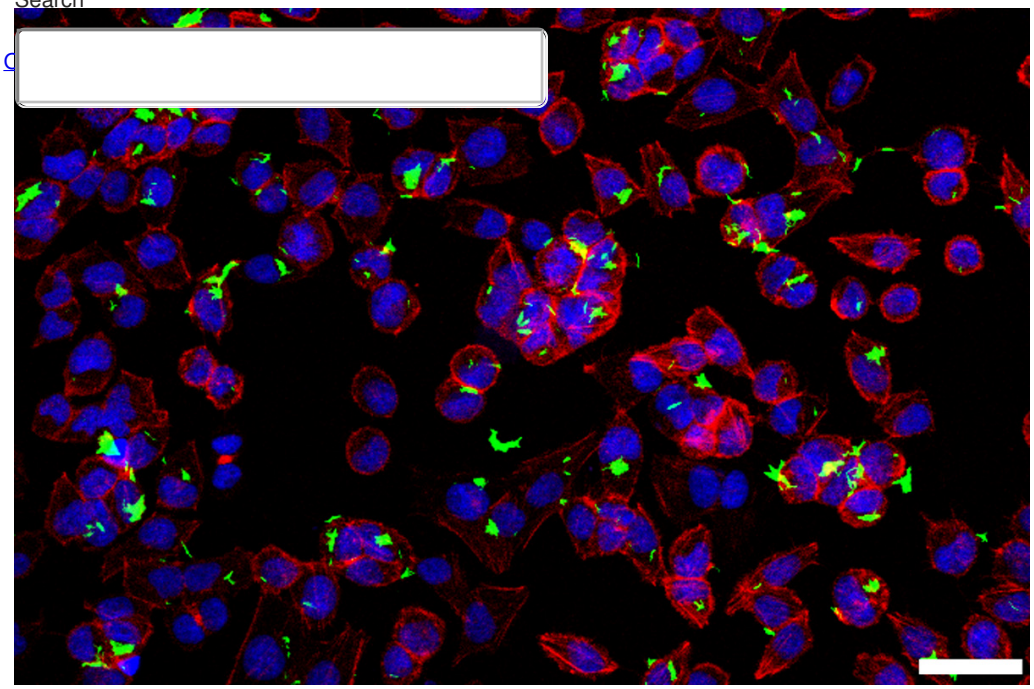
Mechanisms of BCG induced anti-tumor immunity



BCG infection of bladder cancer cells — Shown is a fluorescent image of BCG expressing green fluorescent protein infecting the bladder cancer cell line UMUC3

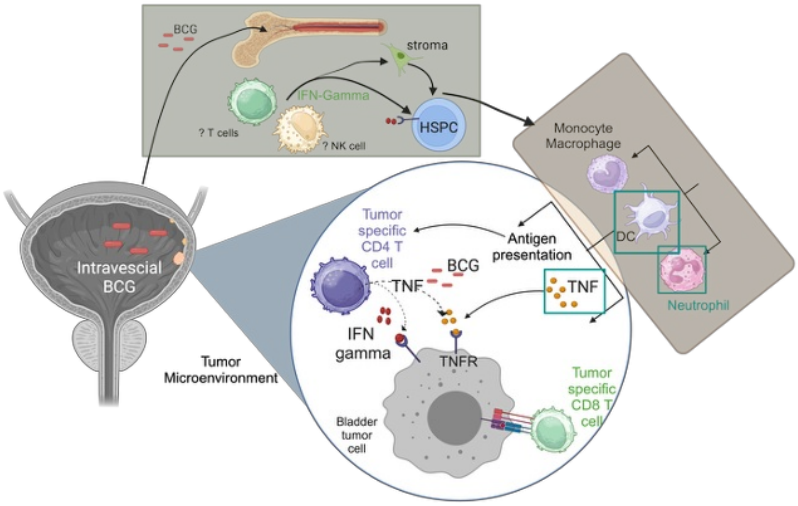
Bacille Calmette-Guérin (BCG), an attenuated strain of *Mycobacterium bovis*, is widely administered as a vaccine for tuberculosis. BCG is also used as a therapy for superficial bladder carcinoma. Despite being the first immunotherapy of cancer, the mechanism of action and determinants of response to BCG remain obscure. We have established that the uptake of BCG by bladder cancer cells is through macropinocytosis rather than phagocytosis. Additionally, we have shown that the difference in susceptibility between BCG-permissive and BCG-resistant bladder cancer cells is due to oncogenic activation of signaling pathways that activate macropinocytosis.

Recent work has examined the immunologic basis for tumor elimination by BCG. A longstanding question in the field has been: Is the anti-tumor immune response that eliminates the tumor directed against BCG, with the tumor killed as a bystander, or against tumor derived antigens? We have recently addressed this question (Antonelli et al) using the MB49 mouse model. We demonstrated that BCG induces tumor specific T cell immunity which is largely dependent of tumor specific CD4 T cells. BCG specific T cell immunity is not sufficient for tumor control. Further, BCG augments the effector functions of tumor specific T cells, which signal through the IFN-gamma receptor on tumor cells.

Our most recent data (Daman et al) demonstrate a surpirsing new mechanism for BCG. We demonstrated that BCG acts systemically to reprogram myelopoesis in the bone marrow, thereby enhancing the antitumor effects of teh myeloid tumor microenvironment. Please see this article for additional perspective:

In collaboration with our clinical colleagues in urology and genitourinary oncology, we are currently expanding our studies to investigate markers of response to BCG in clinical samples and continuing our studies of the immunologic mechanisms of mycobacterial-induced tumor immunity.

More broadly, we believe that there are instructive parallels between the biology of chronic infectious lesions and tumors, both in terms of the immunologic features and in the therapeutic challenges that prevent elimination of microbes and tumor cells (see Glickman and Sawyers below).



Present model for the Mechanism of BCG as an Immunotherapy. Made with BioRender

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