	Research Associate (PhD)				49,010.00	15,242.00	64,252.00
1	Laboratory Technician				19,102.00	5,941.00	25,043.00
1	Histology Technician				8,058.00	2,506.00	10,564.00
6	**Total Number Other Personnel**					**Total Other Personnel**	**125,963.00**

Total Salary, Wages and Fringe Benefits (A+B) **138,714.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 4

ORGANIZATIONAL DUNS*: 0729333930000
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: University of Southern California

Start Date*: 07-01-2019 **End Date*:** 06-30-2020 **Budget Period:** 4

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	

Additional Equipment: File Name:

D. Travel	Funds Requested ($)*
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	4,775.00
2. Foreign Travel Costs	
Total Travel Cost	**4,775.00**

E. Participant/Trainee Support Costs		Funds Requested ($)*
1. Tuition/Fees/Health Insurance		1,121.00
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**1,121.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Tracking Number: GRANT12035015 Funding Opportunity Number: RFA-DK-15-014 . Received Date: 2015-11-06T17:13:20.000-05:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 4

ORGANIZATIONAL DUNS*: 0729333930000
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: University of Southern California

Start Date*: 07-01-2019 **End Date*:** 06-30-2020 **Budget Period:** 4

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	42,978.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	21,490.00
7. Alterations and Renovations	
8 . Mouse Per Diem Costs- 150 cages @$0.93/cage/day	54,035.00
Total Other Direct Costs	**118,503.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**263,113.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	65.00	263,113.00	171,024.00
		Total Indirect Costs	**171,024.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, (b)(6)

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**434,137.00**

J. Fee	Funds Requested ($)*

K. Budget Justification* File Name: 1234-(b)(6) GUDMAP-U01 Budget Justification Final2 11-15.pdf
(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 5

ORGANIZATIONAL DUNS*: 0729333930000

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: University of Southern California

Start Date*: 07-01-2020 **End Date*:** 06-30-2021 **Budget Period: 5**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1.		(b)(6)				PD/PI	(b)(6)				9,920.00	3,085.00	13,005.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **13,005.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
1	Graduate Students	(b)(6)			13,855.00	0.00	13,855.00
	Undergraduate Students						
	Secretarial/Clerical						
1	Project Administrator				9,742.00	3,030.00	12,772.00
2	Research Associate (PhD)				49,991.00	15,547.00	65,538.00
1	Laboratory Technician				19,484.00	6,059.00	25,543.00
1	Histology Technician				8,219.00	2,556.00	10,775.00
6	**Total Number Other Personnel**					**Total Other Personnel**	**128,483.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**141,488.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 5

ORGANIZATIONAL DUNS*: 0729333930000
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: University of Southern California

Start Date*: 07-01-2020 **End Date*:** 06-30-2021 **Budget Period: 5**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	
Additional Equipment: File Name:	

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	4,871.00
2. Foreign Travel Costs	
Total Travel Cost	**4,871.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		1,144.00
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**1,144.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

Tracking Number: GRANT12035015 Funding Opportunity Number: RFA-DK-15-014 . Received Date: 2015-11-06T17:13:20.000-05:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 5

ORGANIZATIONAL DUNS*: 0729333930000
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: University of Southern California

Start Date*: 07-01-2020 **End Date*:** 06-30-2021 **Budget Period: 5**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	43,838.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	21,920.00
7. Alterations and Renovations	
8 . Mouse Per Diem Costs- 150 cages @$0.93/cage/day	55,115.00
Total Other Direct Costs	**120,873.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**268,376.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	65.00	268,376.00	174,444.00
		Total Indirect Costs	**174,444.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, (b)(6)

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**442,820.00**

J. Fee	Funds Requested ($)*

K. Budget Justification* File Name: 1234-(b)(6)GUDMAP-U01 Budget Justification Final2 11-15.pdf
(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Budget Justification

Personnel

(b)(6) (PI): as PI of the proposal salary is requested reflecting the effort and (b)(6) (b)(6) effort (b)(6)

(b)(6)

(b)(6)

(b)(6)

(b)(6)

(b)(6)

(b)(6)

(b)(6)

(b)(6)

Materials and Supplies

Costs reflect projected costs typical for project of this scale with multiple molecular and cellular approaches. In addition, we anticipate significant costs associated with tissue culture as a central aspect of the studies and of antibody reagents.

(b)(4)

2.0% cost inflation factored into years 2-5 of proposal.

Travel

Travel costs are requested for the PI and key team members to attend annual consortium advisory meetings in Bethesda or elsewhere. 3 people at $1500 each/year. 2.0% inflation in years 2-5 of proposal.

Other Costs

The project will require the maintenance and analysis of a large number of mouse strains as detailed in the research proposal. We anticipate this will require approximately 150 cages of isolator-caged mice within the barrier facility ($0.93/cage/day). In addition, we will be performing extensive live imaging and anticipate costs associated with standard imaging center charges. FACS use will facilitate cell isolation for *in vitro* culture experiments.

Mouse Per Diem: (b)(4)

FACS User Fees: (b)(4)

Confocal Facility User Fees: (b)(4)

(b)(4)

Annual Student Health Fee: $1,057/year is requested for partial healthcare cost coverage of graduate student contributing (b)(6) 2.0% inflation factored into years 2-5.

Fringe Benefit Rate:

31.1% for faculty and staff positions (Federal sponsor approved rate)

Indirect Cost (F&A) Rate: 65.0% current approved Federal sponsor rate.

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals ($)	
Section A, Senior/Key Person		62,526.00
Section B, Other Personnel		617,711.00
Total Number Other Personnel	30	
Total Salary, Wages and Fringe Benefits (A+B)		680,237.00
Section C, Equipment		
Section D, Travel		23,418.00
1. Domestic	23,418.00	
2. Foreign		
Section E, Participant/Trainee Support Costs		5,499.00
1. Tuition/Fees/Health Insurance	5,499.00	
2. Stipends		
3. Travel		
4. Subsistence		
5. Other		
6. Number of Participants/Trainees		
Section F, Other Direct Costs		581,126.00
1. Materials and Supplies	210,763.00	
2. Publication Costs		
3. Consultant Services		
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs		
6. Equipment or Facility Rental/User Fees	105,384.00	
7. Alterations and Renovations		
8. Other 1	264,979.00	
9. Other 2		
10. Other 3		
Section G, Direct Costs (A thru F)		1,290,280.00
Section H, Indirect Costs		838,682.00
Section I, Total Direct and Indirect Costs (G + H)		2,128,962.00
Section J, Fee		

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

1. Project Director / Principal Investigator (PD/PI)

Prefix:
First Name*:
Middle Name:
Last Name*:
Suffix:

(b)(6)

2. Human Subjects

Clinical Trial? ● No ○ Yes

Agency-Defined Phase III Clinical Trial?* ○ No ○ Yes

3. Permission Statement*

If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and e-mail address of the official signing for the applicant organization, to organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)?

● Yes ○ No

4. Program Income*

Is program income anticipated during the periods for which the grant support is requested? ○ Yes ● No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

Budget Period*	Anticipated Amount ($)*	Source(s)*

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5. Human Embryonic Stem Cells

Does the proposed project involve human embryonic stem cells?* ○ No ● Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://grants.nih.gov/stem_cells/registry/current.htm. Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used:

Cell Line(s): Specific stem cell line cannot be referenced at this time. One from the registry will be used.

0022

6. Inventions and Patents (For renewal applications only)

Inventions and Patents*: ○ Yes ○ No

If the answer is "Yes" then please answer the following:

Previously Reported*: ○ Yes ○ No

7. Change of Investigator / Change of Institution Questions

❑ Change of principal investigator / program director

Name of former principal investigator / program director:

Prefix:

First Name*:

Middle Name:

Last Name*:

Suffix:

❑ Change of Grantee Institution

Name of former institution*:

PHS 398 Research Plan

Please attach applicable sections of the research plan, below.

OMB Number: 0925-0001

1. Introduction to Application (for RESUBMISSION or REVISION only)		
2. Specific Aims	1240-4. (b)(6)	GUDMAP-U01 Specific Aims 11-15.pdf
3. Research Strategy*	1241-5.	GUDMAP-U01 Main Proposal Body 11-05-15.pdf
4. Progress Report Publication List		
Human Subjects Sections		
5. Protection of Human Subjects		
6. Inclusion of Women and Minorities		
7. Inclusion of Children		
Other Research Plan Sections		
8. Vertebrate Animals	1243- (b)(6)	GUDMAP-U01 VertAnimals 11-15.pdf
9. Select Agent Research		
10. Multiple PD/PI Leadership Plan		
11. Consortium/Contractual Arrangements		
12. Letters of Support	1244-N (b)(6)	GUDMAP_U01 Support Letters.pdf
13. Resource Sharing Plan(s)	1245-N	GUDMAP-U01 SharingPlan 11-15.pdf
Appendix (if applicable)		
14. Appendix		

Four-dimensional Modeling of Mouse and Human Nephrogenesis

Specific Aims

The Genito-Urinary Developmental Molecular Anatomy Project (GUDMAP) has generated information and research tools to enhance the understanding of urogenital development [1]. My group has been a member of GUDMAP since its inception in 2005; I have been the scientific coordinator throughout this time. Our contributions include section and whole-mount *in situ* hybridization (SISH and WISH) with the genome-scale expression mapping of the vast majority of mammalian transcription factors in the fetal mouse urogenital system, transcriptional profiling of developing nephrons, and the generation of a spectrum of new mouse models for the visualization, isolation and genetic modification of key cell populations throughout the developing urogenital system. Most recently, our pilot studies have provided a foundation for a histological atlas of human kidney development. Further, comparative analyses of anchor gene expression, and transcriptional and epigenetic profiles have highlighted similarities and differences in mouse and human kidney programs. We propose to continue our GUDMAP association, focusing on the development of the mammalian kidney, to contribute new insights into mouse and human nephrogenesis.

