

## ARIC Manuscript Proposal # 1002

PC Reviewed: 04/08/04

Status: A

Priority: 2

SC Reviewed: 04/13/04

Status: A

Priority: 2

**1.a. Full Title:** The P-Selectin Thr715Pro Polymorphism and Risk of Stroke and Coronary Heart Disease

**b. Abbreviated Title (Length 26 characters):** PSEL T715P, Stroke and CHD

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

**Lead:** Eric Boerwinkle

**Address:** Human Genetics Center  
University of Texas Health Science Center at Houston  
1200 Herman Pressler  
Houston, TX 77030

Phone: 713-500-9800 Fax: 713-500-0900

E-mail: [eboerwinkle@sph.uth.tmc.edu](mailto:eboerwinkle@sph.uth.tmc.edu)

Writing group members: Kelly Volcik, Christie Ballantyne, Josef Coresh, Aaron Folsom, Kenneth Wu

**3. Timeline:** Genotyping of the P-selectin (PSEL) Thr715Pro polymorphism is complete for the stroke and CHD case-cohort samples. Analyses will be completed subsequently.

**4. Rationale:**

The pathogenesis of atherosclerosis is known to contain an important inflammatory component, involving the adhesion of circulating leukocytes, particularly monocytes, to the vascular endothelium at sites of injury (Ross 1999). The recruitment and binding of circulating leukocytes to the vascular endothelium is mediated through a diverse family of adhesion molecules, including the selectins, which mediate the initial rolling of leukocytes along the endothelium (Albelda et al. 1994). Adhesion of leukocytes to the endothelium and subsequent transendothelial migration is an important step in the initiation and aggravation of atherosclerotic lesions (Price and Loscalzo 1999). P-selectin, a member of the selectin family of adhesion receptors, is expressed on platelets and activated endothelium where it mediates both the binding of activated platelets to monocytes and of monocytes to injured endothelium (Johnson et al. 1997).

Evidence of a key role for P-selectin in the development of atherosclerotic lesions is provided by multiple knockout mouse models showing reduced fatty streaks and attenuated lesion formation resulting from disruption of the P-selectin gene (Molenaar et al. 2003, Manka et al. 2001, Collins et al. 2000, Dong et al. 1999). Studies have shown p-selectin expression to be positively correlated with the extent of atherosclerotic lesion development as well as with arterial wall thickness and arterial stiffness (Koyama et al. 2003, Molenaar et al. 2003). Furthermore, increased levels of P-selectin have been observed in various cardiovascular disorders, including hypercholesterolemia, myocardial infarction and unstable angina, as well as being associated with progressive vascular damage in persons with essential and malignant hypertension (Davi et al. 1998, Xu et al. 1998, Ikeda et al. 1995, Verhaar et al. 1998).

The P-selectin Pro715 allele was previously reported to be potentially protective for myocardial infarction (Herrmann et al. 1998). Another analysis found a strong association between P-selectin gene polymorphisms (including Thr715Pro) and serum P-selectin levels, but was unable to replicate the previously reported association between myocardial infarction and the Thr715Pro polymorphism (Barboux et al. 2001). Zee et al. recently reported that another P-selectin polymorphism, Val640Leu, is an independent predictor of incident stroke (2004). To our knowledge, there are no published reports of the association between the P-selectin Thr715Pro polymorphism and stroke. Therefore, due to the evident role of P-selectin in the progression of atherosclerosis and vascular damage, and due to the conflicting reports regarding the role of the Thr715Pro polymorphism in heart disease, we propose to determine the association of the P-selectin Thr715Pro polymorphism with stroke and coronary heart disease.

