ARIC Manuscript Proposal # 720

1.a. **Full Title:** Immune differences between African-Americans and Caucasians as a risk factor for premature cardiovascular events

b. **Abbreviated Title:** Immunity in African-Americans

2. **Writing Group (list individual with lead responsibility first):**

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3. **Timeline:**

   Proposal prepared 3/1/00
   Publications Committee Review and Recommendations 4/1/00
   Proposal Priority Set 5/1/00
   Dataset Requests/Analysis/Assays 6/1/00
   Writing Group preparation of Draft manuscript 12/1/00
   Distribution of manuscript 2/1/01
   Official Analysis/Data Verification 4/1/01
   Steering Committee/NHBLI approval 6/1/01
   Submission to Journal 7/1/01
4. Rationale:

Racial differences in cardiovascular events (stroke and myocardial infarction) are known to exist, with African Americans having a higher morbidity, mortality, and incidence of stroke and myocardial infarction compared to Caucasians. Young blacks (<65 years of age) lose more years of life compared to whites due to cardiovascular disease among hypertensives. While higher frequencies of hypertension, diabetes, elevated lipoprotein levels, and low socioeconomic class have been identified as risk factors, other potentially treatable factors have not been fully elucidated.

It is known that blacks have higher immunoglobulin concentrations, higher incidences of autoimmune diseases (e.g. SLE, scleroderma, and dermatomyositis), and an increased frequency of autoantibodies compared to whites. Recent evidence has suggested that cytokines such as IL-6, IL-1, TNF or chemokines such as monocyte chemoattractant protein –1 (MCP-1) play a role in or accelerate atherogenesis. Animal models have suggested that interruption of the immune system prevents accelerated atherogenesis or reduces ischemic insult. Others have shown that poor outcomes correlate with increased immune markers (see attached list of references). However, few, if any, studies have directly investigated the hypothesis that the increased incidence, morbidity, or mortality of cardiovascular events in blacks is due to race-based differences in the immune system. Initial regression analysis of ARIC data by Folsom et al. have shown that some hemostatic parameters (vWF, FVIIIc, white blood cell count, fibrinogen) correlated with ischemic stroke, supporting the concept that abnormalities of hemostatic and inflammatory markers are associated with increased risk of stroke. A comparison of immune parameters between African-Americans and Caucasians may identify important immune-based risk factors as well as potential therapeutic targets. Intervention in patients with increased immune responses as risk factors for cardiovascular disease may reduce the excessive cardiovascular morbidity and mortality in African-Americans. Therefore, we propose to examine cytokine and immunoglobulin differences between African-Americans and Caucasians to determine if immune system differences contribute to accelerated atherogenesis and cardiovascular mortality in African-Americans.

5. Main Objectives:

African-Americans with premature (<60 years of age) stroke, myocardial infarction, and coronary heart disease have increased immune response parameters compared to age- and sex-matched Caucasians prior to the incident event.

6. Data (variables, time window, source, inclusions/exclusions)

In a case-control manner the following variables would be compared:

Variables – Controlled – age, sex, hypertension, diabetes, hyperlipidemia, smoking, obesity, stroke, myocardial infarction (MI), coronary heart disease.

Variables – Measured – C-reactive protein, and, if available, IgM/IgG serum concentrations, IL-1, IL-6, TNFα, TGFα, and MCP-1 in serum, if available. We would propose to measure these variables in serum through an ancillary study proposal, if unavailable.
Time window – ARIC study timeline using the baseline visit (visit 1) as the measured immune parameter source with prospective case ascertainment of stroke, myocardial infarction, and coronary heart disease cases.

Methods – Comparison of immune parameters between African-American and Caucasian cardiovascular cases will be made as well as comparison between race/sex/age matched controls.

<table>
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<tr>
<th>Race</th>
<th>Cardiovascular Disease</th>
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<tbody>
<tr>
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<tr>
<td>African-American</td>
<td>Control immune parameter</td>
</tr>
<tr>
<td>Caucasian</td>
<td>Control immune parameter</td>
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As a second level of analysis, a comparison of associations between immune response parameters and cardiovascular events will be made across racial groups (i.e. stratify on race and compare quartiles of CRP or cytokine levels). Ultimately odds ratios (as estimates of relative risk) for cardiovascular events could be made by comparing the upper quartile of measured immune responses with the lower quartile.

Source – ARIC nested case cohort design and available measurements or available serum for additional testing, if necessary, through an ancillary proposal

Expected results - We would expect that if our hypothesis were true, African-Americans with stroke, MI, or coronary heart disease would have increased immune response parameters prior to the incident event, as evidenced by higher IgM/IgG serum concentrations or increased cytokine/chemokine concentrations compared to Caucasians and, perhaps, to control cases. It is also possible that race-based immune differences would be identified in controls. This finding may have implications for other inflammatory disease states such as SLE or sarcoid.