

## ARIC MANUSCRIPT PROPOSAL FORM

MANUSCRIPT #502

1.a. Full Title: Interaction of Smoking and Genetic Polymorphism of GSTM1, GSTT1, NAT2 and Atherosclerosis

b. Abbreviated Title (Length 26): Enzymes x Smoking and Athero

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

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3. Time Line:

Following approval by the Publications Committee, the Coordinating Center can begin preparation of the ID listing. Transfer of the DNA material to Dr. Bell's laboratory can then follow, as arranged during a conference call on July 24.

4. Rationale:

A plausible link between metabolic enzyme systems and atherogenesis can be found in the Benditt hypothesis. 1,2 Cells of atherosclerotic plaques differ from cells of the normal arterial wall in terms of size, an apparent deficiency of cell to cell contacts, and a high degree of monoclonal character. Benditt and Benditt pointed out that atherosclerotic lesions begin as localized, excessive accumulations of smooth-muscle cells in the intima.

Using glucose-6-phosphate dehydrogenase (G-6-PD) isoenzymes as markers to determine whether cells originated from a single progenitor, they concluded that three quarters of the plaques sampled exhibited a monoclonal character.<sup>1,2</sup> Since the publication of Benditt's work (in 1973) at least 26 articles have been published supporting Benditt's hypothesis in studies of animals and using human tissues from surgery or autopsy. For example Majewsky et al. reported that monoclonal smooth muscle proliferation in the thoracic aorta of the chicken can be produced by an initiation-promotion treatment sequence of chemical mutagens,<sup>3</sup> whereas only one article could be found presenting results that contradict Benditt's proposition. To our knowledge, no studies have explored the role of genetic polymorphism in the detoxification/activation of promutagens or

mutagens in tobacco smoke on the risk of atherosclerosis in human populations, much less on atherosclerosis measured in vivo.

5. Main Hypothesis:

- a. Cigarette smoking is associated with increased risk of carotid atherosclerosis among individuals who are not exposed to "at risk" genotypes of GSTM1, GSTT1, and NAT2 activation/detoxification enzymes;
- b. "At risk" genotypes of GSTM1, GSTT1, and NAT2 activation/detoxification enzymes are associated with increased risk of carotid atherosclerosis among never smokers;
- c. There is a synergistic risk of carotid atherosclerosis among those exposed to the "at risk" genotypes of GSTM1, GSTT1, and NAT2 genotypes and cigarette smoking.

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

Analyses will be conducted on the ARIC cohort-representative sample, and the asymptomatic cases of carotid atherosclerosis. Laboratory analyses will include GSTM1, GSTT1, and NAT2. GSTP1 may be included if a new assay can be set up to run this gene in the same PCR reaction.

7. Selected references:

Benditt EP, Benditt JM: Evidence for a monoclonal origin of human atherosclerotic plaques. Proc Natl Acad Sci USA 1973;70:1753-6

Benditt EP: Evidence for a monoclonal origin of human atherosclerotic plaques and some implications Circulation 1974;50:650-2

Majewsky MW, et al. Focal smooth muscle proliferation in the aortic intima produced by an initiation-promotion sequence. Proc. Natl. Acad. Sci. USA 1985;82:3450-4.