Threshold Effects and Non-canonical Functions of the Tumor Suppressor BRCA2 and Interacting Proteins RAD51 and DSS1

Principal Investigator:

- Maria Jasin, PhD, Memorial Sloan Kettering Cancer Center

Co-Principal Investigators:

- Agata Smogorzewska, MD, PhD, The Rockefeller University
- William Holloman, PhD, Weill Cornell Medical College

Abstract: Maintenance of genome integrity is of utmost importance for prevention of cancer. Significantly, treatment responses including development of resistance to chemotherapy are determined by the state of the DNA damage response pathways. In this application we propose to study a key tumor suppressor, BRCA2, and its interacting proteins RAD51 and DSS1, factors necessary for homologous recombination, a repair pathway that is essential for genome integrity in actively dividing cells. Guided by the naturally occurring mutations identified in the tumor predisposition syndrome Fanconi anemia as well as in sporadic tumors, our goal is to answer a number of fundamental questions. We want to understand what is the influence of different levels of functional activity in the homologous recombination pathway on cellular phenotypes, tumor suppression and eventually on treatment responses. We will discover whether the *in vivo* tumor suppression depends on the newly discovered replication fork protection function of BRCA2 and RAD51. Finally, we will investigate whether sporadic tumors with monoallelic point mutations in *RAD51* become deficient for any of the activities of the homologous recombination pathway. Our studies will use human patient cell lines, multiple mouse models, and the powerful genetic system of *Ustilago maydis*, a yeast-like fungus in which the homologous recombination pathway is highly conserved but not essential for growth, making genetic analysis much simpler than in mammalian systems. Our studies promise to enhance basic knowledge of homologous recombination function in tumor suppression and will also provide novel models for testing therapeutic modalities for cancer treatment.