ARIC Manuscript Proposal Form

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Publication Committee Review Date: **02/13/24**
ARIC Manuscript Proposal Number: **# 4408**

1.a. Full Title: Proteomic Profiling of the rs5491 HFpEF risk variant: ARIC validation of MESA findings

b. Abbreviated Title (Length 26 characters): Proteomics of rs5491

2. Writing Group [please provide a middle initial if available; EX: Adam L Williams]:
Writing group members: Michael J. Zhang, Ethan Moser, Lin Yee Chen, Amil M. Shah, Bing Yu, Ravi B. Patel, Sanjiv J. Shah

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _MJZ____ **[please confirm with your initials electronically or in writing]**

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (The ARIC author should be involved enough in ARIC to be able to point the lead author to appropriate ancillary study PIs and to be able to search ARIC manuscript proposals if the lead author doesn't have the access needed to do such a search).

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3. Timeline: 1-2 months for validation analyses

4. Rationale: We have recently demonstrated that rs5491, a missense variant within the intercellular adhesion molecule (*ICAM1*) gene that is common in Black individuals and rare in other race/ethnic groups, is associated with increased risk of incident heart failure (HF) with preserved ejection fraction (HFpEF) in both MESA and ARIC.[1] rs5491 was also associated with higher levels of soluble ICAM-1, lower eGFR, elevated triglycerides and lower HDL. ICAM-1 is involved in leukocyte extravasation through its role in cellular adhesion and transmigration. However, the exact mechanisms in which rs5491 increases risk for HFpEF remains unclear. We therefore investigated possible pathways driving this relationship by evaluating the associations between rs5491 and the circulating proteome in MESA. We identified 7 proteins that were higher among individuals who carry at least one copy of rs5491 in MESA. We aim to validate the association of rs5491 with these 7 proteins, all of which are on the SomaLogic panel in ARIC. Higher levels of circulating proinflammatory cytokines (IL-6, TNF-α) have been associated with increased incidence of HF.[2,3,4,5] These data suggest that evaluation of protein, profiles may be fruitful to understanding inflammatory pathways driving HFpEF.

5. Main Hypothesis/Study Aims: Evaluate the association between rs5491 (from SNP array data set) and 7 plasma proteins in Black participants in ARIC. These 7 proteins were associated with rs5491 in MESA and will be evaluated in ARIC in a validation analysis.

6. Design and analysis:

a) **Inclusion criteria** Black participants in ARIC with the rs5491 genotype, available SomaLogic proteomics data at Visit 2
b) **Exclusion criteria:** prevalent heart failure, missing genotype or proteomics data
c) **Study design:** Cross sectional at Visit 2
d) **Exposure variable:** Presence of rs5491 genetic variant
e) **Outcome variables:** Plasma levels of 7 proteins measured by SomaLogic: ICAM2, TNFR1, TNFR2, LTBR, TNFRSF14, IL1RT, IL17RA
f) **Summary of data analysis:** rs5491 will be modeled in a dominant fashion to mirror MESA analyses. Proteins will be $\log_2$-transformed and scaled to a mean of 0 and SD of 1. The association between rs5491 and these 7 plasma proteins will be assessed using multivariable linear models. The model will adjust for age, sex, and genetic ancestry (principal components 1-3).
g) **Anticipated methodologic limitations or challenges if present**

We will start with ARIC Visit 2 proteomics data because this give us the largest sample size. However, there is some concern about the long storage freezer storage time of Visit 2 plasma samples. We will also consider exploring using non-adaptive normalization maximum likelihood (ANML)-normalized proteomics data and Visit 3 or Visit 5 proteomics data. Visit 3 proteomics data may have more sample variability and Visit 5 proteomics data has substantially smaller sample size, however.

Another methodologic limitation is that ARIC protein validation will be using SomaLogic platform, while MESA (derivation) used Olink proteomics, and there is varying correlation between the two proteomics platforms (Spearman correlations between 0.07-0.81 for the 7 proteins).

h) Will the author need Limited data to complete the proposed manuscript? ☐ Yes, Limited data is needed (Provide a brief (2-3 sentences) justification for requesting PHI data) . ☒ No, De-identified data will be sufficient.

