ARIC Manuscript Proposal #3323

PC Reviewed: 1/8/2019	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Molecular origin of metabolic allostasis: insights into cardiovascular resilience with aging

b. Abbreviated Title (Length 26 characters): **Metabolomics of allostasis**

2. Writing Group:
Writing group members: Ashish Yeri, Bing Yu, Wenshuang Weng, Venkatesh Murthy, Jan Bressler, Christie M. Ballantyne, Katy Tucker, Eric Boerwinkle, Ravi Shah

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __BY___ **[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 (this must be an ARIC investigator).

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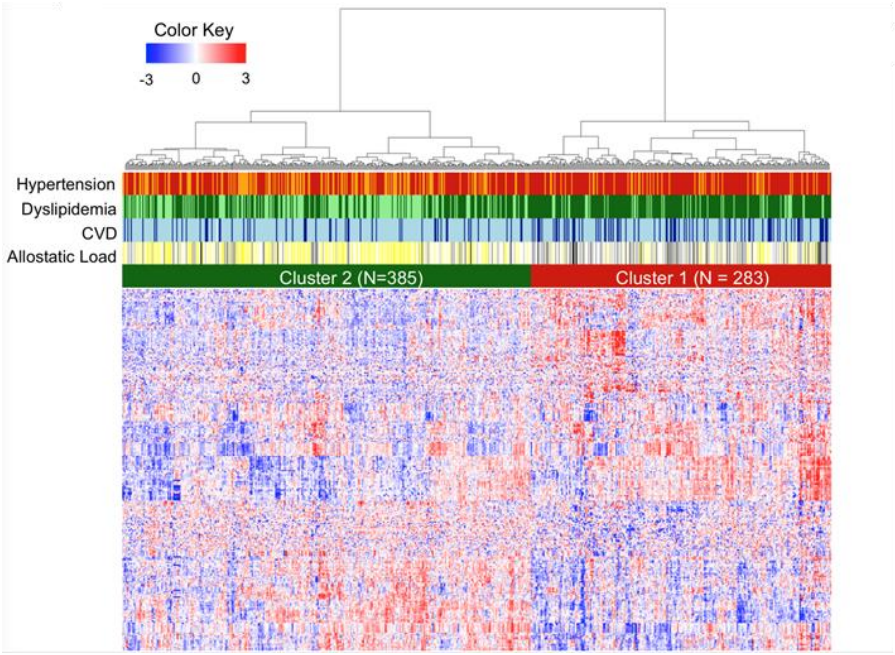
3. Timeline: Submission of manuscript within 1-2 months of approval (this proposal covers a replication of results from another cohort study in ARIC).

4. Rationale: While inflammation, insulin resistance, and adverse lifestyle exposures (diet, inactivity, stress) drive cardiovascular risk at the population level, there remains significant heterogeneity in how stress impacts cardiometabolic disease (CMD) in any individual. This

observation has given rise to the complementary concepts of "allostasis" and "resilience"- the idea that variability in metabolic response to pro-inflammatory stress contributes to cardiometabolic diseases. Indeed, there has been evolving interest in how these phenomena contribute to race-based disparities in CMD[1, 2]: poorer allostasis (as described by an "allostatic load") has been previously demonstrated to be associated with CMD in immigrant Puerto Ricans (PRs) already at high risk relative to other American ethinicities[3]. However, this finding remains primarily descriptive, as allostatic load classically consists of end-phenotypes reflecting a generalized inflammatory state (e.g., diabetes, hypertension, dyslipidemia) that characterize CMD at a population level and lacks clarity on specific underlying molecular perturbations central to CMD in an individual. Identifying these specific metabolic contributors to cardiovascular allostasis and resilience in individuals with highly prevalent CMD may not only inform disease mechanism, but may also more precisely pinpoint those at-risk individuals for aggressive prevention and therapeutic efforts, an especially attractive goal given increasing obesity-related CMD.

