

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

Division of Kidney, Urologic, and Hematologic Diseases Advisory Subcouncil Meeting September 13, 2023

Advisory Council KUH Subcommittee Members:

Dr. Iain Drummond (MDI Biological Laboratory)
Ms. Dawn Edwards (American Association of Kidney Patients)
Dr. Mark Nelson (University of Vermont)
Dr. Keith Norris (University of California at Los Angeles)
Dr. David Penson (Vanderbilt University)
Dr. Kathleen Sakamoto (Stanford University)

NIH/NIDDK/KUH Staff:

Dr. Kevin Abbott	Dr. Deepak Nihalani
Dr. Eric Brunskill	Dr. Jenna Norton
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Ms. Shannon Givens-Bradley	Dr. Matt Portnoy
Dr. Daniel Gossett	Dr. Tracy Rankin
Dr. Raquel Greer	Mr. David Robinson
Dr. Shilpa Hattangadi	Dr. Cindy Roy
Dr. Jason Hoffert	Dr. Anna Sadusky
Dr. Chris Ketchum	Dr. Ivonne Schulman
Dr. Paul Kimmel	Ms. Neha Shah
Dr. Ziya Kirkali	Ms. Aliecia Shepherd
Dr. Karl Malik	Dr. Robert Star
Dr. Susan Mendley	Mr. Jonathan Teinor
Dr. Chris Mullins	Dr. Ken Wilkins

Welcome and Introductions

Dr. Star welcomed council members and attendees to the 223rd KUH subcouncil meeting. Drs. Norris and Nelson led the motion to approve the meeting minutes from May subcouncil. Dr. Star commented that Dr. Barthold has retired from KUH and Dr. Spruance has left NIDDK due to personal circumstances. Additionally, Dr. Star noted that Dr. Conage-Pough started this month at KUH as a Fellow from the American Association for the Advancement of Science (AAAS).

Upcoming Meetings and Workshops

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

Councilor Presentations

Dr. Sakamoto shared her recommendations for projects, ideas, and initiatives for KUH in hematology. To begin the discussion, Dr. Sakamoto detailed hematology efforts listed on the NIDDK website such as drug development; normal and abnormal function of blood; adult blood stem cells and Stem Cell Transplantation; and supporting research in Erythropoiesis and hemoglobin, genetic metabolic diseases, Hematology HIV/AIDS, and Hematopoietic Stem Cell Biology.

Dr. Sakamoto commented that Bone Marrow Failure studies integrate erythropoiesis, genetic diseases, hematopoiesis and stem cell biology as well as within human diseases that are both acquired such as myelodysplastic syndrome and genetic such as Diamond Blackfan Anemia (DBA). She emphasized that many of these diseases are due to Ribosomopathies. Challenges in studying inherited bone marrow failure syndromes (IBMFS) include very few cells in bone marrow of patients with IBMFS and a lack of in vitro culture methods to sustain growth of cells to study as DBA-like patient derived bone marrow grow in vitro. Additionally, there is a lack of animal models that can be developed or recapitulate human disease (e.g., DBA). Dr. Sakamoto highlighted that the field needs more discoveries and research on this disease.

Dr. Sakamoto detailed that the R21 Catalytic Tool and Technology Development in KUH Diseases ([PAR-23-119](#)) could offer an opportunity for future research on this topic as it supports the use of “innovative in vitro or in vivo model systems, (e.g., organoids, tissues, cells, animals). In particular, Dr. Sakamoto detailed that there is a lack of new therapies for IBMFS compared to myelodysplastic syndrome (MDS) or Aplastic Anemia and commented on the need for targeted therapies to treat IBMFS.

The SHINE program funding announcement includes language that notes “potential treatment of nonmalignant hematologic diseases,” would enable the NIDDK to fund applications that feature new drugs or better drug screens, identify new targets for treatment, and introduce novel technologies for future therapies (e.g., target microRNAs, exosomes). Dr. Sakamoto commented that this could also boost the NIDDK research for [translational research for therapeutic discovery and development](#).

