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GRANT APPLICATION NO. 1724 REVIEWER: DR. D. H. BOWDEN

APPLICANT: Howard G. Welgus, M.D. Washington University School of Medicine St. Louis, MO

TITLE: "Human Macrophage Collagenase and Collagenase Inhibitor"

BROAD GOALS:

To define the direct effects of human mononuclear phagocytes upon collagen metabolism in normal states and in diseases characterized by tissue remodeling such as pulmonary emphysema and pulmonary fibrosis.

BACKGROUND:

The author gives a beautifully written description of the background work with a critical review of the literature and the relevant experiments already performed in this laboratory. While the role of the fibroblast in collagen turnover has been studied extensively less is known about the function of inflammatory cells in this process. Preliminary work obtained in Dr. Welgus' laboratory reveals that macrophages secrete both a collagenase and a collagenase inhibitor which are immunologically identical to the collagenase and collagenase inhibitor produced by skin fibroblasts. It is postulated that in inflammatory situations a 5 to 10-fold augmentation in collagenolysis could reasonably be expected. In addition, human macrophage collagenase preferentially degrades type I and III collagens, the predominant species which comprise the connective tissue matrix of the lung.

CONFIDENTIAL

EXPERIMENTAL METHODS:

1. What are the physiologic and/or pharmacologic modulators of collagenase and collagenase inhibitor secretion by macrophages?

Alveolar macrophages will be harvested from healthy, young adult smokers. They will be cultured to examine the effect of regulatory substances on collagenase and collagenase inhibitor expression.

2. Is secretion of collagenase and collagenase inhibitor by human alveolar macrophages regulated in a coordinate manner?

Cultures of human alveolar macrophages will be studied by adding various agents and measuring the overall functional collagenolytic activity

of conditioned media, and then correlating this activity with quantities of immunoreactive collagenase and collagenase inhibitor determined in the samples.

3. Does multinucleation of human mononuclear phagocytes alter production of collagenase and/or collagenase inhibitor?

The authors have observed that multinucleation enhances the capacity of peritoneal macrophages to resorb bone. They now wish to study whether the presence of multinucleated phagocytes may lead to enhanced degradation of tissues other than bone. They will use cultured alveolar macrophages induced to undergo multinucleation by culture on dialysis membrane in the presence of 10% human serum.

4. Is macrophage collagenase and inhibitor production related to interleukin I?

The capacity of interleukin I to stimulate production of the two proteins will be assessed by adding increasing amounts of lipopolysaccharide-free ultrapure IL-1 to macrophage-containing cultures and measuring secretion of the immunoreactive products with time.

5. Do lymphocytes and neutrophils modulate macrophage-mediated collagenolysis?

The importance of cell-cell interactions at inflammatory sites in modulating direct macrophage mediated collagenolysis is presumed. They propose to study the influence of products from stimulated lymphocytes and neutrophils upon collagenase and collagenase inhibitor secretion in vitro.

THE INVESTIGATORS:

Dr. Welgus is a 33-year-old M.D. who is currently Assistant Professor of Medicine and Dermatology at Washington University School of Medicine. For a young man he has an impressive bibliography and for the last several years he has been associated with Robert Senior and Edward Campbell working in the area of macrophages and their enzymes. Dr. Robert Senior also with Washington University is one of the leading macrophage biologists in the country. Dr. Edward Campbell is one of our grantees and his work on elastase and the

pathogenesis of emphysema is well known to us. Dr. Steven Teitelbaum is a pathologist who is a Research Professor of Oral Biology at Washington University School of Dental Medicine.

CRITIQUE:

The questions posed are of importance to basic biology and also to clinical medicine. We are supporting a considerable amount of work related to elastase and the destruction of elastic tissue in the lung. The role of collagenase and its inhibitors and the relationship of macrophages to tissue degradation has received far less attention. Over the past few years a number of investigators have suggested a non-immunologic role for the macrophage in secreting various proteolytic enzyme which chronically degrade tissues and lead to the persistence of chronic inflammation. The work proposed here has implications far beyond the lung. The group associated with Dr. Welgus is probably one of the best clinical investigation groups in North America and the record of Dr. Welgus as a promising young investigator suggests to me that he is one of the young research scientists that we are looking for. This is good work and we should support it.

BUDGET:

The budget is somewhat high, particularly with salaries, but we would probably get good value for money.

RECOMMENDATION:

Approval with high priority.