ARIC Manuscript Proposal # 2967

PC Reviewed: 04/11/16 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Galectin-3 and the incidence of abdominal aortic aneurysm: the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Galectin-3 and AAA

2. Writing Group:

Writing group members: Oluwaseun Fashanu, Aaron Folsom, Christie Ballantyne, Pamela Lutsey, Weihong Tang

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. **OE [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: Begin late spring 2017

4. Rationale:

Galectin-3's role in a number of cardiovascular diseases such as heart failure, atrial fibrillation, and coronary heart disease have been largely explored. Yet, no prospective study has ascertained its association with abdominal aortic aneurysm (AAA).

Infiltration of the wall of the aorta by inflammatory cells, degradation of elastin and collagen in the tunica media, and smooth muscle cell apoptosis lead to the resultant thinning of the media with the subsequent dilatation of the aorta [PMID: 21079638]. Galectin-3, which is a β-galactoside binding lectin produced by number of inflammatory cells including macrophages, plays important regulatory roles in chemotaxis and inflammation. In mouse models, macrophage infiltration of the abdominal aorta was found to be a prominent feature of AAA progression [PMID: 22469240]. Galectin-3 may therefore be associated with the occurrence of AAA.

The aim of our study is to assess the prospective association between plasma galectin-3 levels and the incidence of abdominal aortic aneurysm in the ARIC study.

5. Main Hypothesis/Study Questions:

Higher plasma galectin-3 concentration is positively associated with the incidence of abdominal aortic aneurysm.

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).

Design: prospective with visit 4 as baseline, with galectin-3 as the exposure

Outcome: time to incident AAA determined from hospital records, and death certificates.
Exclusions: prevalent AAA, missing galectin-3, missing covariates

Primary Covariates: clinical AAA risk factors: age, sex, race (black, white), total cholesterol, high-density lipoprotein cholesterol, use of lipid medication (yes, no), systolic blood pressure, antihypertensive medication use (yes, no), diabetes mellitus (yes, no), smoking status and pack-years of cigarettes smoked, height, and weight

Analysis: Examine association of galectin-3 with covariates. Linear splines to examine association with AAA incidence. Main analysis—Cox proportional hazards models. A first model will adjust for age, sex, and race and also test for possible age, sex, race by galectin-3 interactions. The second model will adjust further for total cholesterol, high-density lipoprotein cholesterol, use of lipid medication (yes, no), systolic blood pressure, antihypertensive medication use (yes, no), diabetes mellitus (yes, no), smoking status and pack-years of cigarettes smoked, height, and weight.

Because the *LGALS3* (galectin-3 structural gene) rs4644 SNP appears to affect binding to the galectin-3 assay, we will also adjust for genotype.

We will conduct a sensitivity analysis to further adjust for inflammatory biomarkers (e.g. fibrinogen and white blood cell count) that were associated with AAA in ARIC [PMID:26085454].

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? __x__ Yes ____ 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)?

1505 Risk Factors for Abdominal Aortic Aneurysm (Tang)
1505A Biomarkers and AAA (Folsom)
2771 Galectin-3 and Cardiovascular Outcomes (Aguilar)

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* ___2009.18_____)
___ 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 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.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript __x__ Yes ____ No.