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Fostering Scientific Innovation to Impact AKI: A Roadmap from ASN's AKINow Basic Science Workgroup

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Key Points:

Abstract:

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Fostering Scientific Innovation to Impact AKI: A Roadmap from ASN’s AKINow Basic Science Workgroup

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In 2020, the American Society of Nephrology (ASN) convened AKI/Now as a longitudinal initiative to promote excellence in the prevention and treatment of acute kidney injury (AKI). AKI/Now’s interests span fundamental research, provider education, and patient advocacy. Here we describe current efforts of AKI/Now’s Basic Science Workgroup to foster innovation in AKI research.

Recent investments in kidney research have triggered overlapping waves of progress that are beginning to benefit kidney patients. Advances in transplantation stand alongside breakthroughs in the genetics of nephrotic syndrome and the pharmacological treatment of chronic kidney disease (CKD). These and other achievements raise hope for new ways to recognize and thwart nascent kidney injury; accelerate intrinsic repair mechanisms; and restore kidney health.

In the area of AKI, the scope of potential impact can be described succinctly: AKI affects more than 13 million people worldwide every year, contributing to nearly 2 million deaths annually [1]. Novel technologies, increased collaborations, and the entry of new participants into kidney research will be necessary to reduce these staggering numbers. Leveraging shared interests with patient advocates, investigators within and outside traditional nephrology, and many other stakeholders, our workgroup has developed an AKI innovation roadmap comprised of several achievable proposals—described below—that together could foster a community of AKI innovators.

**AN OPEN ACCESS ONLINE JOURNAL CLUB PLATFORM**

Discussion, debate, and dissemination are critical to weave new findings into the evolving tapestry of AKI knowledge. An AKI/Now sponsored Online Journal Club supported by the ASN should provide a forum for timely interrogation of state-of-the-art research. A platform open to ASN members and non-members alike will regularly unite expert authors and reviewers with community participants ranging from patients and trainees to investigators in unrelated areas. The journal club will utilize ASN’s webinar format that has been highly successful for COVID-19 updates. A volunteer committee of ASN members will survey kidney journals, general interest publications, and other specialties to identify timely articles, e.g., on xenotransplantation.

Each journal club will be hosted and moderated by two members of AKI/Now and in collaboration with other ASN committees. Each meeting will require one-click registration, but will be free of charge. We aim to have first and/or senior authors present the findings and to foster a large, diverse, and highly interactive audience. The entirety of each journal club will last one hour, and we aim to organize four sessions per year. With success, this platform can and should expand quickly beyond AKI to incorporate other areas of Nephrology.

**DEMOCRATIZING DATA SCIENCE THROUGH INTERACTIVE PEDAGOGY**

Data science is transforming fields ranging from political science to finance, commerce and medicine. Democratization of data access and data science literacy could simultaneously unleash new advances and enhance the rigor of Nephrology research [2]. Furthermore, it is crucial to empower young minds with the correct tools to be able to analyze data appropriately as well as critically assess the quality of analyses presented by others. To improve the quality of published data, elevate data science literacy, and increase participants in Nephrology research, we envision an interactive data science bootcamp series. Instruction would be hands-on and interactive. An initial offering could focus on matriculating a cohort of participants new to
statistics and programming through the basics of data manipulation and analysis with different statistical language software such as python and R. In conjunction with traditional didactic sessions, these bootcamps will also offer practical hands-on experience with interactive modules and use of pre-existing real-world kidney datasets to offer relevant coding experience.

The program will be configured to enhance learning via three main facets: Instructor-led learning, interactive dataset-based learning, and student-student interaction (Figure 1). This format will expand beyond the traditional classroom to offer a rich learning environment that will build a community of learners in Nephrology. Important goals of these mini-courses would be to mitigate hesitancy around coding and large datasets; convey principles of rigorous analysis; and build confidence for participants to discuss hypotheses and analytical approaches with members of their home institutions. With success, the platform could expand to more complex analyses or even topical areas such as bioinformatics.

**AN OPEN ACCESS OMICS DATA WAREHOUSE**

Advances in our ability to interrogate kidney tissue and other biospecimens both from patient volunteers and experimental disease models offer an unprecedented opportunity to catalyze innovation in kidney health. Multi-omic techniques include genomics, epigenomics, bulk transcriptomics, spatial transcriptomics, single cell transcriptomics, proteomics, and metabolomics. The combined power of these approaches to understand changes at the levels of DNA, RNA, protein, and chemistry—further refined by anatomy, cell type, and temporal progression of disease—may yield novel markers of kidney disease and new insights into mechanisms amenable to therapeutic restoration of kidney health (Figure 2). Within Nephrology, several consortia are already pursuing publicly available multi-omic interrogation. One highly accessible opportunity for ASN is to increase traffic to such existing resources by providing links and curated introductory content from the creators.

