ARIC Manuscript Proposal #4362

PC Reviewed: 11/21/23	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Plasma Proteomics of Acute Tubular Injury

b. Abbreviated Title (Length 26 characters): ATI proteomics

2. Writing Group:

Writing group members:

Insa M. Schmidt, MD, MPH; Aditya L. Surapaneni, PhD; Ricky Zhao, MS; Dhairya Upadhyay, MS; Wan-Jin Yeo, PhD, Pascal Schlosser, PhD; Josef Coresh, MD PhD; Courtney Huynh, MS; Anand Srivastava, MD, MPH; Ragnar Palsson, MD; Ashish Verma, MD; Taesoo Kim, MD; Isaac E. Stillman, MD; Joel Henderson, MD; Michael Eadon, MD, PhD; Sylvia E. Rosas, MD; Daria Barwinska, PhD; Tarek El-Achkar, MD; Dennis Moledina, MD; Jonathan Barasch, MD; Josef Coresh, MD, PhD; Eugene P. Rhee, MD; Morgan E. Grams, MD, PhD; Sushrut S. Waikar, MD, MPH

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal.

First author: **Insa M. Schmidt**

Address: Boston University Chobanian & Avedisian School of Medicine
Boston Medical Center, Section of Nephrology

Evans Biomedical Research Center, 5th Floor
650 Albany Street, Boston MA 02118
ischmidt@bu.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

Name: **Morgan E. Grams, MD, PhD**

Address: NYU Grossman School of Medicine
550 1st Ave.
New York, NY 10016
E-mail: morgan.grams@nyulangone.org

3. Timeline:

2 weeks: analysis of data
1 month: submission of manuscript

4. Rationale:
Toxic or ischemic injury of the kidney tubular epithelium is responsible for substantial morbidity and mortality from conditions such as drug-induced nephrotoxicity, acute kidney injury (AKI) requiring kidney replacement therapy, and progressive chronic kidney disease (CKD) culminating in kidney failure.[1, 2] Tubular lesions on histopathology have been described across virtually all forms of chronic and acute kidney diseases. The kidney tubules comprise > 80% of the kidneys' cellular mass and have among the highest density of mitochrondria and metabolic workloads of any cell type in the body.[3] The high energy requirements of the tubules are from ATP-consuming reabsorption of over 99% of filtered sodium, glucose, and amino acids from the circulation.[3] The tubules also possess important innate immune characteristics allowing them to act as immune responders to a variety of injurious stimuli.[4] Several studies suggest that kidney function decline show a closer correlation with tubulointerstitial damage rather than glomerular injury.[5-7]

Acute tubular injury (ATI) describes a combination of pathologic findings, including tubular dilatation and epithelial flattening, tubular cell sloughing, and loss of nuclei, that reflect the molecular and cellular responses of the tubules to a diverse range of insults.[8-10] ATI stands as a pivotal hallmark in the diagnosis of acute kidney injury (AKI) but also manifests in the context of chronic kidney disease (CKD).[10] In both AKI and CKD, episodes of ATI and subsequent maladaptive repair in response to injury can lead to the development and progression of kidney disease.[2, 11]

Using the SomaScan proteomics platform, we identified 156 plasma proteins in the Boston Kidney Biopsy Cohort (BKBC), a cohort study of individuals with biopsy-confirmed kidney disease, that were independently associated with ATI severity on kidney biopsies. Whether these proteins are also independently associated with higher risks of incident AKI is unknown.

5. Main Hypothesis/Study Questions:

Objective 1: Utilizing the proteomics data from the ARIC study (SomaLogic, visit 5), our aim is to determine if any of the 156 plasma proteins, previously linked with ATI severity in the Boston Kidney Biopsy Cohort (BKBC), also correlate with an increased risk of developing AKI.

Hypothesis. Several of the 156 plasma proteins associated with ATI severity will also demonstrate a statistically significant association with greater risk of developing AKI in the ARIC cohort.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Participants

Inclusion criteria:
ARIC participants with:

- SomaScan proteomic data at visit 5

Exclusion Criteria:

- Non-white or non-black race
- Missing covariate information

Proteomics: Using plasma collected at ARIC visits 5 (2011-13), proteins were measured using a Slow Off-rate Modified Aptamer (SOMAmer)-based capture array (SomaLogic, Inc, Boulder, Colorado). Using chemically modified nucleotides, this process transforms protein signals to a nucleotide signal quantifiable using relative florescence on microarrays. Previous work indicates a median intra- and inter-run coefficient of variation of approximately 5% and intra-class correlation coefficients of ~0.9.[6–9]

Data analysis plan. We will use Cox proportional hazards regression to examine the association between the candidate proteins (156) and incident AKI. In these models, the protein variable will serve as the exposure variable and incident AKI as the outcome variable. Model 1 will adjust for potentially confounding demographic variables, including age, and sex. Model 2 will additionally adjust models for history of hypertension, diabetes, smoking status, eGFR, and UACR. We will correct for multiple testing using a Bonferroni-adjusted significance threshold.

Limitations. Given the intrinsic limitations of epidemiological association studies, additional clinical and experimental studies are needed to establish the causal role of the AKI biomarkers identified in this study. We also cannot exclude the potential influence of unmeasured confounding variables on our results.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __X__ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? __ Yes __ X_ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"? __X__ Yes _____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php **_X_ Yes ___ No**

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

To our knowledge there are no proteomic analyses of acute kidney injury

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __x__ Yes ____ No

11.b. If yes, is the proposal

__X_ A. primarily the result of an ancillary study (list number* _____)
"Proteomic longitudinal ARIC study: SOMAscan of multiple visits"

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s) * 2013.10)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PubMed Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

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