The functional unit of the kidney is the nephron — hence, our focus on obtaining a thorough understanding of mammalian nephrogenesis. The current GUDMAP view of this process reflects the general view from the literature: largely two-dimensional, mouse kidney focused snapshots depict the progression of a sub-set of mesenchymal nephron progenitors through a mesenchymal to epithelial transition, followed by the complex morphogenesis and patterning process that establishes the nephron. To augment this understanding of the mammalian kidney, we can now harness recent advances in both static and live dynamic cell imaging, the access to human fetal kidney specimens and the development of pluripotent stem cell (PSC) culture-seeded nephrogenesis. With this goal, we will generate comparative 4D views of nephron development in the mouse and human, extending these studies to the imaging of selected mutants in the nephrogenic program. Given the recent advances in the directed differentiation of PSCs into nephron-like structures, a benchmark for normal nephrogenesis will have considerable value to the emerging field of regenerative kidney biology.

Specific Aim 1. To generate comparative 3D morphological maps of nephron progenitor and nephron patterning in the mouse and human kidney

i) We will use cell specific immunolabeling complemented by multi-color *in situ* hybridization to generate 3D maps to visualize the nephrogenic program in optically translucent mouse and human fetal kidney samples.
ii) Optical projection tomography (OPT) and scanning confocal microscopy will be used to render high-resolution 3D views of this data for comparative morphometric analysis of mouse and human nephrogenesis.

Specific Aim 2. To generate high-resolution dynamic views of mouse and human kidney development with genetically modified mouse strains and genetically engineered human pluripotent stem cell lines

i) Partly supported by previous GUDMAP funding, the (b)(6) group has generated a number of useful genetic tools for the study of mouse nephrogenesis. Selected mouse strains producing a cell-type specific CRE recombinase will be crossed with fluorescent protein (FP) CRE-reporter strains to develop live cell imaging views of nephrogenic events in normal and mutant mouse kidney explant cultures and in a novel culture model enriched for the cortical nephrogenic zone (CNZ) of the mouse and human kidney.
ii) Kidney organoid cultures can be generated by directed differentiation of mouse and human PSCs. We will optimize this approach for the dynamic imaging of human nephron forming programs, utilizing CRISPR/CAS9 genome engineering to generate cell type specific reporter alleles to visualize PSC-directed nephrogenesis.

The proposed research builds on the foundation of GUDMAP to extend the GUDMAP view of the developing mammalian kidney. The imaging and analytical approaches will generate new insights into nephron forming processes in mouse and man. The proposed research continues in the tradition of GUDMAP: to develop critical information and resources that enhance our understanding of mammalian urogenital development and stimulate and inform genitourinary research.

Four-dimensional Modeling of Mouse and Human Nephrogenesis

Research Strategy
a) Significance

The kidney is highly complex organ performing multiple essential physiological tasks: maintaining the homeostatic environment for the body's tissues, removing nitrogenous waste products of metabolism, and maintaining blood pressure and specific blood cell composition [2]. Diseases of the kidney are a major cause of morbidity and mortality in the U.S. population, and the incidence of kidney disease is on the rise, particularly within the elderly population, for whom malfunctioning kidneys significantly enhance morbidity associated with diseases of other organ systems [3]. Information compiled by the NIDDK (*kidney.niddk.nih.gov/KUDiseases/pubs/kustats*) indicates that chronic kidney disease (CKD) affects one in 10 adult Americans; nearly 1 million patients are being treated for end state renal disease (ESRD) — a rise of 600% compared to 30 years ago. Of these, approximately 400,000 receive dialysis, a limited solution given the five-year survival rates of only 35% post initiation. These statistics, supplemented by estimates of public and private costs for treatment of ESRD of $40 billion per annum (2009 figures), provide compelling evidence that restoring renal function is the best option for both patients and society in general. Understanding how the kidney is built provides a road map for restoring renal function, a priority for the kidney disease field.

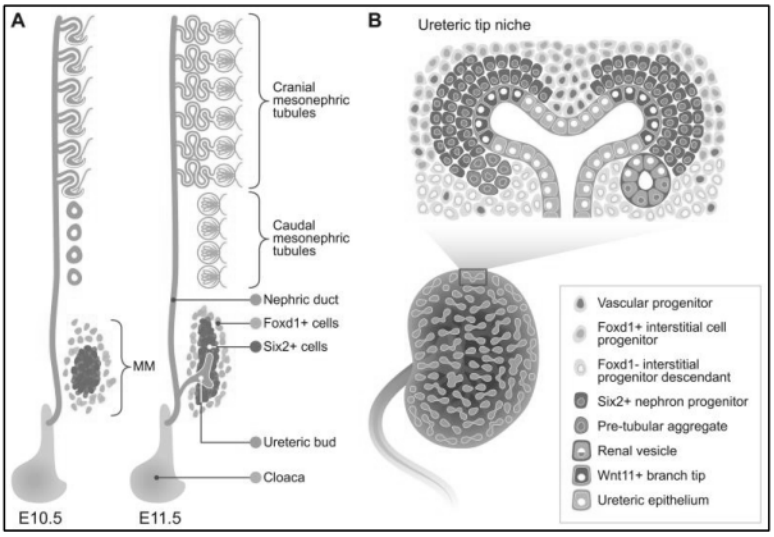

Figure 1. Overview of development of the mouse metanephric kidney

Over the last six decades, mouse and rat studies have provided a reasonable working framework for the development of the mammalian kidney [reviewed in 4–9] (**Figure 1**). The metanephric kidney arises from intermediate mesoderm derivatives at the level of the hindlimb. At embryonic day 10.5 (e10.5) in the mouse and 3.5 weeks in the human, the ureteric bud outgrows from the nephric duct, initiating active kidney development (**Figure 1**). Surrounding the ureteric bud are pre-specified mesenchymal precursors, which induce bud growth and give rise to the main body of the nephron, many interstitial cell lineages and the nephron-associated vascular endothelium. Over days in the mouse and weeks in the human, the ureteric bud branches extensively, supported by multipotent ureteric epithelial progenitors within each branch tip, to generate the arborized, differentiated ureteric epithelium of the collecting duct network. The collecting duct tunes plasma electrolyte and pH balance and removes urine from the kidney via the ureter to the bladder.

Mouse lineage tracing studies indicate that ureteric branch tips and the adjacent metanephric mesenchyme form a mobile stem/progenitor niche harboring the major progenitor pools for the developing kidney [8,9]. The interaction amongst these populations provides the motor that drives the assembly of the mammalian kidney. Both interstitial and nephron progenitor lineages are likely established from a common Osr1+ precursor [10,11]. Each progenitor compartment adopts a specific position within the niche: Six2+/Cited1+ self-renewing, multipotent progenitors that generate the main body of the nephron directly cap ureteric branch tips [12,13]; and Foxd1+ self-renewing, multi-potent progenitors that generate the variety of interstitial cell types are positioned between the nephron progenitors and the kidney capsule [14, 15]. Six2's transcriptional activity is central to maintaining the nephron progenitor state [12,16]. Chromatin immunoprecipitation studies in our laboratory show that Six2 promotes its own transcription and that transcription of other regulatory factors that specify and maintain nephron progenitors [17]. Six2+/Cited1+ cells receive signals from both the branching tips of the developing ureteric epithelium and adjacent interstitial progenitor pools. These signals have opposing actions, promoting progenitor expansion or inducing commitment of nephron progenitors to nephron formation. Canonical Wnt9b and Bmp7 signaling regulates both processes [18, 19]. In nephron development, their action, together with Fat4 signaling mediated by interstitial progenitors [20–22], triggers a pathway of nephrogenesis. In this, a pretubular aggregate (PTA) emerges beneath the ureteric tip and then undergoes a mesenchymal to

epithelial conversion, generating a renal vesicle (RV) in a non-canonical Wnt4 and FGF8 signaling dependent process [23-26]. Patterning and morphogenesis of the renal vesicle generates a comma-shaped, then an S-shaped body. At this stage, proximally, early podocyte development is clearly evident in the developing Bowman's capsule; distally, the connecting segment fuses the S-shaped body with the adjacent collecting duct, establishing a patent luminal interconnection. Developmental genetic studies in the mouse demonstrate a large number of signaling pathways (including Wnt, Fgf and Notch family members), and transcriptional regulatory factors (including Six1/2, Hox11 paralogs, Osr1, Sall1, Wt1, Etv4/5, Lhx1, Pax2, Hnf1b, Brn1*)* control the specification and maintenance of progenitor compartments and subsequent steps in the differentiation of nephron structures [4-9]. Analysis of CAKUT patients indicates that many of these genes are also critical in human kidney development [27].