Staff and Councilors provided the following comments:

- Dr. Nelson noted issues with zebrafish and commented that other models do not recapitulate the defect. Dr. Sakamoto noted that she is unaware of other animal models that may simulate this effect to bind to the ribosome and activate cells or rescue the phenotype.
- Dr. Rodan commented on effects within organoid research. Dr. Sakamoto noted that these are rare human diseases and acquiring human samples is challenging. Dr. Roy commented that the Rare Diseases Clinical Research Network (RDCRN), led by NCATS, has an RFA in development to form networks that incorporate the development of the outcomes of clinical trials and observational cohort trials nationally and internationally. Dr. Roy queried how to leverage rare disease studies for bone marrow failures. Dr. Sakamoto noted the need to define less toxic and more effective methods of treating and studying these diseases, respectively. Also, she noted the need to study long-term effects of gene therapy/editing.

Dr. Rodan opened her presentation by discussing a 1967 paper titled “[Nephropathy Associated with Heat Stress and Exercise](#)” by Dr. Schrier, which focused on healthy military recruits with AKI who required dialysis associated with heat stress and physical exertion. She also detailed

that between 2007 and 2014, 40% of active duty U.S. military service members with exertional heat stroke were diagnosed with AKI. The paper “[Cause-specific risk of hospital admission related to extreme heat in older adults](#)” demonstrated that, in patients over the age of 65, there were increased rates of hospitalizations for fluid and electrolyte disorders, renal failure, and urinary tract infections on days in which average daily temperatures exceeded the 99th percentile of daily temperatures for that county. Dr. Rodan commented that older individuals experience impaired thermoregulation, thirst, urinary concentration, and lower renal blood flow. Investigators also observed a correlation between maximum daily temperature and renal and urologic diseases (e.g., urolithiasis, acute kidney injury, and urinary tract infections) in Adelaide, Australia in the general population, as shown in “[The impact of daily temperature on renal disease incidence: an ecological study](#).” A sampling of additional studies showing associations between heat and kidney and urologic injury or disease include “[Association Between High Environmental Heat and Risk of Acute Kidney Injury Among Older Adults in a Northern Climate: A Matched Case-Control Study](#),” “[Mobile COVID-19 Screening Units: Heat Stress and Kidney Function Among Health Care Workers](#),” and “[Exposure and Emergency Department Visits Related to Kidney Disease](#).” A perspective co-authored by Dr. Norris, “[Extreme Heat Can Exacerbate Disproportionate Burden of Severe Kidney Disease in Historically Marginalized Communities: Call to Action](#),” highlighted disparities in the exposure of marginalized populations to heat stress, their increased susceptibility to heat-stress related kidney injury, and possible solutions.

Dr. Rodan also discussed chronic kidney disease of unknown origins (CKDu), noting that while there are many hypotheses, there are few certainties regarding this disease as the literature speculates on a wide variety of potential causes, referencing the following papers:

- [Chronic Kidney Disease of Unknown Cause in Agricultural Communities](#)
- [Chronic kidney disease with unknown cause across the global spectrum](#)

However, she commented that the [NIDDK/NIEHS/FIC “Chronic Kidney Disease of Uncertain Etiology \(CKDu\) in Agricultural Communities \(CURE\) research consortium”](#) is investigating further, which should improve understanding of this important disease.

Dr. Rodan reviewed some of the literature examining the pathophysiology of kidney injury during heat stress, including the influence of exercise and dehydration – conditions which affect some of those with CKDu, but are also relevant to other populations:

- [Kidney physiology and pathophysiology during heat stress and the modification by exercise, dehydration, heat acclimation and aging](#)
- [Renal responses to exercise, heat and dehydration](#)
- [Effect of the volume of fluid ingested on urine concentrating ability during prolonged heavy exercise in a hot environment](#)
- [Fructokinase activity mediates dehydration-induced renal injury](#)

These findings are of public health importance, since new laws have been emerging limiting water breaks for workers, such a new Texas law discussed in this [article](#).

