ARIC Manuscript Proposal # 1243

PC Reviewed: _5__/_8_/07	**Status: ___A_**	**Priority: __2_**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Cell markers and carotid remodeling

b. Abbreviated Title (Length 26 characters): cell markers remodeling

2. Writing Group:
Writing group members: (alphabetic listing) Nena Aleksic, Diane Catellier, Josef Coresh, Aaron Folsom, Richey Sharrett, Bruce Wasserman

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

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3. Timeline: Complete data are expected by April, 2007. It is anticipated that data analysis and manuscript preparation will be completed by July 2007.

4. Rationale: Platelet activation and aggregation, marked by expression levels of GPIIb, GPIIIa, P-selectin, or CD40L and by measured platelet-platelet aggregates are certainly prothrombotic and believed to relate to several atherogenic processes, including plaque stability affected by matrix lysis[1]. Circulating platelet aggregates with monocytes, granulocytes, and lymphocytes may be even better markers of cellular activation[1]. Monocyte myeloperoxidase may generate reactive oxidants which damage host tissues in plaque, and monocyte or leukocyte COX-2 levels may reflect the macrophage activity at the shoulders of vulnerable plaques. The members of the toll-like receptor (TLR) family play a critical role in the inflammatory components of atherosclerosis. Toll-like receptors are expressed preferentially on monocytes/macrophages.

Arterial walls react to plaque growth with varying levels of lumen compromise[2]. Plaques with outward remodeling and minimal stenosis are thought to be especially vulnerable to rupture[3-7]. They manifest signs of increased inflammation, such as higher concentrations of macrophages and T-cells[8-11] and matrix metalloprotein levels[11], and are more associated with circulating adhesion markers[12] and markers of plasmin activation[13]. For these reasons, we expect more evidence of platelet and leukocyte activation and aggregation in persons whose internal carotid artery is outwardly remodeled than in those with similar size plaque with more stenosis.

5. Main Hypothesis/Study Questions:

Outward remodeling of the internal carotid artery is associated with increased evidence of platelet and leukocyte activation and remodeling. This will be examined by comparing persons with lumens which are either greater than expected (outward remodeling) or less than expected (constrictive remodeling) based on regression of the lumen on wall thickness. Persons with outward vs. constrictive remodeling will be compared with respect to the following flow cytometry variables:

- Platelet GPIIb GPIIIa expression level
- Platelet expression of P-selectin
- Circulating platelet-platelet aggregates
- Circulating platelet-monocyte aggregates
- Circulating platelet-granulocyte aggregates
- Circulating platelet-lymphoocyte aggregates
- Leukocyte PSGL-1 expression level
- Monocyte expression of toll-like receptors -2, -4
- Monocyte myeloperoxidase (MPO)
- Monocyte COX-2 (cyclo-oxygenase-2)
- Granulocyte MPO, COX-2

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).

Analyses will include data from all participants with the needed variables. We will model lumen area as a function of mean (or maximum) wall thickness, body size (to account for anatomical differences in expected lumen area) and each of the cellular markers of interest. Body size will be represented by height, height^2 and possibly other variables. Carotid lumen and wall measurements will be taken from specified locations (e.g., one slice above the flow divider). For a given wall thickness, a greater body-size adjusted lumen area represents outward remodeling and a smaller lumen area represents constrictive remodeling. Additional adjustments will be made for age, race, sex and other potential confounding variables in a sequential manner to explore their impact on the associations between each cellular marker and lumen area. Non-linear models (e.g., splines) will be used to determine whether these associations differ between those with a wall thickness below, as compared to above, a specified cut-point.

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 ICTDER02 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 ICTDER02 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 ICTDER02 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/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)?

MS#1216-1219 relate the same flow cytometry variables to overall plaque dimensions (wall size and volume) and lipid core size and cap.
MS#1165-66 relate arterial wall and lumen measurements to plaque characteristics.

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* 1995.07___)
___ 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/

12. 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.

References

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