GUDMAP has significantly enabled kidney research, a major focus of early GUDMAP funding. Transcriptional profiling and *in situ* expression studies generated large gene expression datasets that were annotated to developing kidney anatomy, while a variety of approaches were used to create genetically modified mouse strains to facilitate kidney research. The combined result is an annotated, high quality, two-dimensional molecular anatomy for the developing mouse kidney. The (b)(6) laboratory contributed to each component in the development of this resource [1, 28–37]. Our subsequent funding focused on the generation and validation of a variety of new mouse strains, consistent with a new emphasis on the development of the lower urogenital system. In addition, one year of supplementary funding for a human GUDMAP initiative enabled pioneering studies of human fetal kidney development. (See later.) Considering the current strengths of GUDMAP, the goals of the RFA, and our own interests and expertise, we propose to enhance and expand the GUDMAP kidney resource, extending our understanding of both mouse and human kidney development.

In thinking about the significance of our effort, we considered GUDMAP and, more broadly, current knowledge in the scientific literature to draw several conclusions. First, there is a need to incorporate more human data. Second, our understanding of kidney development is largely two-dimensional, whereas nephron structures have complex morphologies. Whether nephron morphogenesis is similar at different stages of mouse kidney development and how nephrogenic programs compare from mouse to human is not clear. Third, the GUDMAP database is centered on the normal mouse; analyzing mouse mutants that compromise nephron formation or patterning will expand and enhance the resource. Fourth, current data provides snapshots of specific stages that do not capture the fluid cellular dynamics of nephrogenesis. The absence of 3D and dynamic insight into the cellular events generating the mammalian nephron highlights a prominent deficiency in the literature.

Our proposal directly addresses these limitations within GUDMAP. (b)(4); (b)(6)

specimens as needed. (See letters of collaboration.) In **Aim 1,** we will develop high-resolution 3D views of mouse and human nephrogenesis. In the mouse, normal nephrogenesis will be compared to nephron development in selected mouse mutants. Comparative 3D atlases of nephron patterning and morphogenesis will be generated for mouse and human kidneys. In **Aim 2**, we will take advantage of improvements in imaging and organ culture approaches, and a bank of genetically modified mouse strains, to perform time lapse imaging of the nephron progenitor niche, and the formation, morphogenesis and patterning of the mouse nephron. Dynamic imaging studies will be extended to pluripotent stem cell (PSC)-derived models of human nephrogenesis. These studies will significantly enrich the GUDMAP resource. Further, considering recent advances in the directed development of PSCs into nephron-like structures, our data will provide a critical knowledge base and important benchmark for directed translational research.

b) Innovation

Aim 1: The first comprehensive 3D comparative atlas of mouse and human nephrogenesis, state-of-the art imaging, reconstruction and quantitative analysis of the nephrogenic program, multiplex spatial gene expression mapping

Aim 2: Modifications to imaging approaches that have enhanced live explant imaging, novel incorporation of genetic models into live cell studies, development of CNZ cultures for synchronous nephrogenesis from late-stage kidneys, live imaging of pluripotent stem cell models of human nephrogenesis

c) Research Plan

Overview of previous human kidney studies in GUDMAP

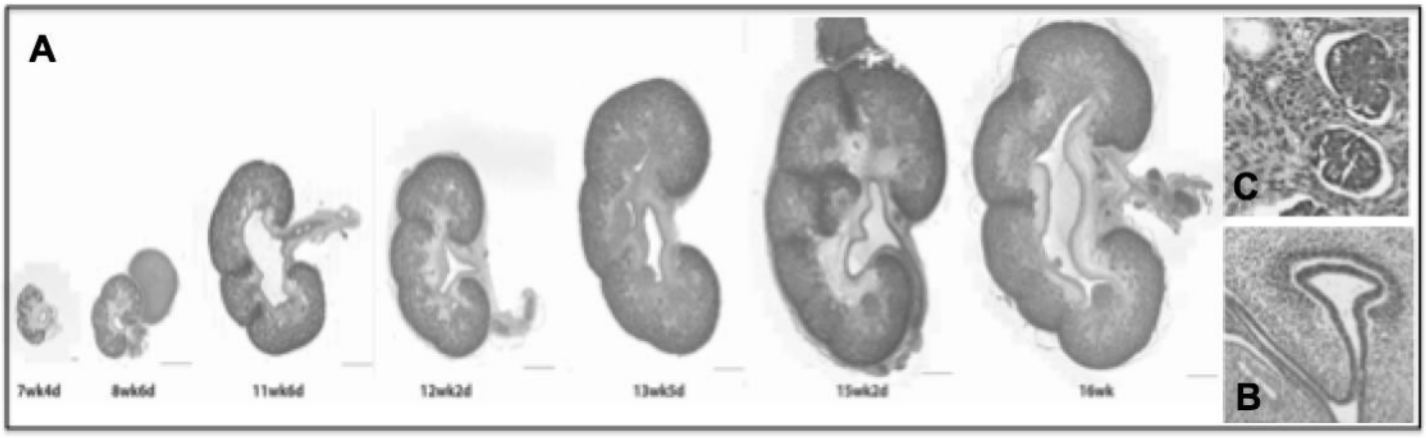

Figure 2. A) Atlas of human kidney development: 7 to 16 weeks. Zeiss Axioscan views of high-resolution image generated by tiling 10 or 20X image views. B) Ingrowth of ureteric bud in five-week human kidney. C) Zoom view of renal corpuscles in 16-week section in panel (A). Browser for GUDMAP viewing is being development by Edinburgh database coordinators.

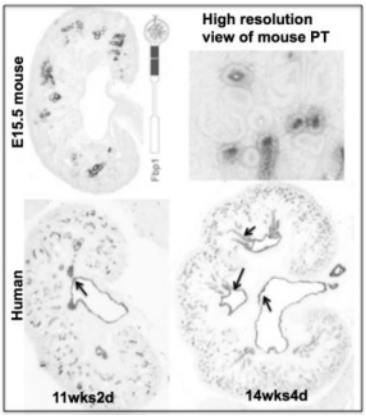

Figure 3. FBP1: mouse proximal tubule anchor gene shows additional ureteric epithelial expression in human fetal kidney (arrowed).

Our proposal focuses on generating high quality comparative datasets that introduce new components to GUDMAP's kidney resource: expanding both mouse and human kidney datasets with comparative 3D analyses of nephron formation and time-lapse imaging of cellular dynamics. A one-year supplement to our GUDMAP2 funding from 2013–2014 enabled our group to pilot a number of approaches critical for our project's success. First, we established methods for effectively procuring and shipping human fetal kidneys and validated those specimens through conventional histological analysis, section *in situ* hybridization (SISH), antibody-mediated immunofluorescence staining, RNA-seq and ChIP-seq.

In addition, extending our efforts beyond GUDMAP funding, we isolated and expanded nephron progenitors in human kidney samples, demonstrating viable cell culture from kidney specimens and supplying GUDMAP's first human kidney data. Highlights include: a histological atlas spanning the entire period of kidney development from five weeks to term (post 20 week specimens from (b)(6) Monash University), and ongoing annotation of this data in conjunction with the development of a browser application by the Edinburgh database to enable seamless viewing of the high content (~15 gigabyte) image files (**Figure 2**); comparative analysis by SISH of the expression of human counterparts of a mouse kidney anchor gene marker set, defined on the basis of highly restricted, cell type specific expression in the mouse kidney, were composite tiled-images generate a single, high-content image to the histological material; and RNA-seq and ChIP-seq studies comparing regulatory programs in mouse and human nephron progenitors.

These studies identified a number of the mouse anchor genes [38] displaying distinct expression in the human fetal kidney (**Figure 3**). Further, comparative ChIP-seq, RNA-seq and immuno-staining studies highlighted distinct regulatory interactions for two critical nephron progenitor regulators, Six1/SIX1 and Six2/SIX2, in mouse and human kidney development (**Figure 4**).

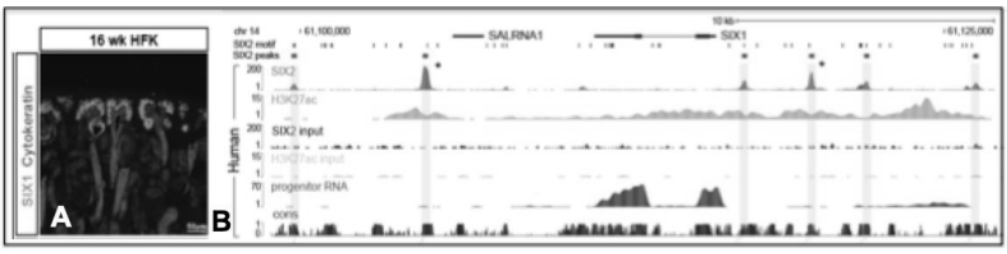

Figure 4. A) SIX1 is active in human but not mouse nephron progenitors after the onset of nephrogenesis. B) SIX1 activity correlates with SIX2 binding at active SIX1 enhancer modules (highlighted, confirmed by transgenic analysis).

(b)(4)

(b)(4); (b)(6)

Further, in the course of this work, we demonstrated that our documented expertise in a wide variety of important technical procedures essential to the success of the proposed studies translates from the mouse to the human kidney.