ASN could also consider going further by creating an open-access, one-stop, tractable, online searchable data warehouse that can accelerate the translation of research from disease models to actual patients. Increasing accessibility for researchers with relatively scarce resources—including those from developing countries—will promote ASN’s initiative to disseminate equitable distribution of knowledge to promote kidney health. Development of a searchable -omics repository that can be either downloaded or analyzed in the ASN environment could foster a global, collective, and interactive research community not only for academic researchers, but also other groups. This resource could also facilitate education in multi-omics data analysis, for example by hosting hack-a-thons and didactic webinars, thereby helping to attract prospective trainees into our field. Initially, we envision this unique warehouse to become a site of choice for data deposition by investigators publishing in ASN-affiliated journals.

**ALIGNING DISCOVERY TO DRUG DEVELOPMENT**

Health care costs and resource utilization for managing hospitalized patients with AKI are estimated to cost $5.4 to $24.0 billion annually [3]. However, the investment of research funding from the NIH for kidney disease including AKI is significantly lower compared to the support for cancer, diabetes, heart disease or HIV/AIDS [4]. The COVID-19 pandemic has highlighted the impact of kidney involvement in hospitalized patients requiring renal replacement therapy that resulted in unprecedented stress on major health systems.
Recognizing the significant burden of AKI and CKD, a positive recent trend is the increasing interest in pharmaceutical companies and venture capitalists to consider funding for these conditions. Multiple areas are poised for investments including preventive strategies for AKI, rapid and real time monitoring of kidney function, and developing pro-recovery interventions. The exciting developments for new CKD therapies such as SGLT2 inhibitors and the overlapping pathways between AKI and CKD offer new opportunities for a developmental path for such innovative therapeutic approaches. In this regard, the Kidney Health Initiative (KHI, https://khi.asn-online.org/), a public-private partnership between the American Society of Nephrology and the US Food and Drug Administration as well as >100 industry members, will play a critical role to catalyze innovation for patient-centered therapies for AKI. Among the charges of KHI is the collaborative re-examination and development of regulatory milestones that can facilitate clinical development of drugs, diagnostics, devices, and other patient care innovations.

Finally, a key transition from discovery to drug development is how to apply animal models of AKI in the study of human AKI [5, 6]. Whereas clinical trial design is crucial in establishing the efficacy of a drug in the prevention or treatment of AKI, identifying meaningful molecular targets is of paramount importance. The traditional approach is to identify rodent biological targets, test in animal models and validate in clinical trials. A more useful approach may be to determine molecular targets in humans, test in relevant animal models, and then validate in clinical trials [7, 8]. Omics analysis of human molecular targets and identification of endophenotypes [9] will be facilitated by the National Institutes of Diabetes and Digestive and Kidney Diseases' Kidney Precision Medicine Project (KPMP https://www.kpmp.org/), which is aimed at identifying critical pathways and targets for novel therapies. Rather than the traditional linear path of bench to bedside, a recursive cycle that starts at the bedside, goes to the bench, and returns back to the clinic offers new promise that AKI discoveries will successfully translate to patients.

