

## Bankhead-Coley Cancer Research Program

**Radisky, Evette**

*Cancer Basic Science  
Mayo Clinic Cancer Center*

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

**Project Title:** Structural and Mechanistic Studies of Mesotrypsin, An Oncogenic, Inhibitor-Resistant Serine Protease

**Project Summary:** Proteases are proteins that digest other proteins; they fulfill many important biological roles, but misregulated proteases can promote tumor initiation, growth, and metastasis. The protease mesotrypsin promotes malignancy in culture models of human breast cancer, suggesting that this enzyme may provide a novel target for development of cancer therapeutics. Naturally-occurring protein protease inhibitors serve as a promising starting point for the development of new drugs targeting oncogenic proteases; however, mesotrypsin is unusually resistant to these inhibitors, having a unique ability to digest and inactivate them. By identifying mechanisms responsible for the capacity of mesotrypsin to degrade proteins that strongly inhibit other, similar proteases, we will learn how mesotrypsin promotes cancer, as well as how it might be more effectively blocked in the context of cancer therapy. We hypothesize that mesotrypsin undergoes specific structural changes upon binding to protein protease inhibitors, and that these structural changes are responsible for the subsequent digestion of the inhibitors. The aims of this project are (1) to determine the protein structures of mesotrypsin bound to protein protease inhibitors and to identify the structural changes that take place upon binding using X-ray crystallography; (2) to determine the physical criteria by which mesotrypsin selects protein targets for degradation, both in test tubes and in live cancer cells; and (3) to determine how the structure of mesotrypsin promotes degradation of protein protease inhibitors using enzyme kinetic approaches. The completion of these aims will reveal how mesotrypsin activity promotes cancer and why known protein protease inhibitors fail to block mesotrypsin. The knowledge gained will further provide a critical foundation for the optimization of naturally-occurring inhibitors to more effectively target and block mesotrypsin as a new approach for cancer intervention and therapy.