Specific Aim 1. To generate comparative 3D morphological maps of nephron progenitor and nephron patterning in the mouse and human kidney

SA 1a. Strategy: The current view of mammalian genitourinary development is largely two-dimensional (2D). Addition of 3D gene expression maps generated by optical projection tomography has provided significant new insights into development of the external genitalia (b)(6) group in GUDMAP2 round of funding). We will generate detailed 3D insights into mouse and human nephrogenesis through optical imaging and secondary image analysis generating a comparative morphological atlas for mouse and human kidney development.

SA 1b. Preliminary Data:
Our goal is compare human with mouse kidney development. To this end, we have built a large bank of more than 70 4% paraformaldehyde-fixed human kidney samples from 3.5–20 weeks of development, in part through a one-year pilot human GUDMAP (hGUDMAP) supplement to GUDMAP2. For most samples, we have wax embedded and cryopreserved material (stored at -80 °C). Sample quality has been assessed by standard histological analysis, section *in situ* hybridization (SISH) and immunolabeling with antibodies recognizing key cellular components. **Figures 2–4** illustrate examples of data transmitted to the Edinburgh editorial office. In

(b)(4); (b)(6)

Our goal is to generate comparative 3D maps of mouse and human kidney development. Our published studies and prior GUDMAP work demonstrate our expertise in mapping gene activity through conventional RNA *in situ* hybridization (whole-mount and section) and immunodetection-based approaches. Given the advantages of different imaging approaches for different types of analysis, we have been exploring a number of complementary approaches to obtain 3D views of the developing mouse and human kidney.

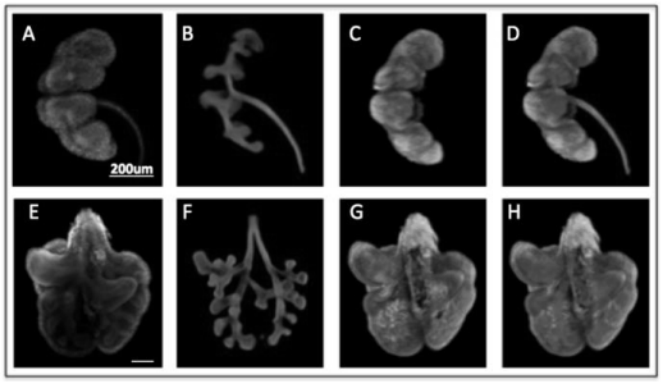

Figure 6. A and E), Zeiss Axiozoom views; B-D) and F-H), OPT reconstructed views. A-D) E12.5 mouse kidney and E-H) E12.5 mouse lung showing ureteric and lung epithelium (red, anti-cytokeratin immunolabeling) and Six2+ nephron progenitors and lung mesenchyme (white, anti-Six2 and anti-vimentin immunolabeling, respectively).

Some years ago, OPT emerged as a useful tool to obtain 3D views of relatively large biological specimens, consistent with imaging developing organ systems such as the kidney [39]. Typically, cell type specific mRNA (*in situ* hybridization) or protein (immunofluorescence labeling or enzymatic activity in the case of transgenic β-galactosidase reporters) activity is detected in whole-mount specimens cleared in benzyl alcohol/benzyl benzoate (BABB). The refractive index of BABB matches that of the tissue, minimizing the scattering of light passing through the sample. 3D volumetric projections

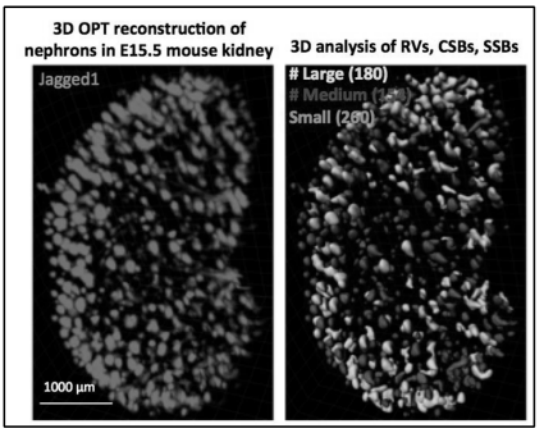

Figure 7. OPT reconstruction of Jag1+ nephron stages. Small: renal vesicle; medium: comma-shape/early S-shape body; large: late stage S-shape-body.

are reconstructed from the transmitted light collected from a variety of specimen orientations. As OPT microscopes can no longer be purchased, we collaborated with students within the USC Viterbi School of Engineering to assemble one. The microscope generates an optical magnification of 0.75–7.5x, and is configured with low light CCD cameras and five excitation and four emission filters that can operate in a broad range of typical fluorescence dyes (Alexa 430–633). Scans are generated at 0.3 degree intervals, rotating the specimen, and the resulting 1,080 images are reconstructed in nRecon (Bruker Instruments). **Figure 6** shows views of the developing mouse lung and kidney at e12.5 generated with our OPT microscope. This approach can rapidly generate excellent 3D relational data, though not at a single cell resolution. As an example of how OPT microscopy can be used to look at nephron forming processes, we immunostained the e15.5 mouse kidney to visualize Jag1; Jag1 expression is polarized to the distal renal vesicle (RV) and becomes restricted to the mid-section of the developing S-shaped body. Combining OPT microscopy with Imaris software enables quantitative spatial image analysis of this sample, mapping different sized Jag1-domains — and likely reflecting different stages of S-shape body development — to distinct regions of the developing kidney (**Figure 7).**

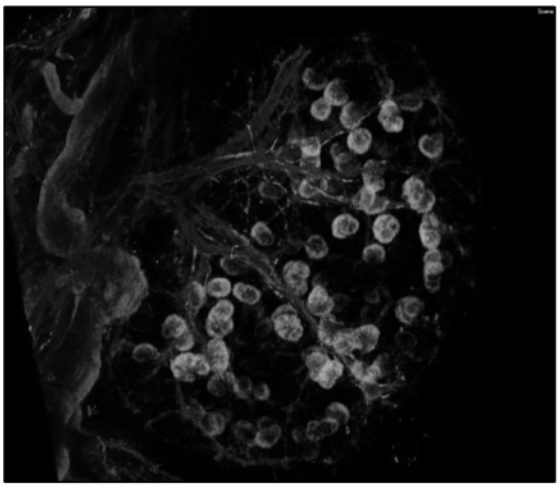

Figure 8. Reconstruction of tiled confocal Z-stacks through iDISCO-immunolabeled e15.5 mouse kidney highlighting podocytes (gold), vascular tree (red) and innervation (blue)

A number of recent protocols have described alternative approaches for rendering whole organs transparent to facilitate deep optical imaging. We have examined two of these: Clarity and iDISCO [40–43]. Both can give good results, but for speed, ease and reduced sample distortion, we currently favor iDISCO. We optimized iDISCO, which combines organ clearing with immunolabeling, to obtain detailed 3D views of the developing mouse urogenital anatomy. As one example, the entire e15.5 urogenital system was immunostained with antibodies to Nphs1 (nephrin, a podocyte marker), Pecam1 (a vascular marker) and Tubb3 (Tuj1, a neuron marker). **Figure 8** shows a rendering of a composite view of a complete tiled series of 10X images focusing on the kidney component of the urogenital sample; the images were collected on a Leica SP8 confocal microscope. These views highlight the close association between major vascular and nerve inputs and the initial organization of renal corpuscles, combining a "big-picture" overview of the developing anatomy with single cell resolution deep into the kidney sample.

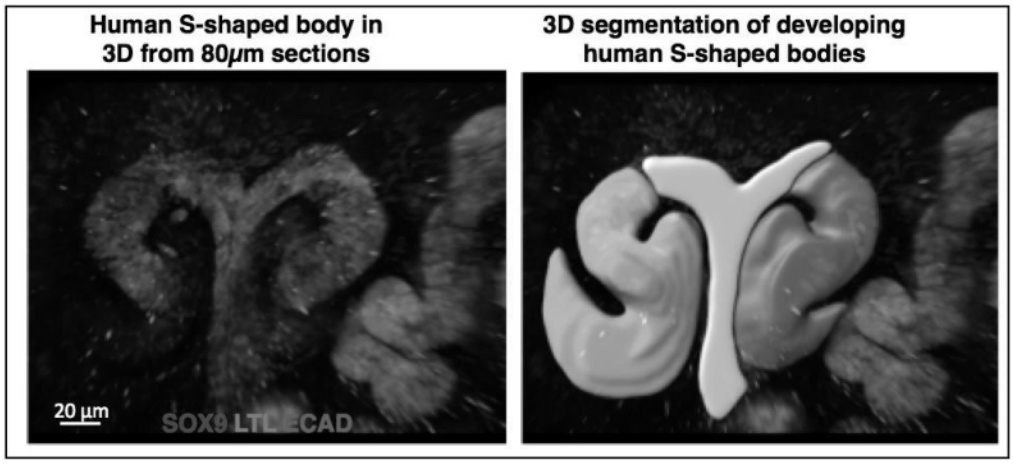

Figure 9. 80um tile-scan assembly of S-shape bodies with Imaris segmentation of the S-shaped bodies and adjoining collecting duct. Sox9 *and* Ecad/Cdh1 *demarcate distal nephron structures and tip of collecting duct.*

The iDISCO approach can provide an imaging platform for resolving the structure of developing nephrons in the mouse kidney with previously characterized antibodies. However, the preferred sample fixation protocol with methanol modifies target reactivity, rendering well-characterized antibodies ineffective in an unpredictable way. Further, the approach will require considerable optimization for equivalent studies of the

human kidney to generate comparative 3D analysis of the emerging molecular anatomy of forming nephrons, given the large range in sample size and limited tissue availability. Additional strategies that maximize information gathered from any one specimen will be most valuable.