**SUMMARY**

The individual and societal costs of AKI remain astonishing. The future success of AKI innovation hinges on our collective ability to incorporate new technologies, increase collaborations and dialog, and lower the barriers for new entrants into the field. ASN's AKINow Basic Science Workgroup seeks to foster a community of AKI innovators. To this end, we have developed a roadmap of achievable initiatives around knowledge dissemination, data science literacy and data access, and new ways to align discovery to clinical development. As each component of this first-generation roadmap is explored and implemented, we continually seek input from AKI's diverse set of stakeholders (twitter handle @ASN_AKINow). A posture of impatience for progress will remain essential to achieve the goal of reducing the burden of AKI.
DISCLOSURES
S. Parikh reports the following: Consultancy: Aerpio; Alkermes; Astellas; Boehringer Ingelheim; Cytokinetics; Flagship Pioneering; Janssen; Leerink Swann; Merck; Mission Therapeutics; Mitobridge; NovMeta; Pfizer; Entrada Therapeutics; Research Funding: Baxter; Patents or Royalties: UpToDate; Advisory or Leadership Role: Journal of the American Society of Nephrology; Kidney360; and Other Interests or Relationships: American Society of Nephrology; International Society of Nephrology; American Society for Clinical Investigation; American Association of Physicians. A Agarwal reports the following: Consultancy: Dynamed - my role is to review content related to AKI for Dynamed and review updated materials prepared by the Dynamed editorial team for AKI topics.; Akebia Therapeutics - I have been invited to serve on an Expert Panel to review new therapeutics based on the HIF pathway for AKI. I serve on the medical advisory board of Creghe Pharmaceuticals.; Ownership Interest: Goldilocks Therapeutics, Inc.; Creghe Pharmaceuticals; Research Funding: Genzyme/Sanofi Fabry Fellowship Award; Honoraria: University of Toledo, University of Maryland, University of Virginia; Patents or Royalties: I have a pending patent that describes small molecule inducers of heme oxygenase-1 for the treatment of acute and chronic kidney disease.; Advisory or Leadership Role: Editorial Board of AJP Renal, Kidney Int and Lab Investigation.; I have been invited to serve on the Advisory board of Goldilocks Therapeutics, a NY based company investigating delivery of drugs in the kidney using nanotechnology for acute and chronic kidney disease. I serve on the Advisory Boards of Angion, Creghe Pharmaceuticals, Zy dus and Alpha Young, LLC.; and Other Interests or Relationships: My wife, Lisa Curtis is President for Women in Nephrology (2020-2022). J. Cerda reports the following: Ownership Interest: New York Nephrology - Shareholder; Advisory or Leadership Role: International Society Nephrology AKI Committee and CoChair, 0by25 Initiative; American Society of Nephrology: Chair, AKI!!Now Initiative; International Society of Nephrology Chair, Advocacy Working Group; and Other Interests or Relationships: Member of the ASN Online AKI Community; Associate Director, 0 by 25 Initiative, International Society of Nephrology; ASN AKI!!Now Initiative. M. Okusa reports the following: Employer: University of Virginia Health System; Consultancy: HemoShear; Janssen; Ownership Interest: AAPL; ; Allstate (ALL), Citigroup (C), Nextera Energy (NEE), Pepsico (PEP), Walmart (WAL); ; BABA, AIG, BK, BCS, BP, CAH, CRRFY, CI, C, CMCSA, CRH, CVS, ERJ, EMR, ENIC, ENGY, E, EBKDY, FNMA, FDX, FISV, FLEX, FMX, F, FCX, GE, GD, GEBHY, GSK, GRFS, HAL, HCA, HDEFY, HMC, INGR, JSAIY, JPM, KGFHY, LH, MCK, MRK, MU, MKH, OM, OGN, PFE, PNC, PUBGY, REPYY, RDS B, S NY, SBGSY, STT, SMFG, VIV, TSCDY, TXT, TTE; Research Funding: NIH - research grant; AM Pharma/Pfizer; Honoraria: UptoDate, University of Tokyo, Cleveland Clinic Foundation, Korean Society of Nephrology; Patents or Royalties: University of Virginia Patent Office; Advisory or Leadership Role: NIDDD/NIDDK DSMB; and Other Interests or Relationships: John Bower Foundation; Travel. The remaining authors have nothing to disclose.

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Samir Parikh: Conceptualization; Writing - original draft; Writing - review and editing. Anupam Agarwal: Conceptualization; Writing - original draft; Writing - review and editing. Amandeep Bajwa: Conceptualization; Writing - original draft; Writing - review and editing. Sanjeev Kumar: Conceptualization; Writing - original draft; Writing - review and editing. Sherry Mansour: Conceptualization; Writing - original draft; Writing - review and editing. Mark Okusa: Conceptualization; Writing - original draft; Writing - review and editing. Jorge Cerda: Conceptualization; Writing - original draft; Writing - review and editing.

REFERENCES

Figure 1: An ASN hosted interactive educational series to increase literacy in data science

Figure 2. ASN hosted multi-omics platform to catalyze innovation and education in kidney health.
Data Science Bootcamp Series

To empower creative minds with the proper skillset to improve data quality in the field of nephrology and to ultimately advance care for kidney patients.

- Instructor-led learning
- Interactive database learning
- Student-student interaction

Learning statistical software languages with emphasis on:
- Accuracy and precision
- Data mining
- Methodology
- Statistical computations