

THE COUNCIL FOR TOBACCO RESEARCH-U.S.A., INC.

File

TO: Drs. Boutwell, Sato, Sommers, Jacobson, Hockett, Stone, Ford
Messrs. Hoyt and Hobbs

FROM: W.U. Gardner

SUBJECT: Charles S. Greenberg, M.D., University of California, San
Francisco, San Francisco, CA 94143
New Application No. 1591
"Transglutaminases and Atherosclerosis"

Applicant - Age, 33 year; MD., Hahnemann Medical College, 1976; intern
and resident, University of MN 1977-79; fellowship, U. CA., 1978-81;
American Heart Fellowship, 1981- He has worked on a number of topics, most
recently on the one indicated by this application. He has 11 titles, sub-
mitted or published and a number of abstracts in addition.

Background - "Cigarette smoke contains two distinct coagulation inhibitors;
One which prolongs the clotting times of plasma by inducing delayed fibrin
aggregation and requiring the COOH-terminal region of fibrin alphachains
to exert its effect; the other inactivates XIIIa, thus preventing the cross
linking of fibrin polymers." This statement by Janoff and associates appeared
in Science, 217, 642-45, 1982. The PI has found that vascular cells contain
transglutaminase (TGlase) activity; confluent cells more than nonconfluent.
Transglutaminase activity has been shown in sonicates of adult bovine endo-
thelial cells (ABAE) and vascular smooth muscle (VSM) by incorporation of
³H-putrescine into dimethylcasein. TGlases catalyze glutamyl and lysyl
bonds similar to those in cross-linked fibrin. Functionally TGlase stabilizes
the fibrin clot during blood coagulation and assists in the formation of the
vaginal plug in rodents. The functions of possible TGlase inhibitors are also
controversial. Little work has been done on the structure and biochemistry of
TGlases.

Projection - The methods to be used are referred to briefly. The ³H-putrescine
assay will be used. Homogenates of cultured cells and probably intact aortas
will be used. Studies are projected on the effects of HDI of several enzyme
inhibitors, lysosomal complexes and cigarette smoke fractions will be done. The
general plan is to characterize the TGlases in vascular tissues and determine
their physiologic role in cell proliferations and pathologic role in atherosclerosis.

Budget - \$14,190 for permanent equipment that will be used for the proposed
investigations. He has a Am. Heart Assoc. grant; \$14,000; and has 3 applications
pending that might overlap the CTR application.

Comment - Rating high for both merit and relevance. It is cleverly designed
to open and close with reference to smoke exposure aspects.

W.U.G.

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