

James & Esther King Biomedical Research Program

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*2007 Program
New Investigator (3-year project)*

Project Title: Matrix Metalloproteinase-induced Lung Fibrosis and Malignancy

Project Summary: The structure and form of the body is defined by networks of proteins known as the extracellular matrix (ECM). Organ development and wound healing require remodeling of the ECM, which is accomplished in part by matrix metalloproteinases (MMPs). Sustained expression of MMPs in the lung is associated with lung fibrosis and lung cancer. Because of the critical role of MMPs in fibrosis and cancer progression, considerable research effort has focused on inhibiting MMPs as a therapeutic strategy for treating lung cancer and other cancers. However, because MMPs also function in many normal physiological processes such as wound healing and development of new blood vessels, most drug trials evaluating MMP inhibitors have found them to be more detrimental than beneficial. What is needed is a better understanding of the tumor-specific activities of MMPs so that we can design more effective therapeutics targeting these tumor-specific pathways. We previously found that MMPs can stimulate the development and multiplication of myofibroblasts, the principal cellular mediators of lung fibrosis. We have now developed sophisticated cell culture models and transgenic mouse models for studying MMPs and MMP-related processes in lung cells. We have found that expression of a single MMP is sufficient to induce early characteristics of lung fibrosis. In this grant, experiments will determine how this MMP stimulates lung fibrosis and potentiates lung cancer. The objective of this grant is to identify MMP-dependent, fibrosis/tumor-specific processes and to develop animal models for evaluating potential therapeutic interventions in these processes. This work is innovative because it investigates wholly unexplored pathways by which a key element of the pathological microenvironment facilitates fibrosis development and tumor progression. This work is significant because elucidation of these pathways will provide key insight into mechanisms of lung fibrosis and cancer and will enable the development of new therapies for lung cancer targeting these pathways. Our experience with the experimental models, extensive preliminary data, new transgenic mouse models, access to the excellent support facilities at Mayo Clinic Cancer Center, and the expertise and insights of our world-class collaborators combine to secure a high probability of success for this project.