This study involves two cohorts - the Boston Puerto Rican Health Study (BPRHS) and the ARIC study. In the BRPHS, we have obtained an index of allostasis/resilience, a score composed of the following components: hypertension, waist circumference, dyslipidemia, dysglycemia (e.g., blood sugar control), urinary cortisol, urinary epinephrine, urinary norepinephrine, serum DHEA-S, and C-reactive protein. (This score had been associated with incident CVD and other inflammatory conditions in the BPRHS.) In a subgroup of these individuals, we have assayed the circulating metabolome (via Metabolon, similar to ARIC). In preliminary analyses, we assessed 720 metabolites in >600 participants in the BPRHS to test the association of each metabolite with allostatic load (represented in a composite score of the components above), adjusted for age, sex, BMI, and smoking. 260 metabolites survived type 1 error correction at 5% level. These metabolites were used to classify the study participants into clusters using Bayesian clustering optimization (Manhattan Ward distance), with the following result:



In this study, we plan to (1) "project" cluster membership (Cluster 1 and Cluster 2) into ARIC using shared metabolites assayed in both studies and (2) testing the association of cluster membership in ARIC with long-term outcome.

5. Main Hypothesis/Study Questions:
The main hypothesis is that a metabolic fingerprint in ARIC visit 1 (defined by metabolite-based clusters that we found in BPRHS) will be associated with long-term outcomes relevant to cardiovascular aging. The primary study questions will include:

1) *Using metabolites shared between BPRHS and ARIC, can we define cluster 1 vs. 2 membership in ARIC, and what do those clusters look like phenotypically?*

2) *What is association of cluster membership in ARIC with long-term development of coronary heart disease and mortality?*

As noted here, the Cluster memberships have been defined in BPRHS (derived on an index of allostatic load), and ARIC data will provide validation of the clinical significance of these metabolite-based clusters.

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).

We will describe the general flow of this data analysis. We have previously derived cluster memberships within BPRHS.

Study design, inclusion/exclusion: Observational cohort design; we will include study participants with metabolite profiling in this analysis from ARIC

Summary of data analysis: This will be conducted in stages.

1) **"Projection" of cluster membership into from BPRHS into ARIC** (specifically those metabolites that were associated with allostatic load within BPRHS): In our preliminary discussions between BRPHS and ARIC, we used lasso regression to generate a parsimonious list of metabolites that describe cluster 1 vs. cluster 2 membership in BPRHS. Of the 40+ metabolites that define clusters in BPRHS, we will use logistic regression in BRRHS to generate an "equation" that will be used to "predict" cluster 1 vs. cluster 2 in ARIC, using only common metabolites. Of note, all metabolites are log-2 transformed and subsequently mean-centered and standardized (mean 0 and variance 1) such that units or batch differences in measurement do not interfere with cross-study comparison.

2) **Testing descriptive characteristics between clusters in ARIC:** We will use standard descriptive characteristics to test differences in clinical, demographic, and biochemical characteristics by cluster. Specifically, we will include age, sex, race, medical history, and traditional cardiometabolic risk factors.

3) **Testing association of cluster with long-term outcome in ARIC:** This is a standard Cox proportional hazards regression model for the following outcomes relevant or concordant with cardiovascular aging:

   a. **Incident CHD**
   Defined as fatal CHD, definite or probable myocardial infarction, silent myocardial infarction between examinations as determined by electrocardiography, and coronary revascularization that occurred on or before December 31, 2017.

   b. **Mortality**
   Defined as death from any cause that occurred on or before December 31, 2017.

   These models will be minimally adjusted (age and sex) and fully adjusted, including ARIC risk factors. We will test incremental characteristics beyond association, including discrimination and reclassification with addition of cluster membership (e.g., IDI, NRI, C-statistic).

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes __X__ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? ____ Yes ____ No
(This 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"? ____ 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/mantrack/maintain/search/dtSearch.html

____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)?

MS# 2867 Metabolomic predictors of incident coronary heart disease: findings from the Atherosclerosis Risk in Communities (ARIC) study

MS# 2380 Associations of the Serum Metabolome and Mortality among African Americans in the Atherosclerosis Risk in Communities (ARIC) Study

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

11.b. If yes, is the proposal

_X__ A. primarily the result of an ancillary study (list number* 2008.16 and 2014.20)

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

*ancillary studies are listed by number at https://www2.cscc.unc.edu/aric/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.

Agreed.

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.

Agreed.