To this end, we have been employing thick, frozen sections (80 µm), having determined that this thickness can incorporate the full structure of a mouse or human S-shaped body and capture an effective fluorescent signal through 100 µm of BABB cleared tissue. **Figure 9** shows an Amira (FEI software) reconstruction of tiled Z-series extending 80 µm into BABB-cleared 16-week human fetal kidney sections. Images were obtained on the Leica SP8 with a 20X, 1.0 NA objective imaging. We can visualize the complete S-shaped body attached to the ureteric epithelium; the most distal cells are Cdh1^{+}/Sox9^{+}. Imaris software enables segmentation and analysis of parameters, such as the volume of the S-shaped body or specific antibody highlighted domains.

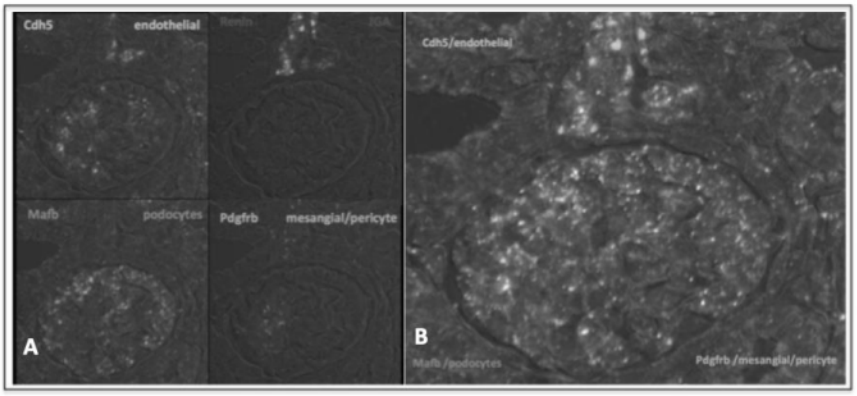

Figure 10. HCR multiplex fluorescent in situ *hybridization highlighting a renal corpuscle in a 16-week human fetal kidney section (10 µm) with indicated probes. A) Individual views. B) Composite view overlay onto bright-field image of*

Multiple labeling with well-characterized antibodies is certainly the simplest approach to visualizing the emerging cellular complexity of the developing nephron. However, there is no guarantee of the availability of antibodies with suitable avidity and specificity, and species overlap confounds the use of primary antibodies recognizing distinct proteins of interest. We also expect new genes of interest to emerge over the course of funding — hence, having a more "generic" approach to gene expression mapping will be valuable. Recent reports have documented a sensitive single-molecule RNA *in situ* hybridization procedure: hybridization chain reaction (HCR) [44,45], which enables simultaneous expression mapping of multiple genes by section and whole-mount *in situ* hybridization (SISH and WISH, respectively). To examine the utility of this procedure on our human fetal kidney tissue bank, we performed HCR to simultaneously visualize the renal corpuscle and juxtaglomerular apparatus. **Figure 10** demonstrates the high specificity and sensitivity of multiplex HCR, distinguishing closely associated podocytes (MAFB), vascular endothelium (CDH5), glomerular mesangial cells and extraglomerular pericytes (PDGFRB), and secretory juxtaglomerular cells (REN1).

SA 1c. Experimental Plan:

Initially, we will focus on generating a broad overlapping framework of the nephrogenic program at different stages of mouse and human kidney development, using, wherever possible, antibodies recognizing key protein markers of cell types of interest to visualize the emerging pattern. Antibodies have been selected that recognize epitopes conserved between the mouse and human protein target. We have optimized protocols with a number of antibody combinations on 10 µm mouse and human frozen sections. (See later.) We will collect data in parallel for the mouse and human kidney with the goal of generating three-dimensional views and associated quantitative metrics of the transition of the nephron progenitor population to a late-stage S-shaped body fused to the collecting duct network, completing the data collection at one kidney stage (e.g., 16-week human kidney) before moving to another selected stage. In this way, GUDMAP viewers can profit from a comprehensive analysis of a selected stage without requiring completion of the project.

NP	PTA	RV	CSB	SSB
SIX2^{+}	SIX2$^{+}_{(p)}$	Wt1$^{+}_{(p)}$	WT1$^{+}_{(p)}$	Wt1$^{+}_{(p)}$
CITED1^{+}	CITED1^{-}	JAG1$^{+}_{(d)}$	JAG1$^{+}_{(d)}$	JAG1$^{+}_{(m)}$
	JAG1$^{+}_{(d)}$	LEF1$^{+}_{(d)}$	LEF1$^{+}_{(d)}$	LEF1$^{+}_{(d)}$
				CDH1$^{+}_{(d)}$

Table 1. Stage-specific markers highlighting the development and patterning of the nephron (p, proximal; m, medial; d, distal)

The transition of nephron progenitors to a pretublar aggregate (PTA), renal vesicle (RV), comma (CSB) and S-shaped body (SSB) is a fluid process. Highlighting specific stages of nephrogenesis in this developmental program will be determined, to some degree, by the developmental age of the donor. For example, e12.5 mouse kidneys have no SSBs. The relative "stability" of a particular stage in the nephron-forming program will be another variable. For example, in the mouse kidney, the CSB is a relatively

short-lived stage in the RV to SSB transition. We will aim to generate a minimum of 10 examples of each stage within a given kidney sample with these provisos in mind. The actual distinction of stages will likely require actual 3D data collection, but there are several molecular, cellular and anatomical organizational features that can be recognized from current analysis of mouse kidney development that are highlighted in **Table 1**. **Figure 11** shows comparable views of mouse and human kidney sections highlighting antibodies recognizing NPs and SSB organization in mouse and human fetal kidney sections.

Figure 11. S-shape body in mouse and human kidney sections

Given the wealth of GUDMAP data around e15.5 (TS23) and our optimization of whole-mount and section material at this stage, we will first examine the e15.5 mouse kidney. Additional stages in order of priority will be: P2 and P4 (cessation of new nephrogenesis and last wave of forming nephrons) [46,47]; P0 (early postnatal kidney, which represents a marked shift in the rate of nephron formation) [48]; and e12.5 and e13.5 (first formation of renal vesicles and S-shaped bodies, which is most reflective of the nephrogenesis observed in organ explant culture). Human data will focus first on 16-week samples, with which we have the most experience, and a good bank of samples validated on 10 µm sections. Later analysis will extend to 20 weeks and potentially to later stages, depending upon the specimens available from the GUDMAP-funded tissue resource. Earlier analysis will center on 12 weeks, eight weeks, and one-week intervals to the onset of kidney development at four weeks. Working at the earliest stage will be the most difficult due to the limited accessibility of material. (b)(4)

(b)(4)

As highlighted earlier, we use tiled confocal imaging to generate 3D images and computational reconstructions on 80 µm sections. The procedures and validated cross-reactive antibodies are in place for ALL protein targets in **Table 1,** except for the absence of a working antibody against mouse Cited1. Here, we can use the previously validated Cited1$^{RFP\text{-}CRERT2}$ allele generated in our earlier GUDMAP efforts. At each stage, we will segment 3D structures and use Imaris and visual analysis to obtain metrics for the length (proximal-distal), volume, orientation (relative to the ureteric epithelium), cell number, general features of epithelial cell organization (columnar, squamous) and epithelial transitioning (proximal nephron podocyte forming region). Initial analysis of PTAs suggests the human renal primordium is larger from the outset. We will also examine vascular invasion with anti-Cdh5 antibodies, given the co-development of vascular structures. To obtain more global information about the spatial distribution at a given stage, we will use tiled image scans and develop OPT methods that are particularly well-suited to recognizing shapes and generating volumes for specific domains highlighted by regional antibody staining. With data from the high-resolution analysis, we can readily identify comparable structures at each stage in OPT samples. In the mouse kidney, this can even been done by simple whole-mount staining, as cortical penetration is not an issue even at the latest stages. Further, as shown earlier, we can also employ clearing approaches, such as iDISCO or CLARITY, which are both working in the laboratory, depending on the current state-of-the-art and limitations of these procedures. We will initially focus on mouse kidney samples to develop the “best fit” comparison with human tissue section data.

We will also use mouse transgenic and mouse mutant analysis to obtain critical information on the nephron patterning process. Through our previous GUDMAP funding, we developed a *Lnfg*$^{GFP\text{-}CREERT2}$ transgenic line. This has been preliminarily characterized as showing *Lnfg*, which encodes a modifier of Notch receptor activity, specifically activated early in the RV, showing a similar pattern to the Notch ligand Jag1 (gudmap.org/Docs/Mouse_Strains/17_Lfng_allele_characterisation_011812.pdf). We will carefully map transgene activity relative to Jag1. We will label Lnfg+ cells (Lnfg$^{nuc\text{-}tagRFP\text{-}CREERT2}$ x R26$^{mT/mG}$/R26$^{mT/mG}$) with a pulse of tamoxifen (2 mg/30 g body weight) to visualize the relationship amongst labeled cells (myristoylated-GFP), the parent domain (nuclear-tagRFP and CRE), Jag1 and Cdh1 — at 12, 24 and 36 hours following an e15.5 TM injection. In our 10 µm section studies, we have observed Jag1/Lnfg activation in the distal RV prior to the onset of Cdh1. However, by the SSB stage, Jag1/Lnfg are confined to cells in the mid-section of the

SSB. This raises two possibilities: (1) As in patterning of the ventral neural tube, initial gene expression states do not remain fixed, but change over time. (2) New cells, added to the RV over time, establish a Cdh1+ distal domain. In the former, we would expect that myristoylated-GFP (mG) labeled cells will distribute all the way to the connection of the S-shaped body with the ureteric epithelium in some but not all S-shaped bodies, depending on the developmental stage labeled. In the latter model, there would always be a close concordance between labeled cells and the Lfng+ domain in SSBs.

