National Diabetes and Digestive and Kidney Diseases (NIDDK) Advisory Council Meeting

Division of Kidney, Urologic, and Hematologic Diseases Advisory Subcouncil Meeting
September 10, 2021

Advisory Council KUH Subcommittee Members:

Dr. Linda Baker (UT Southwestern) (Ad Hoc)
Dr. Iain Drummond (Mount Desert Island Biological Laboratory)
Ms. Dawn Edwards (American Association of Kidney Patients) (Subject Matter Expert)
Dr. Mark Nelson (University of Vermont)
Dr. Keith Norris (University of California at Los Angeles) (Subject Matter Expert)
Dr. Kathleen Sakamoto (Stanford University)
Dr. Ian Stewart (Commissioned Corps of the US Public Health Service)

NIH/NIDDK/KUH Staff:

Dr. Kevin Abbott
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Mr. Robert Pike
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Dr. Cindy Roy
Dr. Anna Sadusky
Dr. Ivonne Schulman
Ms. Neha Shah
Ms. Aliecia Shepherd
Dr. Victoria Spruance
Dr. Robert Star
Mr. Jonathan Teinor
Dr. Ken Wilkins

Welcome and Introductions

Dr. Star welcomed council members and attendees to the KUH subcouncil meeting. Dr. Star formally welcomed Dr. Linda Baker as an ad hoc councilor. Drs. Nelson and Norris led the motion to approve the meeting minutes from May subcouncil.

Upcoming Meetings and Workshops

Dr. Star noted several upcoming meetings and workshops and commented that this information was available on the ECB for future reference.

Consortia Management Board (CMB) and External Expert Panel (EEP) Updates

Mr. Teinor detailed the list of KUH CMB and EEP meetings and commented that the Hematology Centers met following the May council meeting. In addition, he also provided a list of the following upcoming CMB, EEP, and upcoming meetings:

CMBs

- Chronic Kidney Disease Biomarkers Consortium (CKD BioCon II)
- Hematology Centers
- Kidney Precision Medicine Project (KPMP)
- New England Research Institutes Underactive Bladder Project
- Polycystic Kidney Disease Research Resource Consortium (PKD RRC)
- (Re)Building a Kidney (RBK) Consortium
- United States Renal Data System (USRDS)
- Urology O'Brien Centers
- Urologic Diseases in America (UDA)

EEPs

- Chronic Kidney Disease in Children (CKiD) Study
- Chronic Renal Insufficiency Cohort (CRIC) Study
- Kidney O'Brien Centers

Upcoming Meetings

- Rebuilding a Kidney (RBK) CMB - September 21-23, 2021
- Urology O'Brien Centers CMB – October 5, 2021
- KPMP EEP – October 12-14, 2021
- NERI-UAB CMB – November 23, 2021
- USRDS CMB – January 13, 2022
- UDA CMB – March 14, 2022

Councilor Presentations

Dr. Nelson opened his presentation by detailing several successful urology initiatives, including:

- The Collaborating for the Advancement of Interdisciplinary Research in Benign Urology (CAIRIBU), which includes many junior investigators,
- The George M. O'Brien Urology Cooperative Research Centers,
- The Multi-disciplinary Urologic Research (KURe) Career Development Programs (K12),
- The Urological Epidemiology (KUroEpi) Institutional Research Development Programs (K12),
- The GenitoUrinary Development Molecular Anatomy Project (GUDMAP), which provides data and tools that facilitate research on the GU tract for the scientific and medical community and,
- The UroEDIC project, which was founded to study the mechanisms of diabetic bladder dysfunction.

Dr. Nelson provided several recommendations for the following research programs:

- Increase the award funding within the Pilot and Feasibility (P&F) program at The George M. O'Brien Urology Centers (U54 grants) O'Brien Urology Center to attract and recruit more urology trainee applicants.
- Create a urology-specific award similar to the National Institute of General Medical Sciences' Centers of Biomedical Research Excellence (COBRE), to support the establishment and development of innovative, state-of-the-art biomedical and behavioral research centers at institutions in IDeA-eligible states through awards for three sequential five-year phases.
- Establish an R35 program to recruit and retain investigators, support junior investigator training needs, and attract outside investigators to the field.

