**"An Integrated Host and Pathogen Genetic Strategy to Elucidate the Mechanism of Action of BCG in Therapy of Bladder Cancer"**

*Principal Investigator:*

- Michael Glickman, MD, Memorial Sloan-Kettering Cancer Center

*Co-Principal Investigators:*

- William C. Hahn, MD, PhD, The Broad Institute of MIT and Harvard
- David Root, PhD, The Broad Institute of MIT and Harvard
- Eric Rubin, MD, PhD, The Broad Institute of MIT and Harvard

Funding Category: A

**Abstract:** Bladder Cancer continues to causes significant morbidity and mortality. The preferred therapy for carcinoma in situ (CIS) of the bladder is intravesical therapy with BCG, a live attenuated strain of *Mycobacterium bovis*. Despite longstanding use, the mechanism of action and determinants of response to BCG are largely unknown. We have established a model system of BCG infection of a panel of bladder cancer cell lines and find that bladder cells differ substantially in their susceptibility to BCG infection. We find that bladder cancer cell susceptibility to BCG infection is conferred in part by activation of the PI3K pathway and that susceptible cells have an activated macropinocytosis pathway. In this project, we propose to use this novel model system to comprehensively interrogate the host and bacterial genetic requirements for BCG infection of bladder cancer cells. We will execute both gain and loss of function shRNA screens in both sensitive and resistant Bladder Cancer cell lines to determine the genetic networks that control entry and intracellular survival of BCG. To understand the bacterial determinants of infection, we will identify BCG genes required for entry and intracellular persistence in bladder cancer cells. We expect that these studies will yield a set of host and bacterial pathways that mediate the BCG-Bladder Cancer interaction. These studies may enhance BCG therapy in several ways, including allowing prediction of efficacy of BCG therapy in individual patients based on tumor cell characteristics, and the construction of recombinant BCG able to more efficiently infect tumor cells.