Dr. Rodan raised several open questions for discussion:

- Who is at greatest risk of AKI and/or CKD from heat stress? Age, gender, occupation, underlying comorbid conditions and medications, socioeconomic factors (esp. non-CKDu)
- Is CKDu pathophysiology the same in different countries/populations, and is it generalizable to other forms of heat stress nephropathy?

- Do single or recurrent episodes of decreased GFR/AKI during heat stress lead to CKD over time? Or have other adverse consequences?
- What are pathophysiologic contributors? Dehydration (copeptin), inflammation, ischemia, oxidative stress, uric acid, vasopressin, polyol/fructose pathway, ATP depletion, toxins, others?
- How do epidemiologically identified risk factors (e.g., a specific pesticide for CKDu [[Holliday Clin J Am Soc Nephrol 2022 17: 1293-1304](#)]) feed into these pathways?
- How else can heat stress nephropathy be mitigated against? (Some trials underway for CKDu e.g., stepped wedge design examining hydration and rest/shade: [Smyth Kidney International 2023 103: 6-12](#))
- What are optimal hydration strategies?
- What happens with heat adaptation/acclimation?

Staff and Councilors provided the following comments:

- Dr. Star commented that these are complicated diseases and queried on how to determine the causes solely through epidemiology vs pathology/pathophysiology studies.
- Dr. Mendley commented on heat stress and extreme exertion young men have to perform as a result of these jobs and queried if it is climate change or severity of the work that causes this illness or if there a family genetic component. She emphasized that communities which suffer from this disease believe they are exposed from environmental sources. She also commented that the CKDu study also collects soil and water and has partnered with colleagues from National Institute of Environmental Health Sciences (NIEHS) and Fogarty International Center to form the [CKDuCURE](#) research consortium.
- Dr. Norris commented on gender differences, noting migrant workers in CA participate as a family activity and noted dehydration rates may be higher among women and children. He emphasized the need to determine who is participating in this activity.
- Dr. Star queried if animals are susceptible to this illness such as horses.
- Dr. Penson commented on the relevance of this topic to kidney stones and noted there are climate versus environmental factors. He suggested to explore the differences in cases between the north and southern hemisphere and queried if this had been done. Dr. Rodan noted the study in Australia that was previously mentioned but commented that she was unsure of studies performed at different latitudes.
- Dr. Abbott noted efforts within the USRDS and commented that it is not well delineated whether all cases of end-stage kidney disease attributed to hypertension are actually due to hypertension. He noted that the Rio Grande area and central valley CA are being looked at in certain high risk groups such as agricultural (e.g., sugar cane cutters) and construction workers.
- Dr. Nelson noted that problems such as hyponatremia can also result from too much water and not enough salt. The group discussed optimal hydration. Dr. Abbott commented that this occurs in the military as well as in the marathon runner population.

Dr. Penson discussed training in urologic research with a focus on developing the next generation of researchers in the current environment. He detailed several strong forces working against the next generation of urologic researchers:

- Federal budgets not growing at an adequate rate
- Reduced clinical reimbursements mean that academic medical institutions have fewer unrestricted funds to support research
- Physician-scientists are being pressured to do more clinical work
- Basic scientists are being lured away to industry
- Basic and clinical research in benign urologic disease isn't perceived as "sexy"

Dr. Penson detailed KUH “unique” applicants, noting that this rate for urology investigators is relatively flat, possibly due to the end of COVID and fewer investigators writing applications. He detailed that more than 2/3 of these investigators are Ph.D. and noted a decline in investigators with an M.D. Dr. Penson emphasized that while R01 and U01 awards have increased for urology, competing urology applications are relatively flat and added that competing R01 awards in urology have been flat for the past 10 years. Of immediate concern is the low number of ESI competing R01 applications. While MPI applications have increased, possibly due to increased staff responsibilities among investigators, there has been a decline in R01 basic research as well.