Following Dr. Nelson's presentation, Dr. Baker offered her recommendations on timely areas of study within urology, which included suggestions for trans-KUH topics such as:

- Therapies/clinical trials to reverse lower urinary tract (LUT) fibrosis (ureter, bladder, prostate, penis),
- Therapies/clinical trials to improve LUT smooth muscle function (ureter, bladder, prostate, penis),
- Studies into the genetic basis of Urolithiasis to understand etiology and enhance personalized medicine using pediatric and adult cohorts,
- Polyuria: renal correction and effects of treatment on the LUT as a topic to study,
- Studies involving smooth muscle cell myopathy and therapies, including:
    - Studies of the Colon GI, corpus cavernosum, bladder, ureter
    - Mechanotransduction – sensation of organ shape (a trans-NIH relevant topic)
    - Roles of vascular physiology and pathology in NIDDK organ dysfunction
    - Wearable sensors
    - Ambulatory urodynamics
    - Lab on a chip/3D models
    - Detrusor underactivity – models and translation
    - Role of nutrition on LUT function – NIH Nutrition Research Task Force (NRTF). Dr. Baker noted the NRTF was established in 2016 to coordinate and accelerate progress in nutrition research across the NIH, and to guide the development and implementation of the first NIH-wide strategic plan for nutrition research for the next 10 years.

Additionally, Dr. Baker commented on several areas of potential trans-NIDDK collaborations:

- Studies involving the gastrointestinal tract, GU system, and Nephrology
- Whole-genome sequencing (WGS) and whole-exome sequencing (WES) approaches to stone disease. Dr. Baker commented that no pharmaceuticals for stone disease have been introduced since the 1980s. Timely areas of study would include:
    - GU genetics of extreme cases/rare diseases as avenue to breakthroughs
    - Phenotypic narrowing to extreme cases/families
- Integration of omics into studies
- Stone studies as they relate to metabolism/obesity/genetics
    - Nutrition (Accelerating Precision Nutrition Research)
    - Clinically relevant Mouse/Goat/Drosophila
- Prevention targets for therapies
- Sickle Cell Anemia-associated Priapism
- Potential collaborations with the NIH/NHLBI Cure Sickle Cell Initiative (CureSCi) to promote gene therapy efforts.

She also detailed that trans-NIH topics may include:

- Strategies to evaluate a diagnosis of antimicrobial resistance using point of care testing for UTIs and other bacterial infections. This may assist in advancing science to translational/clinical trials.
- Human genetics of recurrent UTIs is another potential topic for exploration.
- Methodology based strategies focused on:
    - a GU human urine biorepository for uIPSC generation from genetic cases related to bladder development, LUT symptoms, and stone disease.
    - CRISPR-Cas9/gene editing as it applies to urinary tract genetic diseases.
    - Google Alphafold2 as it applies to therapies for urinary tract dysfunction. There is potential for collaborative teams including AI, protein chemists, and the pharmaceutical industry.

Participant feedback:

- Dr. Drummond noted gene therapy and urology as a potential initiative topic. Dr. Baker commented that she would opt to focus on Cystinuria therapy as a gene therapy.
- Dr. Germino noted genetics of stone formers and measuring oxalate levels.

Dr. Sakamoto opened her presentation and detailed projects, ideas, and initiatives for KUH-hematology below:

- Developing *in vitro* models of human disease relevant to NIDDK
    - Lack of models of bone marrow failure: Dr. Sakamoto commented that there are few cells from these patients and added that most cells from these patients do not grow in culture. Additionally, alternatives such as bone marrow, peripheral blood, and iPSCs are not optimal. Research in this area would enable investigators to study the pathogenesis of disease, to study the microenvironment (e.g., stromal cell, cytokines), and to study immune cells and regulation (e.g., inflammation). Potential ideas for initiatives include funding opportunities for new methods to study cells from bone marrow failure patients, (e.g., Organoids, 3D models, animal models), as well as opportunities to study genomics (patient cells), proteomics (patient cells), and drug development (screening). Also, this effort could be absorbed into the U54 pilot studies program within the Hematology Centers of Excellence where institutions can advertise these projects.

    - Dr. Sakamoto noted that this addresses Scientific Goal #1 in the NIDDK Strategic Plan Major Goals: "Advancing understanding of biological pathways and environmental contributors to health and disease" as stated in: "Research Opportunity 1.1: Identifying and characterizing genetic and molecular mechanisms of health and disease." as it relates to study the microenvironment of diseases relevant to NIDDK. Additionally, this initiative applies to "Promoting cross-disciplinary research into the biological, environmental, and social factors that affect risk and progression of multiple diseases" as it relates to multidisciplinary (genetics/genomics, therapies, cell phenotype) and Immune system regulation of cell function.
        - "Engaging stakeholders in basic research." Opportunities could include designing a study that will involve research volunteers of diverse backgrounds to donate cells or tissues to study. After samples are obtained, a collaboration could be formed with drug companies and other federal agencies to test these samples in new models.