We will also use the Lnfg$^{nuc\text{-}tagRFP\text{-}CREERT2}$ line to address the role of Notch and Wnt signaling in patterning the nephron. Work in the (b)(4); (b)(6) , in which we participated [49] and in the (b)(4); (b)(6) by (b)(6) (b)(6) has invoked opposing roles for Notch and Wnt/PI3K signaling in proximalizing and distalizing the developing nephron precursor. We will use the Lnfg$^{nuc\text{-}tagRFP\text{-}CREERT2}$ line to activate canonical Wnt signaling — non-cell-autonomously by activating a CRE-dependent Wnt1-GFP fusion protein at the R26 locus (a line previously employed in nephron progenitor induction analysis [18]), and cell-autonomously by conditionally removing the GSK-destabilizing domain of β-catenin (enabling β-catenin co-activation of Lef/Tcf transcriptional complexes) [51]. We will employ the same marker sets in Table 1 in 80 µm sections and whole cleared kidneys together with anti-GFP antibodies and Wnt-pathway reporters (Lef1) to analyze any changes in cell fate and patterning of the developing nephrons. We will perform similar experiments activating conditional Notch signaling though CRE-dependent production of the intracellular transcriptional regulatory domain in a R26^{NICD} strain [52]. Importantly, all strains have been verified as to their activities, and all are available in the (b)(6) laboratory. We anticipate that the first two years will provide a general framework for mouse and human nephrogenesis. The remaining three years will focus on the genetic studies addressing the perturbation of this pattern by modifying patterning signals. In the later part of the funding period, we will also likely explore multiplex HCR approaches to selected stages, determined by the outcome of multistage nephron patterning studies. This will enable us to generate finer relational mapping of patterning in the transition of renal vesicle to S-shape body, anticipating larger gene sets of interest emerging from GUDMAP and other kidney studies. Mapping novel genes relative to genes indicated in Table 1 through multiplex HCR will relate *in situ* and antibody datasets. (b)(4); (b)(6)

(b)(4); (b)(6)

SA 1d. Problems, alternatives and benchmarks

This Aim builds upon 2D datasets that provide some initial concept of the structures. Importantly, though our focus is 3D analysis, we will be adding novel 2D data as a matter of course. We do not anticipate any problems in the immunostaining procedures, and the strategy utilizes different approaches to collect 3D image data (OPT and tiling of confocal image scans), recognizing the distinct value of lower resolution quantitative metrics readily gained through OPT versus highly detailed individual 3D structural views better suited to confocal reconstructions. As we point out, iDISCO is simplest, and the quality is optimal, with antigens that are insensitive to methanol fixation; here, methods are improving rapidly. We anticipate incorporating any new procedures that improve the depth of tissue immunostaining, data collection and cellular resolution, recognizing physical limits such as the working distance of the objective lens. In genetic strategies, though the outcomes have not been determined, all strains are available, and we are confident each will be informative. If not, there are several other approaches. We can replicate our earlier study with the (b)(4); (b)(6) conditionally removing Notch2 from forming nephrons with a Six2^{TGC} allele [12]. Likely, the biggest challenge will be in rendering and generating image views that capture the data in the most effective way for the benefit of GUDMAP users. (b)(4); (b)(6)

(b)(4); (b)(6)

Specific Aim 2. To generate high-resolution dynamic views of mouse and human kidney development utilizing genetically modified mouse strains and genetically engineered human pluripotent stem cell lines

SA 2a. Strategy: Time lapse imaging of the ureteric epithelium branching in kidney organ culture has provided important new insights into progenitor cell dynamics in the development of the collecting duct. This Aim focuses on visualizing the cellular dynamics underlying mammalian nephrogenesis through live cell imaging. The data will complement studies in Aim1 that incorporate selected mutants into live cell imaging studies. Recent advances in genome editing and directed differentiation of PSCs will enable imaging of human models of nephrogenesis.

SA 2b. Preliminary Data: Kidney explant cultures have been optimized for visualizing development on either Zeiss 780 or Leica SP8 inverted confocal microscopes. The former is better suited for longer term (multiday imaging), with a stage fully enclosed in a heated incubator chamber. The Leica SP8 uses a stage-mounted incubated chamber that enables good development over a 24–36 hour period. The Leica SP8 is one of the most sophisticated confocal microscopes available, equipped with pulsed white-light lasers (WLL) to reduce photo-damage and photo-bleaching. Hybrid Detectors (HyD) allow effective use of the WLL laser in the 0.1–10% power range, which compares favorably with the 10–25% laser power range for imaging with PMT detectors. Lower laser power translates into more extensive imaging ability. In one example, we have imaged two fluorescent proteins every five minutes over a 24 hour period in 1.5 µm Z-steps extending through ~30 µm using a HC PL APO CS2 63x 1.40 oil objective with 488 nm and 554 nm excitation.

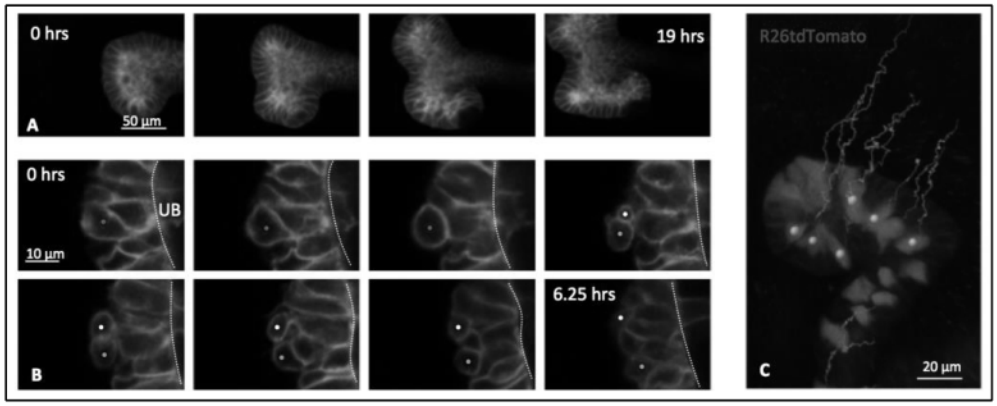

Figure 12. Dynamic imaging of kidney explant morphogenesis. A) Hoxb7-venus ureteric bud branching. B) Tamoxifen induced Six2$^{GC/+;}$ R26mT/mG reporter highlighting cell division event in nephron progenitors. C) Wnt11mCiresCE/+; R26 tdt reporter showing Imaris tracking of tip cell migration over 10 hours of culture.

In addition to improvements in the microscopes themselves, we have optimized imaging by dispensing with filter bound cultures, mounting specimens in Matrigel under a coverslip, growing cultures in low fluorescence Gibco Fluorobrite medium and performing direct imaging with a variety of immersion lenses through optical quality glass, minimizing aberration introduced by other materials. Only a #0 coverslip with a 0.085–0.13 mm thickness separates the kidney culture in the MatTek plate from the objectives. As an example of the development and quality of image views, **Figure 12A** shows progressive 20x objective views over a 19-hour period of a single branching event initiated by ureteric epithelial tip cells. **Figure 12B** highlights a single cell division made by a Six2+ nephron progenitor tracked by Imaris software. **Figure 12C** uses Imaris software to track the migratory trajectory of individual cells within the ureteric branch tips over a 10-hour culture period. This enables the measurement of various parameters, such as relative speed of tip versus stalk cell migration (0.05 versus 0.04 µm/sec), displacement and distance travelled. Each model uses genetic strains generated in or acquired by the laboratory.

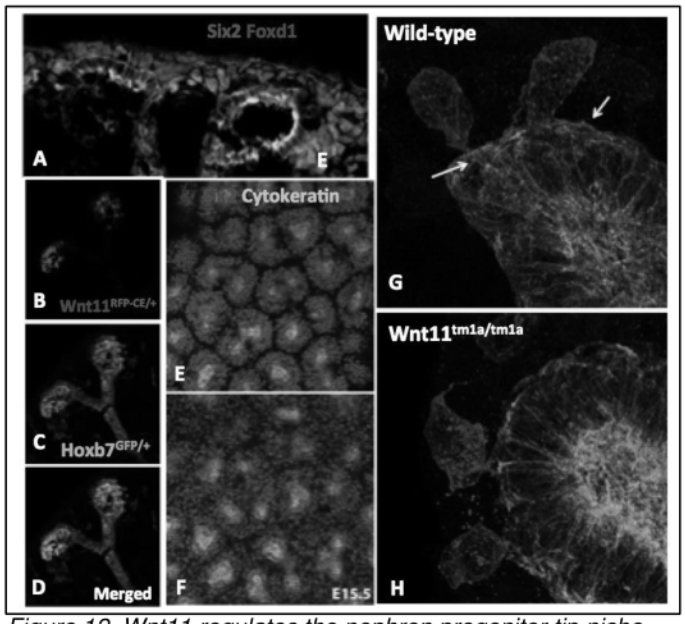

Figure 12. Wnt11 regulates the nephron progenitor tip niche

We will use these platforms to specifically analyze cellular events within the nephrogenic compartment. However, given the importance of interactions between nephron progenitors and adjacent collecting duct progenitors, the Hoxb7^{venus} mouse strain [53] will be included in crosses to highlight the branching ureteric network (**Figure 12A**).