*Please note, Limited dataset access is strict and rarely provided. Limited data includes identifiable information such as dates (birthdays, visit dates, etc.). CMS, Genomic, Geocoded, Proteomics/Somalogic, and other -omic data all fall under the limited data category. De-identified data does not include dates. All dates are date adjusted to "Days since Visit 1".

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? (Non-ARIC analysis means that the authors are not regarded as ARIC investigators and the "ARIC author" is essentially just a facilitator rather than an integral part of the writing group.) ☐ Yes ☒ 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 is distributed to ARIC PIs annually, 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 ☐ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the current derived consent file ICTDER05 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ☒ Yes ☐ No

9. The lead author or the "sponsoring" ARIC 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 website at: https://aric.cscc.unc.edu/aric9/proposalsearch [ARIC Website Publications Proposal Search]

☒ 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)?
#3324 Whole Genome Sequence and Proteomics for Gene Discovery in the Atherosclerosis Risk in Communities (ARIC) Study – this study examines the genome and protein levels, whereas our study examines a specific genetic variant and protein levels. Therefore the overlap is *minimal*. We have also invited Dr. Bing Yu, sponsor of #3324, to be a collaborator on our study.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or does it use current [or ongoing] ancillary study data (this includes ACHIEVE)? ☒ Yes ☐ No → Skip to question 12

11.b. If yes to 11.a., is the proposal

☒ **A. primarily the result of an ancillary study**

☐ **B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables)**

11.c. If yes to 11.a., list number* 2014.18, 2017.14, 2017.27

*ancillary studies are listed by number https://aric.cscc.unc.edu/aric9/researchers/ancillary_studies/approved_ancillary_studies [ARIC Website Ancillary Studies Approved Ancillary Studies]

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 https://aric.cscc.unc.edu/aric9/publications/policies_forms_and_guidelines [ARIC Website Publications Publication Policies, Forms, and Guidelines]. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

References: References

1. Giro P, Cunningham JW, Rasmussen-Torvik L, Bielinski SJ, Larson NB, Colangelo LA, Jacobs DR, Jr., Gross M, Reiner AP, Lloyd-Jones DM, Guo X, Taylor K, Vaduganathan M, Post WS, Bertoni A, Ballantyne C, Shah A, Claggett B, Boerwinkle E, Yu B, Solomon SD, Shah SJ and Patel RB. Missense Genetic Variation of ICAM1 and Incident Heart Failure. *J Card Fail*. 2023.
2. Chia YC, Kieneker LM, van Hassel G, Binnenmars SH, Nolte IM, van Zanden JJ, van der Meer P, Navis G, Voors AA, Bakker SJL, De Borst MH and Eisenga MF. Interleukin 6 and

Development of Heart Failure With Preserved Ejection Fraction in the General Population. *J Am Heart Assoc*. 2021;10:e018549. PMC8483531
3. Putko BN, Wang Z, Lo J, Anderson T, Becher H, Dyck JR, Kassiri Z, Oudit GY and Alberta HI. Circulating levels of tumor necrosis factor-alpha receptor 2 are increased in heart failure with preserved ejection fraction relative to heart failure with reduced ejection fraction: evidence for a divergence in pathophysiology. *PLoS One*. 2014;9:e99495. PMC4055721
4. Nayor M, Short MI, Rasheed H, Lin H, Jonasson C, Yang Q, Hveem K, Felix JF, Morrison AC, Wild PS, Morley MP, Cappola TP, Benson MD, Group CH-HFW, Consortium CH-E, Ngo D, Sinha S, Keyes MJ, Shen D, Wang TJ, Larson MG, Brumpton BM, Gerszten RE, Omland T and Vasan RS. Aptamer-Based Proteomic Platform Identifies Novel Protein Predictors of Incident Heart Failure and Echocardiographic Traits. *Circ Heart Fail*. 2020;13:e006749. PMC7236427
5. Katz DH, Tahir UA, Ngo D, Benson MD, Gao Y, Shi X, Nayor M, Keyes MJ, Larson MG, Hall ME, Correa A, Sinha S, Shen D, Herzig M, Yang Q, Robbins JM, Chen ZZ, Cruz DE, Peterson B, Vasan RS, Wang TJ, Wilson JG and Gerszten RE. Multiomic Profiling in Black and White Populations Reveals Novel Candidate Pathways in Left Ventricular Hypertrophy and Incident Heart Failure Specific to Black Adults. *Circ Genom Precis Med*. 2021;14:e003191. PMC8497179

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