        - "Analyze links between biology, behavior and environment including social determinants of health that contribute to disease heterogeneity and health disparities." Opportunities include correlating genetic and biochemical data with environmental exposures, behavioral patterns, and social influences and link basic research with other factors, including stress, poverty or exposure to toxins and biological mechanisms.
        - "Develop innovative technologies and resources to advance scientific progress and enhance health" as stated in Research opportunity 1.3. Opportunities include to study new drugs, diagnostics, and technologies; to develop new screening approaches for therapeutic targets, develop or improve research technologies (lab on a chip, organoids, animal models); and to initiate studies using preclinical tissue or animal models.

- Training underrepresented minority physician scientists:
    - Dr. Sakamoto noted that this initiative addresses the NIDDK Strategic Plan to "advance stakeholder engagement, especially diversity" (Scientific Goal 4) through Research Opportunity 1.4 to "Strengthen the research investigator pipeline by enhancing and diversifying workforce development and training." Opportunities include to:
        - Train physician scientists to conduct research relevant to diversity in NIDDK disease areas, i.e., "health disparities among minority and other underserved populations and increasing health equity."
        - "Strengthening biomedical research workforce diversity and training" as both of the above are cross-cutting topics for NIDDK.
        - Train future role models and filling the pipeline, which will benefit training programs at academic institutions.
        - Train physician scientists who will benefit underserved communities who have NIDDK-relevant diseases.

    - Dr. Sakamoto outlined her proposal for training URM physician scientists:
        - RFA for training programs specifically for URMs MD trainees studying topics related to underserved communities
            - Residents – Similar to an R25 for 8-week rotations
            - Medical students – 1 year fellowship (similar to the Howard Hughes Medical Institute)
            - Fellows – URM residents to Faculty
        - K12 mechanism for physician scientists?
        - Activities to increase networking across institutions and disciplines (common themes)
        - Workshops for career development addressing topics relevant to URM training, e.g. Near-peer mentors, role models, navigating promotion, etc.

Participant feedback:

- Dr. Nelson noted that CAIRIBU offers this opportunity for junior investigators in urology. Dr. Sakamoto noted enthusiasm for a CAIRIBU community within hematology. Dr. Star noted CMB reviewers cited more collaborations are needed. Dr. Spruance discussed the U2C mechanism and commented that the focus of this program is on creating a national network for KUH trainees and faculty. Dr. Sakamoto noted that enthusiasm for this mechanism but that it needs ample funding for faculty slots.

- Dr. Drummond commented that inflammation impacts many diseases across KUH and added that inflammatory mediator studies are needed across NIDDK.
- Dr. Sakamoto also noted support for machine learning studies.

Dr. Norris presented the following potential trans-NIDDK kidney initiatives for consideration:

- Related to Scientific Goal 1:
    - Tool development: Single cell multi-omics and spatial transcriptomics
        - Potential to reclassify and sub-phenotype human disease in diverse populations
        - Distinguish subclones (cancer, inflammatory disorders)
        - Identify expansion of cell transcript expression (e.g., viral infections)
        - More fully describe cell communication in disease; identify target pathways
        - Extend the approaches of Kidney Precision Medicine to other KUH research areas.

    - Tool development: CRISPR genome and Epigenome/DNA Methylation Editing
        - Recruitment of epigenome editing effector domains using CRISPR/Cas systems allows site-specific control over modifications to DNA, histones, and chromatin architecture.
        - Epigenome editing may enable graded control over gene regulation.
        - Many downstream biologic effects of KUH chronic disease are likely mediated in part through epigenome modifications.

    - Addressing health disparities through understanding fundamental biological pathways: Addressing pathways amplified in disparities affected populations should target the most relevant pathways for all persons using a framework for social determinants of racial disparities in CKD (Adapted from Norton JM, Moxey-Mims MM, Eggers PW, Narva AS, Star RA, Kimmel PL, Rodgers GP. Social Determinants of Racial Disparities in CKD. J Am Soc Nephrol. 2016 Sep;27(9):2576-95). Potential opportunities could include:
        - Artificial Intelligence (AI) driven: image analysis / diagnosis / phenotyping: human pathology screening / better animal model phenotyping
        - Machine Learning (ML) driven: electronic health records (EHR) & Big data
        - Reducing AI/ML disparities? Can AI/ML reduce bias in diagnostics? A diverse training set is key.