Our goal is to obtain dynamic insights into key developmental events, then to examine mutants where these events are perturbed. As one example, Six2+

nephron progenitors normally form a tight, contiguous capping mesenchyme immediately abutting the Wnt11 branch-tip domain, while Foxd1+ interstitial progenitors are sandwiched between Six2 cells and the developing kidney capsule (**Figure 13A-D**). In wildtype kidneys, Six2+ cells elongate at right angles to the adjacent ureteric epithelium, send out long cytoplasmic processes to contact the ureteric tip and, in live imaging, move in close contact with the migrating tip (**Figure 13G**). In contrast, mutants lacking Wnt11, a non-canonical Wnt signal secreted by epithelial cells at the branch tips, show a more widely dispersed Six2+ cap population with intermingling Foxd1+ cells (**Figure 13E, F**). Further, Six2+ nephron progenitors adopt a more rounded morphology, and tip directed cytoplasmic extensions are reduced (**Figure 13H**). At birth, *Wnt11* mutants display a premature depletion of nephron progenitors, and the adult glomerular count is halved. These observations suggest that there are interesting migratory behaviors in the nephron progenitor niche controlled by Wnt11 signaling.

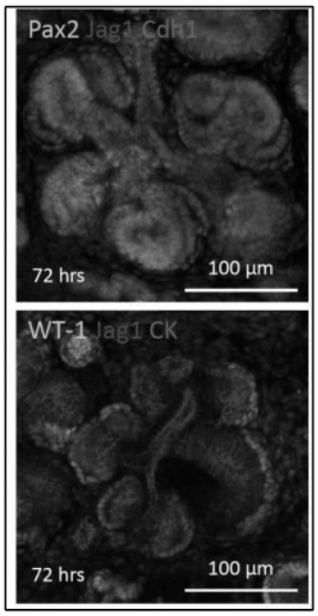

Figure 14. CNZ seeded nephrogenesis in vitro

To complement dynamic analysis of early organ cultures, we have developed a platform for rapid, synchronous development of nephrons that can be scaled to a multiwell format. In brief, neonatal mouse kidneys (P0) are collected, the capsule removed and an enriched cortical nephrogenic zone (CNZ) isolated by a brief (15 minutes at 37 °C) digestion with collagenase A and pancreatin. With gentle shaking (450 rpm on a Nutator), the nephrogenic zone loosens and "falls off" of the underlying epithelial network. After fetal bovine serum-mediated enzymatic inactivation, a single cell suspension is obtained by passing the cell extract through a cell strainer. One litter (20 kidneys) yields around 20–25 million cells. Approximately 125,000 cells are seeded into each well in a 96-well low adhesion microtiter plate (we have tested starting cell numbers ranging between 50,000 to 300,000 to determine this optimum number), cells are pelleted by spinning at 300 g for 5 minutes, and pellets are incubated at 37 °C overnight in culture medium with 10 µM Y27632 Rho-kinase inhibitor. The next day, the small sphere can be transferred to kidney explant culture, where it undergoes spontaneous nephrogenesis, likely triggered by ureteric epithelial cells in the culture. **Figure 14** shows examples of nephrogenesis in CNZ cultures. This model complements early explant models. The ability to simultaneously seed many cultures facilitates optimizing conditions (e.g., culture media and associated matrices) prior to extensive imaging. The approach also enables the incorporation of existing mouse mutants and cell reporters into the *in vitro* assay.

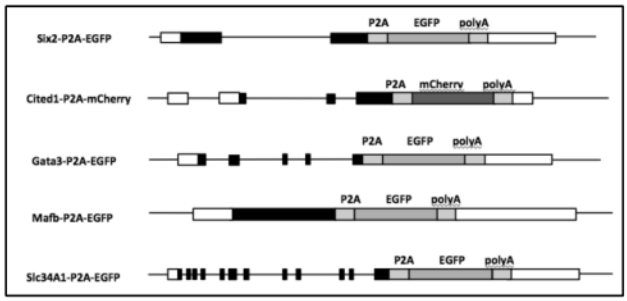

Figure 15. Predicted gene structures produced by CRISPR/CAS9 HDR editing in hESC9 cells

We anticipate transitioning dynamic mouse kidney imaging studies to dynamic analysis of human kidney development in the course of funding. Recently, several groups have demonstrated human kidney-like structures generated from PSCs [54–58]. We have generated early nephron-like structures from ESC cultures, using the Taguchi protocol [11]. Anticipating the importance of genome engineering in genetically configuring hPSCs for *in vitro* organoid analysis of human development, our center has invested in a stem cell engineering facility that generates designer models through CAS9 gene editing. This strategy enables the engineering of indel-generated deletion mutants through non-homologous end joining repair processes, replicating genetic mutant models or targeted knock-in (KI) of cassettes encoding fluorescent proteins through homologous donor repair (HDR). To date, we have used HDR to target tandem Tomato (tdT) and GFP to the CITED1 and SIX2 loci, respectively, generating a dual-tagged HuESC9 [59] nephron progenitor reporter cell line. Additional reporters demarcating the collecting duct (KI to GATA3) and differentiating nephron components (KI to MAFB: podocytes; KI to SLC34a1: proximal tubule) will be available shortly (**Figure 15**).

SA 2c. Experimental Plan:

Our live imaging studies will focus on three key aspects of the nephrogenic program: cell dynamics within the nephron progenitor niche, formation of the RV, and morphogenesis and patterning of the RV to generate an

SSB. Primary organ explants, CNZ-seeded nephrogenic cultures and PSC-derived organoids will provide overlapping insights into these developmental events in mouse and human kidney models.

Cell dynamics in the mouse nephron progenitor niche
We will continue our analysis of nephron progenitor movements in relation to Wnt11 signaling through live cell imaging in the enhanced organ culture system described earlier. We will focus on sporadic labeling of the Six2+ progenitor population (crossing $Six2^{CE/+}$ [12] to either $R26^{mTmG/mT/mG}$ [60] or $R26^{tdT/tdT}$ [61] reporters) in $Wnt11^{+/+}$ or $Wnt11^{-/-}$ backgrounds, where the ureteric epithelium is visualized by the $Hoxb7^{venus}$ transgene. We have "built" the crosses. Importantly, as Wnt11 mutant and all reporter alleles are homozygous viable, we can efficiently produce informative organ explants, despite requiring multiple alleles for optimum analysis. Tamoxifen (CRE activation *in vivo*) or 40H-tamoxifen (CRE activation *in vitro*) dependent sporadic labeling of progenitor cells facilitates the resolution of key events, such as the utereric tip orientated membrane extensions that are masked if the entire progenitor pool is labeled. Imaris tracking will enable recording of information on the movements (direction, speed), shape (round, elongated) and membrane process formation relative to the "anchor" — the branching ureteric tip. Preliminary live imaging suggests that progenitors positioned several cell diameters from a bud-tip Wnt11 source undergo extensive random migration, even crossing to neighboring progenitor domains. In contrast, those within 2–3 cell diameters migrate with the tips, continuously sending processes to the tip that maintain extended tip contact. We have also used the Six2 enhancer identified in the laboratory to generate mice ectopically activating Wnt11 throughout the progenitor domain; we will be screening these shortly for ectopic Wnt11 activity. It will be interesting to contrast normal progenitor movements in relation to a localized Wnt11 source to those in transgenics with a more uniform Wnt11 distribution throughout the progenitor domain.

Cell dynamics in mouse renal vesicle formation in organ explant
To visualize RV formation, we will label the entire Six2 progenitor pool or sporadic nephron progenitors, as above. Initially, we will track events in wildtype kidney explants. We are particularly interested in visualizing and measuring cellular parameters (number of cells, shape, polarity) in the mesenchymal to epithelial transition that generates the RV. Sporadic labeling will help distinguish any relationship between a cell's position in the Six2 capping mesenchyme and its contribution to the first waves of nephrogenesis. Opposing models argue for cells closest to either the inductive ureteric epithelium or the FAT4 producing interstitial progenitors as the targets of primary inductive events [18,22,23,62]. In Six2 mutants, nephron progenitors commit prematurely, forming a small cluster of ectopic (above the ureteric tip) RVs by e12.5 [16]. Interestingly, progenitors generate discrete, segregated RVs similar in size to normal renal vesicles. These observations suggest self-organizing, size regulating processes may direct this critical mesenchymal to epithelial transition. Wnt4 mutants show molecular hallmarks (transcriptional activation of Fgf8, Pax8, Wnt4) indicative of PTA formation [23]. However, PTAs fail to transition to RVs, though their actual fate is uncertain; live imaging studies can potentially resolve this issue.

