

Bankhead-Coley Cancer Research Program

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*Cancer Biology
Mayo Clinic*

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Postdoctoral Research Fellowship
(3-year project)*

Project Title: Defining Binding Determinants of Tissue Inhibitor of Metalloproteinases-1 (TIMP-1) Responsible for Paradoxical Roles in Cancer

Project Summary: Matrix metalloproteinases (MMPs) are a family of enzymes in the body important for prenatal development and wound healing, but in cancer, MMPs are overproduced and contribute to cancer growth and spread. Drugs that block MMP function might slow cancer growth and limit cancer spread, but synthetically produced MMP-blocking drugs performed poorly in a series of cancer clinical trials due in part to strong negative side effects. Tissue inhibitors of metalloproteinases (TIMPs) are a family of natural inhibitors of MMPs that are produced by the body. Among these, TIMP-1 is the best inhibitor of MMP-9, an MMP that has been specifically implicated in cancer growth and metastasis. Thus, TIMP-1 represents a possible anticancer therapeutic. However, use of TIMP-1 at potentially therapeutic levels has been shown to interfere with important cellular processes by binding to CD63, a protein found on the surface of all cells. Our purpose is to create a modified TIMP-1 that does not interact with CD63 but that retains the ability to block the cancer-promoting effects of MMP-9, using sophisticated molecular structural analysis and protein engineering tools. We hypothesize that the modified TIMP-1 that we will generate will be an important starting point for a novel therapeutic strategy that will be both well tolerated and much more effective than existing anti-MMP compounds.