    - Immune system and Inflammation in Stress and Disease (trans-KUH)
        - Immune/Inflammatory cell signaling impact on the progression and severity of genetic diseases (e.g., ADPKD), as well as chronic diseases.
            - Major downstream biologic pathways of disparities from oxidative stress and inflammatory/immune pathways (e.g., CRP, IL-6, E-selectin, intracellular adhesion molecule-1 [ICAM-1], to epigenetic modifications increased allostatic load, etc.
        - Social Genomics
            - Conserved transcriptional response to adversity (CTRA) gene expression profiles, which are characterized by up-regulation of

genes involved in inflammation and down-regulation of genes involved in antiviral defenses.
        - Senescence-associated secretory phenotype (SASP)
            - Better understand cell senescence and its role in expressing and secreting extracellular modulators such as cytokines, chemokines, proteases, growth factors and bioactive lipids.
            - Expand Senolytics in KUH disease states (e.g., DKD).
        - Macrophages as key mediators of productive tubule repair, etc.

- Related to Scientific Goal #2: Advance pivotal clinical studies and trials for prevention, treatment, and cures in diverse populations. Research Opportunity 2.3 discusses the need to bolster workforce development and training to increase and diversify the pipeline of clinical investigators.
    - Advances in understanding SGLT-2 inhibition:
        - Diabetes, CKD
            - SGLT-2 Inhibitor Trials for Acute Kidney Injury prevention, prediabetes
            - Cardiovascular outcomes as well (perhaps in collaboration withNHLBI)
        - Novel Inflammation & immune fx targeted therapeutic trials to improve outcomes and reduce disparities in Obesity, Diabetes, CKD, GI Disorders & more
            - Contemplative/restorative practice studies to do the same
        - A CRISPR genome editing trial.
    - Microbiome and Diabetes Kidney Disease: Studies in Gut Microbiota Dysbiosis

- Related to Scientific Goal #3: Advance research to disseminate and implement evidence-based prevention strategies and treatments in clinics and community settings to improve the health of all people more rapidly and effectively. Research Opportunity 3.3 discusses the need for study during major unanticipated events toward future implementation of preparedness in response efforts.
    - Leveraging the lessons from COVID-19 (telehealth) to enable tele-research:
        - The Dialysis-Like Therapeutics (DLT) program aims to support military readiness by improving critical care in low-resource environments. DLT uses cartridge-based nanoparticles to selectively bind and remove harmful pathogens or toxins and returning clean blood back to the patient. Within KUH, this technology might be used for removing activated cells, exosomes, and cytokines for transplant rejection and more.
        - Develop Large scale, national, randomized controlled trials using tele-assessments:
            - Explore ways to integrate health system and local contract labs (e.g., Quest, LabCorp)
            - This is particularly helpful for pediatric research and rare/uncommon diseases
        - *In situ*, non-invasive wearable biosensors for molecular analysis of key biomarkers related to KUH chronic disease and rare disease management
            - Technology for timely data acquisition – e.g., Continuous glucose monitoring

- Studies for patients treated with Dialysis? Transplantation? Other?
    - Support for high-throughput fabricated nano-biosensors

Dr. Norris commented that Ms. Dawn Edwards will present topics from a patient perspective. Ms. Edwards emphasized that serving on council has been an important opportunity for community engagement and commented on her own experience while participating as a patient advocate.

- Related to Scientific Goal #4: Advance stakeholder engagement including patients and other participants as partners in research.
    - Consider how to engage minority communities and how to focus the research agenda to drive patient-centered research on issues such as quality of life (QOL), as this is a concern for many patients. Ms. Edwards suggested integrated QOL/social genomic studies to achieve more patient centered/science-relevant outcomes and promote new Clinical Practice Guidelines/Performance Measures.

Participant feedback:

- Dr. Nelson commented on research community efforts in high schools in his area. Dr. Norris noted that KUH has a program geared toward engaging high school students in science that is very effective.
- Ms. Edwards commented on the need to improve QOL for patients on dialysis.
- Dr. Baker suggested a trans-NIDDK workshop on patient support groups.
- Dr. Drummond noted his lab promotes science in high school and undergraduate populations by supporting this structure through policy and politics, in addition to science.
- Ms. Givens noted gaps in research which include understanding how clinical trials work for patients, how current policies work (COI), and the different phases of clinical trials. She noted the scientific community needs to translate this information more effectively to patients.
- Dr. Drummond noted interest in promoting SBIR efforts in an R21 tool development webinar/workshop. This applies to trans-KUH efforts such as fibrosis.

KUH Closed Session

Dr. Star commented on confidentiality during closed session. Council members approved all payplans, restorations, a special council review, and a foreign application.