Dr. Penson commented that NIDDK has done a good job at providing opportunities for training at many levels. These include numerous in-house/on campus opportunities for trainees at all levels and external opportunities such as undergraduate summer research programs, pre- and postdoctoral programs (e.g., F30, F31, F32, K99/R00, K12), junior faculty (e.g., K01, K08, K23) and the U2C/TL1 program.

Dr. Penson discussed several collaborative opportunities for NIDDK such as industry, academic institutions, disease-focused foundations, and professional societies such as the Society for Basic Urologic Research. He also requested that staff consider opportunities for partnering with the AUA on [Urology Care Foundation](#) research grant programs. Such as the [Boston Scientific Corporation](#), which pairs mentees with mentors. Additionally, he commented that there are several AUA workshops and opportunities available for investigators such as the Career Investigators Workshop. AUA has also placed a strong focus on obtaining new grant funding or re-purposed existing funding for underrepresented minority (URM) applicants (e.g., LEAD program, BSc Medical Student Innovation Fellowship, section sponsored RSA awards).

Dr. Penson opened up a discussion and solicited participant feedback with the following questions:

- How do we attract more qualified individuals into the field?
- How do we increase diversity in the field?
- How do we maximize their training?
- How do we get them to maintain their commitment to academic research?

Staff and Councilors provided the following comments:

- Dr. Nelson commented that more than half Ph.D. graduates are going to industry and added that there is a national movement to raise postdoctoral salaries, noting that he raised his postdoctoral salaries by 10%. Dr. Nelson emphasized the need to increase pay to compete with industry. Additionally, he commented that while daycare, cost of living, and housing financial pressures are high for young basic and clinical scientists, the field must encourage people to go into research. Dr. Nelson detailed that academia budgets vary according to funding levels and having a “safety net” within academia would be helpful as investigators are likely to have more job security with industry rather than academia.
- Dr. Rodan commented on the time allotted for residency with increasing clinical pressure and decreasing institutional revenue. She also noted the need to engage medical students in more exciting research.
- Dr. Sakamoto noted residents need protected time and queried if there are opportunities to allow trainees to spend more time in research. Dr. Penson commented that this is not equal to getting more time for residents and added that he could use another Resident per year, but academia cannot bill for a Resident.

- Dr. Norris noted NIDDK could consider allocating a year for discovery research and medical student research experiences. He also asked participants to consider how the loan repayment program can be structured for added value to recruit students into those areas. He suggested extending the training period for a few years while the trainee is in junior faculty. Dr. Rankin noted that there is a program for sabbatical students, but the program receives few applications. She also commented that the R25 program is underused for KUH medical interests. Dr. Norris suggested allocated supplemental funds within these programs.
- Dr. Hattangadi suggested that the field may recruit industry collaboration to help pay for Residents in academia. She also noted that the peer network in the U2C program is helpful and engages peers with one another.
- Dr. Ketchum queried if recruitment efforts should focus on M.D./Ph.D.s. Dr. Penson noted the need to support people who want to do research, regardless of degree. While NIDDK does not administer a M.D./Ph.D.-specific program, staff can look into this. Dr. Norris commented that this is an interesting idea and shared that his institute has a “Star” program as a pathway for trainees into research.
- Dr. Penson commented that it is easier for researchers to receive funding for cancer projects over benign disease. Additionally, trainees want to make a bigger impact in their community which includes cancer patients.
- Dr. Norris commented on the importance of getting URM investigators in projects outside heart disease, dementia, and cancer.
- Dr. Gipson noted concern about the low numbers of pediatric urology and queried how to boost recruitment of this expertise in the field. Dr. Penson noted there is not a single entity that represents this group, and a group is needed to represent this workforce.

KUH Closed Session

Dr. Star commented on the importance of confidentiality during closed session. Council members approved several closed business items.