#### References:

- Albelda SM, Smith CW, Ward PA. 1994. Adhesion Molecules and Inflammatory Injury. *FASEB J* 8:504-512.
- Barboux SC, Blankenberg S, Rupprecht HJ, et al. 2001. Association Between P-Selectin Gene Polymorphisms and Soluble P-Selectin Levels and Their Relation to Coronary Artery Disease. *Arterioscler Thromb Vasc Biol* 21:1668-1673.
- Collins RG, Velji R, Guevara NV, et al. 2000. P-Selectin or Intercellular Adhesion Molecule (ICAM-1) Deficiency Substantially Protects Against Atherosclerosis in Apolipoprotein E-Deficient Mice. *J Exp Med* 191:189-194.
- Davi G, Romano M, Mezzetti A, et al. 1998. Increased Levels of Soluble P-Selectin in Hypercholesterolemic Patients. *Circulation* 97:953-957.
- Dong ZM, Brown AA, Wagner DD. 2000. Prominent Role of P-Selectin in the Development of Advanced Atherosclerosis in ApoE-Deficient Mice. *Circulation* 101:2290-2295.
- Herrmann SM, Ricard S, Nicaud V, et al. 1998. The P-Selectin Gene is Highly Polymorphic: Reduced Frequency of the Pro715 Allele Carriers in Patients with Myocardial Infarction. *Hum Mol Genet* 7(8):1277-1284.
- Ikeda H, Takajo Y, Ichiki K, et al. 1995. Increased Soluble Form of P-Selectin in Patients with Unstable Angina. *Circulation* 92:1693-1696.
- Johnson RC, Chapman SM, Dong ZM, et al. 1997. Absence of P-Selectin Delays Fatty Streak Formation in Mice. *J Clin Invest* 99(5):1037-1043.
- Koyama H, Maeno T, Fukumoto S, et al. 2003. Platelet P-Selectin Expression is Associated with Atherosclerotic Wall Thickness in Carotid Artery in Humans. *Circulation* 108:524-529.
- Manka D, Collins RG, Ley K, et al. 2001. Absence of P-Selectin, but not Intercellular Adhesion Molecule-1, Attenuates Neointimal Growth After Arterial Injury in Apolipoprotein E-Deficient Mice. *Circulation* 103:1000-1005.
- Molenaar TJM, Twisk J, de Haas SAM, et al. 2003. P-Selectin as a Candidate Target in Atherosclerosis. *Biochem Pharm* 66:859-866.
- Price DT, Loscalzo J. 1999. Cellular Adhesion Molecules and Atherogenesis. *Am J Med* 107:85-97.
- Ross R. 1999. Atherosclerosis: An Inflammatory Disease. *N Engl J Med* 340:115-126.
- Verhaar MC, Beutler JJ, Gaillard CA, et al. 1998. Progressive Vascular Damage in Hypertension is Associated with Increased Levels of Circulating P-Selectin. *J Hypert* 16:45-50.
- Xu D, Zhao S, Peng W. 1998. Elevated Plasma Levels of Soluble P-Selectin in Patients with Acute Myocardial Infarction and Unstable Angina: An Inverse Link to Lipoprotein(a). *Int J Cardiol* 64:253-258.
- Zee RYL, Cook NR, Cheng S, et al. 2004. Polymorphism in the P-Selectin and Interleukin-4 Genes as Determinants of Stroke: A Population-Based, Prospective Genetic Analysis. *Hum Mol Genet* 13(4):389-396.

5. **Main Hypothesis/Study Questions:** PSEL T715P polymorphism predicts stroke case and/or CHD status after controlling for traditional risk factors
6. **Data (variables, time window, source, inclusions/exclusions):** ARIC's stroke and CHD case-cohort groups will be utilized for the analyses. The dependent variable is stroke or CHD case status. Independent variables include, but are not limited to, PSEL T715P genotype status and traditional risk factors such as age, gender, race, smoking status, plasma lipid levels, body mass index, hypertension status, etc.

7.a. **Will the data be used for non-CVD analysis in this manuscript?**  Yes  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  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.csc.unc.edu/ARIC/search.php>

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)?** The most closely related manuscript proposals are #871 and #677, both of which Eric Boerwinkle is a part of the writing group.

11. **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.**

Yes  No