ARIC Manuscript Proposal # 870

PC Reviewed: 03/12/02	**Status: __A__**	**Priority: __1__**
SC Reviewed: 03/19/02	**Status: __A__**	**Priority: __1__**

1.a. Full Title: Plasma MMP-1 and TIMP-1 Concentrations and Risk for Coronary Heart Disease.

b. Abbreviated Title (Length 26 characters): MMP-1 and TIMP-1 and incident CHD

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

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3. Timeline: All sample analyses have been completed by the Lipid Laboratory. Statistical analysis will start February, 2002 and manuscript will be completed by August 2002.

4. Rationale:

Atherosclerosis is a complex inflammatory process that is characterized by the formation of atherosclerotic lesions, containing lipid-laden macrophages, in the neointima of major arteries (Ross, 1999). Disease progression results in formation of mature atherosclerotic plaques, which consist of a necrotic lipid core overlaid with a fibrous cap. The fibrous cap is mainly composed of collagens, elastin and proteoglycans (Shah, 1996). Disruption of atherosclerotic plaques leads to the release of thrombogenic molecules into the blood circulation and subsequent thrombus formation can result in acute myocardial infarction, the leading cause of death in the United States (Libby, 1995).

Recent studies suggest that matrix metalloproteinases (MMPs) may contribute to the rupture of vulnerable plaques by degrading the insoluble fibrillar components of the fibrous cap (Libby, 1995). Inflammatory cytokines induce MMP expression in endothelial cells,

smooth muscle cells and macrophages and the proteolytic activities of MMPs are tightly regulated by a variety of endogenous inhibitors, including tissue inhibitors of metalloproteinases (TIMPs) (Nagase and Woessner, 1999). It has been proposed that an imbalance between MMPs and their respective inhibitors (TIMPs) may constitute an etiologic factor for cardiovascular disease.

Increased expression of interstitial collagenase (MMP-1) has been found in vulnerable atherosclerotic plaques compared to nonlesional areas of the vessel (Galis et al., 1994). Furthermore, overexpression of TIMP-1 by adenovirus-mediated gene transfer inhibits smooth muscle cell migration and neointimal formation in human saphenous vein (George et al., 1998). Similarly, adenovirus-mediated overexpression of TIMP-1 in atherosclerosis-susceptible apoE-deficient mice significantly reduces atherosclerotic lesions (Rouis et al., 1999).

Although a significant number of research studies indicate a role for MMP-1 and TIMP-1 in the etiology of atherosclerosis, there are relatively few prospective epidemiological studies investigating the relationship between circulating MMP-1 and TIMP-1 levels and incidence of CHD. In a recent study, plasma levels of MMP-2, MMP-3, MMP-9, TIMP-1, and TIMP-2 were measured in 53 male patients with premature stable coronary artery disease and 133 age-matched male control subjects (Noji et al., 2001). Significant differences were found in all MMPs and TIMPs between patients and controls. However, results from this study indicate that the association of circulating MMP and TIMP levels with premature atherosclerosis may be more complex than a simple inverse correlation between MMP and TIMP plasma levels.

References:

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George SJ, Johnson JL, Angelini GD, Newby AC, Baker AH. Adenovirus-mediated gene transfer of the human TIMP-1 gene inhibits smooth muscle cell migration and neointimal formation in human saphenous vein. Hum. Gene Ther. 1998; 6:867-877.

Libby P. Molecular bases of the acute coronary syndromes. Circulation 1995; 91:2844-2850.

Nagase H, Woessner JF, Jr. Matrix metalloproteinases. J. Biol. Chem. 1999; 274:21491-21494.

Noji Y, Kajinami K, Kawashiri MA, Todo Y, Horita T, Nohara A, et al. Circulating matrix metalloproteinases and their inhibitors in premature coronary atherosclerosis. Clin. Chem. Lab. Med. 2001; 5:380-384.

Ross R. Atherosclerosis—an inflammatory disease. N Engl J Med 1999;340:115-126.

Rouis M, Adamy C, Duverger N, Lesnik P, Horellou P, Moreau M, et al. Adenovirus-mediated overexpression of tissue inhibitor of metalloproteinase-1 reduces atherosclerotic lesions in apolipoprotein E-deficient mice. Circulation 1999; 100:533-540.

Shah PK. Pathophysiology of plaque rupture and the concept of plaque stabilization. Cardiol. Clin. 1996; 14:17-29.

5. Main Hypothesis/Study Questions:

Increased plasma levels of MMP-1 and decreased plasma levels of TIMP-1 are associated with increased risk for CHD events.

Secondary hypotheses are that:
1) circulating levels of MMP-1 and TIMP-1 correlate with plasma LDL-cholesterol and HDL-cholesterol levels.
2) plasma MMP-1 and TIMP-1 levels are associated with markers of inflammation (WBC, ICAM-1, VCAM-1, CRP, fibrinogen, E-selectin, L-selectin, P-selectin).

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

MMP-1 and TIMP-1 measurements were made on Visit 2 plasma samples of CHD cases and cohort stratified random sample (CRS)**.**
Data will include incident CHD case status and date of CHD diagnosis.
Covariates will include visit 2 age, gender, race, center, BMI, years of cigarette smoking, incident diabetes, triglycerides, LDL cholesterol, HDL cholesterol, treatment with statins, inflammatory markers (WBC, ICAM-1, VCAM-1, fibrinogen, CRP, E-selectin, L-selectin, P-selectin).

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://bios.unc.edu/units/cscc/ARIC/stdy/studymem.html

____X__ Yes _____ No