

## Bankhead-Coley Cancer Research Program

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*Cancer Basic Science  
Mayo Clinic*

*2009 Program  
Bridge (1-year project)*

**Project Title:** Development of Highly Selective MMP-9 Inhibitors for Breast Cancer Therapy

**Project Summary:** We aim to develop a new anticancer drug for selectively blocking MMP-9, an enzyme that facilitates the growth and metastasis of breast cancer, using as a prototype a natural inhibitor of MMPs produced within our bodies called TIMP-1. In many studies TIMP-1 has shown an ability to slow cancer growth and spread by blocking MMP-9 and related enzymes, but under some circumstances, TIMP-1 can exhibit an opposite effect by interfering with apoptosis, a natural mechanism of programmed cell death. Apoptosis plays a vital role in maintaining breast function by balancing cell division with cell death; acquiring the ability to escape apoptosis is a key step in the development of breast cancer. Previous investigations of how TIMP-1 interferes with apoptosis suggest that it will likely be possible to separate the MMP-blocking function from the apoptosis-blocking function, to produce an altered TIMP-1 that can still inhibit MMPs, while having no effect on apoptosis. In this Bridge Grant application, we propose to determine the specific component of TIMP-1 that is responsible for blocking apoptosis in breast cancer cells and to construct an altered TIMP-1 that is devoid of any apoptosis-blocking function but that retains its antitumor properties. This altered TIMP-1 will then serve as a prototype for further optimization toward development of a novel and effective therapy for treatment of breast cancer.