Cell dynamics and patterning of the RV to s-shaped body transition in organ explant
Extending the kidney explant culture period, using the several labeling strategies discussed, can also provide a visual insight into the transition of RVs to SSBs. To more specifically examine the emergence of pattern in a strategy that complements studies in Specific Aim 1, we can use the $Lnfg^{nuc\text{-}tagRFP\text{-}CREERT2}$ allele with an appropriate reporter to visualize sporadically labeled cells in the mid-distal segment. The nuc-tagRFP allele is not readily detectable by native fluorescence. However, we have recently acquired a published $Lnfg^{GFP}$ allele that displays strong fluorescence in the kidney that will likely be detected in live culture [63]. This line will enhance the analysis of Six2 progenitor descendants (red) while also enabling the viewing of distinct regional patterning (green). In separate crosses with the $Lnfg^{nuc\text{-}tagRFP\text{-}CREERT2}$ strain, the line will also allow for tracking of ongoing ($Lnfg^{GFP}$, green) and historic Lnfg activity in descendant cells following tamoxifen-mediated activation of a $R26^{tdT}$ reporter (red). Further, the goal in Aim1 to examine Notch/Wnt pathway modulation in nephron patterning would be significantly enhanced by these live imaging studies. However, we cannot use the same genetic tool (CRE) to broadly label the forming nephron and, at the same time, discretely modify a subset of cells in the Lnfg population. Some years ago, we generated a $Pax8^{YFP}$ Bac transgenic that showed readily detectable YFP activity in forming renal vesicles [cover image reference 1]. Pax8 is broadly present throughout renal vesicle derivatives. We are currently resuscitating this strain to determine its usefulness as another direct non-CRE-dependent reporter of nephrogenesis.

Cell dynamics in CNZ and PSC-derived organoid cultures

All the above analyses focus on the earliest nephron forming events, as diffusion limited oxygen/nutrient uptake restricts culture to small early explants. However, our development of CNZ-derived nephron cultures from P0 kidneys offers the potential for generating multiple nephrons under different conditions while harnessing the precise genetic combinations of the neonatal donor kidney. We anticipate first assessing nephrogenesis using general live-labeling approaches: $Six2^{TGC/+}$; $R26^{tdt/+}$ labeling all nephron progenitors and their descendants and $Wnt4^{CE/+;}$ $R26^{tdT}$ activation with 4OH-tamoxifen labeling all nephron stages from pretubular aggregate. Either can be potentially supplemented with $Lnfg^{GFP}$ as a direct marker for polarity and patterning. With data from Aim1, we will have a good sense of potential differences in nephrogenesis between early and late mouse kidney stages, and expected differences in live CNZ explant imaging. The CNZ approach also lends itself to drug-mediated modification of signaling pathways, a simple complementary approach to the genetic mutant models discussed [50].

We anticipate that the first three years of funding will focus on mouse directed studies of nephrogenesis in normal and mutant kidney cultures. In this period, we will optimize strategies for human kidney nephrogenesis and assess the value of the genetically engineered fluorescent reporters in human ESC-derived kidney organoid culture or through chimeric CNZ cultures seeded with human nephron forming cell types. The final two years will focus on live imaging of nephrogenesis in these human models.

SA 2D. Problems, alternatives and benchmarks

Culture in any form will compromise normal developmental programs. The flattening of kidney cultures inherent in all protocols may distort *in vivo* processes. We have to carefully benchmark dynamic imaging studies to expectations generated through high-resolution, 3D analyzes of fixed material in Aim1. Our approach visualizes key cell types by utilizing a number of genetic strains, with which we (and others) have worked productively for years. The untested lines, while adding value, are not absolutely essential to our aims. Kaede labeling [64] is a widely used, flexible cell labeling approach that could offer broad utility in maximizing the usefulness of a single allele, particularly important for human PSC-derived nephrogenesis. A 405 nm laser photo-converts a GFP variant to a photo-stable red fluorescent. By precisely directing the laser, cells can be labeled at precise positions, and their descendants tracked as long as the photo-converted protein persists. An alternative to continually generating genetic crosses for mouse CNZ culture would be to generate iPSCs in our stem cell core from appropriately genetically configured embryo-derived fibroblasts. These could be used to replicate genetic outcomes in iPSC-derived, kidney organoid cultures. With more evidence that organoid-derived nephrogenesis closely parallels normal nephrogenesis, this could be a useful approach. We can potentially expand on the CNZ-derived cultures. Mouse nephron progenitors can be expanded several thousand fold while retaining nephrogenic potential in newly identified culture media from the (b)(4); (b)(6) laboratory [65], a result we have replicated in collaboration with (b)(6) (b)(4) (b)(4)

Potentially, direct progenitor expansion can generate very large numbers of nephron progenitors for a variety of experiments and even direct genetic modification of those progenitors. Practically, the expense of the current medium ($7,000/liter) limits this approach at present. Further, there is uncertainty about the “normality” of nephrogenesis from induction of purified nephron progenitors versus the CNZ-enriched fractions that harbor other progenitor cell types. This will be addressed. As an alternative to genetic approaches to modify Wnt and Notch signaling, chemical genetics with pathway inhibitors offer an alternative, productively employed in recent studies by (b)(6) in organ explant models of nephrogenesis [50]. Finally, imaging approaches and image analysis are moving fast. We have developed a robust platform, but there is always room for improvement. Professor Fraser will keep us abreast of new imaging approaches, and we are excited about two-photon light sheet approaches to rapid long-term live imaging being developed in his laboratory. (b)(6) s an acknowledged expert on live imaging and 2 photon confocal imaging. (b)(6) (b)(6) (b)(4) Further, the advice of (b)(6) on data-driven alternatives for display and analysis will complement our own expertise with Imaris, and a variety of other rendering and imaging software.

Vertebrate Animals

(b)(4)

Tail Clipping and Ear punch to maintain transgenic lines: To mark specific progeny from each transgenic line, it will be necessary to remove small biopsies of tail samples for DNA extract from mice no older than 25 days and to mark the mice by ear punch. 1-3 pieces of less than 1 mm2 area will be removed from an ear using an ear punch. Very little impairment will occur with these procedures. Tail biopsies and ear punch will be performed in bio-safety hood. Tail biopsies and ear punch are not generally performed under anesthesia. To maintain lines as active breeding colonies we expect to use sacrifice where only 50% of progeny are carriers we expect to use 1-2,000 mice

Matings and sacrifice to obtain embryonic kidney samples: the appropriate matings will be set up and pregnant dams euthanized by CO2 inhalation (primary) and cervical dislocation (secondary) at the appropriate stage to obtain kidneys and isolate kidney progenitors. All projects will require the sacrifice of strains carrying transgenic alleles and to obtain wild-type kidney samples for control experiments. We expect to sacrifice on average 500-1,000 mice per annum.

2) The mouse is chosen for the genetic abilities and as an animal system that has already been used extensively for the assays within the proposal. Although much of the proposal utilizes in vitro test systems, we need to work out whether these accurately reflect in vivo development by direct comparison of in vivo and in vitro generated cell types, and we need to use mouse assays to assess engineered kidney cells. Consequently, the mouse is the appropriate model and we have no other alternative but ultimately our approaches are designed to actually reduce the burden of live animal work.

3) Veterinary care is provided by the (b)(6) (b)(6) all facilities overseen by USC-DAR the have full AAALAC accreditation. The animal housing area for the (b)(4); (b)(6) independently ventilated micro-isolator cages is housed in a state-of-the art, pathogen free barrier facility within the vivarium in the basement of the (b)(4) (b)(4) Surgical suites with flow hoods are positioned adjacent to the animal holding rooms. The facility is monitored by attending veterinarians and veterinary technicians together with skilled animal technicians. Veterinary care is available via weekly routine rounds and a rotating on-call schedule. Procedures in progress at the time of rounds are observed and cage-based medical records are reviewed to assure adequate and timely administration of pain relieving drugs and palliative provisions. The veterinarians/veterinary technicians work directly with the animal care staff on programs designed to reduce the prevalence of infectious disease, the monitoring of animal health, and the diagnosis and treatment of illness and disease. The veterinary staff reserves the right to intervene in all cases in which animals are experiencing unalleviated pain or distress that has not been justified in the protocol as necessary to accomplish scientific objectives and for which provisions for palliative care have not been provided.

4) All surgical manipulation will use (90-120mg Ketamine)/kg; 10 mg Xylazine/kg) as the anesthetic. The surgical procedures are straight -forward and relatively non-invasive. Our observation, based on many years of experience, is that mice recover extremely rapidly following surgery. Post surgery the animals will be monitored continually for signs of distress or discomfort. Buprenorphine (0.05-0.1 mg/kg) will be administered subcutaneously immediately post surgery upon recovery demonstrated by the ability to achieve sternal recumbency and then every 12 hours, for a minimum of 48 hours post surgery. If there is any sign of distress, animals will be sacrificed immediately.

5) Euthanasia in all instances will be terminal inhalation of carbon dioxide and secondary euthanasia by cervical dislocation. This method of euthanasia is consistent with the AVMA Guidelines on Euthanasia updated 05/08/2013.

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of the Freedom of Information and Privacy Act

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October 22, 2015

(b)(6)

Keck School of Medicine of the University of Southern California
1425 San Pablo Street
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(b)(4)

(b)(6)

(b)(4)

Sincerely,

(b)(6)

(b)(6)

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Contact PD/PI: (b)(6)

Resource Sharing Plan

(b)(4); (b)(6)