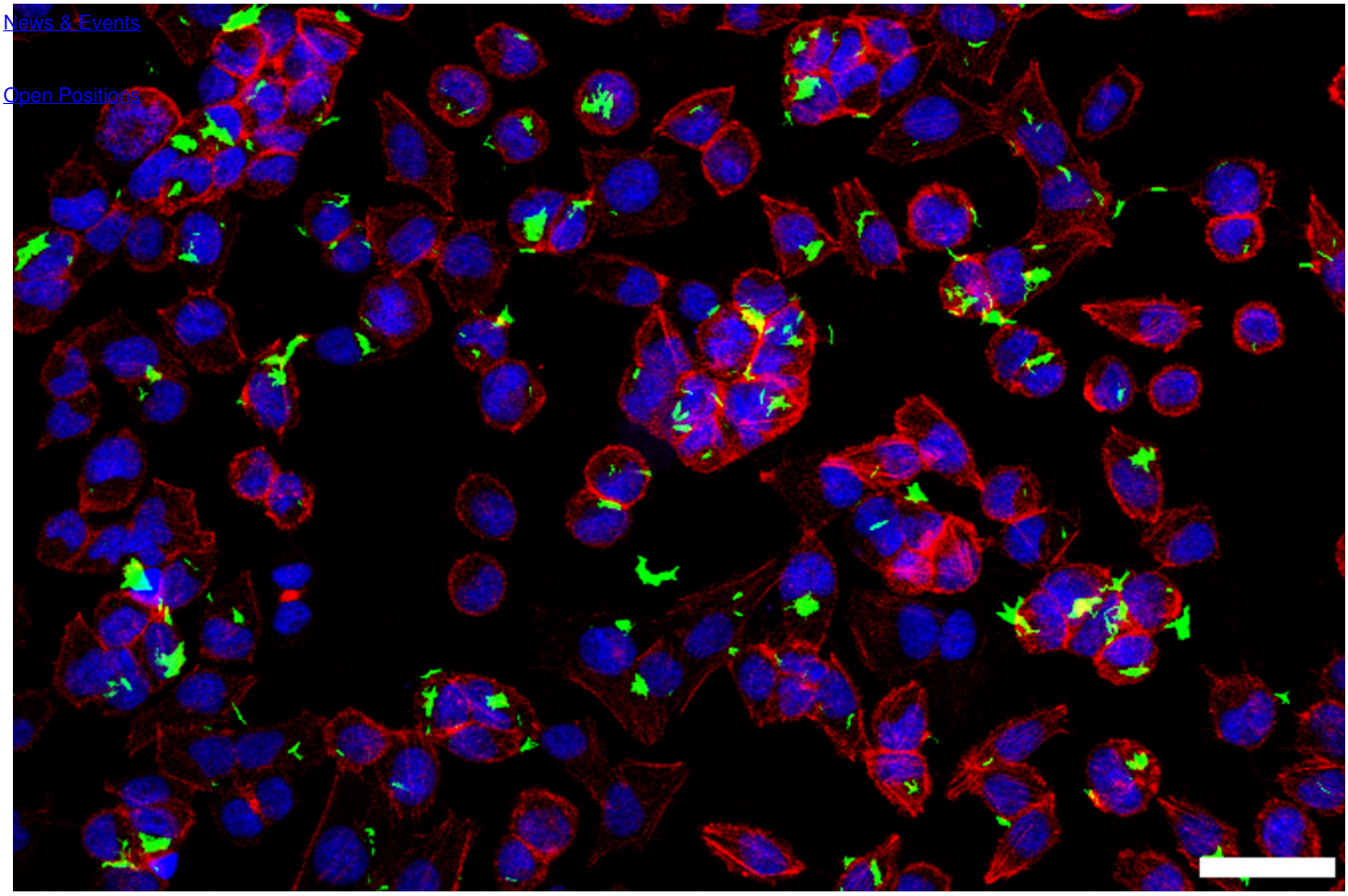
Mechanisms of BCG induced anti-tumor immunity



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

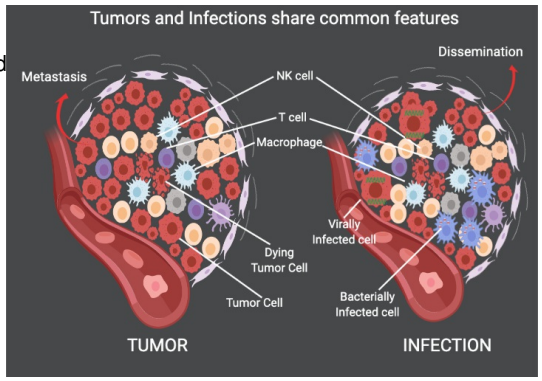
Bacille Calmette-Guérin (BCG), an attenuated strain of *Mycobacterium bovis*, is widely administered as a vaccine for tuberculosis. BCG is also used as a biotherapy for superficial bladder carcinoma. Despite being the most successful cancer biotherapy, the mechanism of action and determinants of response to BCG remain obscure. We have established that the uptake of BCG by bladder cancer cells is through macropinocytosis rather than phagocytosis. Entry of BCG into bladder cancer cells is dependent on Rac1, Cdc42, and the downstream kinase Pak1. 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. These results demonstrate that oncogenic activation of macropinocytosis determines uptake of BCG by bladder cancer cells, and imply that tumor responsiveness to BCG may be governed by the complement of tumor promoting mutations in the treated cancer cell.

Recent work has examined the immunologic basis fo 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.

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).



Tumors and chronic infections share common features.

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Project Members

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