

James & Esther King Biomedical Research Program

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*Cancer Basic Science
Mayo Clinic*

*2008 Program
New Investigator (3-year project)*

Project Title: Development of Highly Selective MMP-10 Inhibitors for Lung Cancer Therapy

Project Summary: Lung cancer is the leading cause of cancer mortality in Florida and elsewhere in the U.S. Extremely poor survival rates associated with this deadly disease highlight a need for new and improved treatment strategies. Matrix metalloproteinase-10 (MMP-10) is an enzyme produced by lung tumors that promotes tumor invasion and metastasis; inhibitors of MMP-10 may be useful as drugs for lung cancer therapy. However, currently available inhibitors target a broad spectrum of MMPs (including some with beneficial functions) and cause problematic side effects. We have proposed a new approach to the development of highly selective MMP-10 inhibitors for lung cancer therapy through modification of a human protein, the tissue inhibitor of metalloproteinases-1 (TIMP-1). We are creating a library of modified TIMP-1 proteins displayed on the surface of cells, and plan to select from this library the TIMPs with greatest potency and selectivity for inhibiting MMP-10. We are also studying the molecular structures of MMP-10 and TIMP-1 to discover how they interact; this information will lead to further optimization of TIMPs as drugs to target MMP-10. Finally, we plan to test TIMP-1 and improved TIMPs for the ability to prevent or slow the growth or metastasis of human lung tumors implanted into mice. These studies will enable evaluation of MMP-10 inhibition as a therapeutic strategy for treating lung cancer, and of modified TIMPs as a new class of drugs for lung cancer therapy.