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Targeting Cancer Initiating Cells/Cancer Metastasis with CXCR4 Antagonist-Expressing Oncolytic Vaccinia Virus

Ref# RP09-014

Keywords: Immunotherapy, cancer initiating cells (CIC), metastasis, oncolytic vaccinia virus (OVV), ovarian cancer, breast cancer, head/neck cancer, CXCL12, CXCR4

Collaboration Research Opportunity: Roswell Park Cancer Institute is seeking partners to help co-develop the use of oncolytic vaccinia virus immunotherapy for targeting head/neck, ovarian, and breast cancer.

Summary: The chemokine receptor CXCR4 and its cognate ligand, CXCL12 form a pivotal axis for enabling metastasis by many solid tumor types, including head/neck, ovarian, and breast cancers. First, CXCR4 is essential for metastatic spread to organs where CXCL12 is expressed. Second, CXCL12 can stimulate survival and growth of neoplastic cells in a paracrine fashion and modulate the tumor microenvironment.

Novel advances in viral oncotherapy require effective direct oncolysis of stem cell-like cells or otherwise known as cancer initiating cells (CICs) and manipulation of the tumor microenvironment, which has proven to be an important target in cancer treatment. CICs contribute to tumor generation, metastasis, and chemotherapy resistance through hypoxia-resistance metabolism, have a reduced response to chemotherapeutic drugs *in vitro,* and plays an important role in metastatic disease.

The signals generated by the tumor microenvironment that regulate CICs are not fully understood, but recent studies provide strong evidence for the important role of the CXCL12 chemokine receptor CXCR4 for CIC maintenance, dissemination, and consequent metastatic colonization. In addition to a direct effect of CXCL12/CXCR4 axis on survival and growth of neoplastic cells, this signaling pathway plays a pivotal role in modulating the tumor microenvironment by inducing angiogenesis as well as recruiting pro-tumor myeloid cells and T regulatory cells, which impede innate and adaptive immune mechanisms of tumor destruction.

Technology: Engineering an oncolytic vaccinia virus (OVV) armed with a CXCR4 antagonist represents an innovative strategy that targets multiple elements within the tumor microenvironment while overcoming concerns related to the systemic delivery of soluble CXCR4 antagonists. Inhibition of this pathway by oncolytic viruses expressing the CXCR4 antagonist increases efficacy over that mediated by oncolysis alone. A systemic delivery of the armed virus after resection of the primary tumor was found to be efficacious in inhibiting the development of spontaneous metastasis and increased overall tumor-free survival. This inhibition was associated with destruction of tumor vasculature, reductions in expression of CXCL12 and VEGF, and decreased in intratumoral numbers of bone marrow-derived endothelial and myeloid cells.

Altogether, these finding demonstrate that oncolytic virotherapy with the CXCR4 antagonist represents a potent treatment for metastatic tumors with a broad antitumor repertoire including direct cytolysis of CICs, decreased angiogenesis, and reduced intratumoral infiltration of immunosuppressive elements which led to higher spontaneous

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antitumor immunity. OVV therapy with a CXCR4 antagonist may therefore be considered a method to achieve vaccination in situ, with the adaptive immune response being able to clear minimal residual disease and provide long term protection against tumor relapse.

Potential Commercial Applications:

- Findings illuminate a new paradigm for treatment of cancers involved in CXCR4/CXCR12 signaling, especially for ovarian, breast, head/neck cancers, and glioblastoma.
- This immune based technology opens up the possibility of engineered oncolytic viruses which selectively infect CICs and express high concentrations of therapeutic molecules in metastatic tumors to potentiate the eradication of cancer.
- Inhibition of angiogenesis in tumor treated with the armed virus together with the direct cytopathic effect of the virus on the malignant population could contribute to a lower metastatic burden and increased overall survival.

Competitive Advantages:

- This technology shows that a CXCR4 antagonist delivered intravenously by an OVV attains higher intratumoral concentrations than its soluble counterpart and results in a systematically effective virus with increased efficacy over that mediated by oncolysis alone.
- This technology is unique in demonstrating that targeting CXCR4 signaling through an oncolytic vaccinia virus yields significant therapeutic impact against primary and metastatic cancers.
- The CXCR4 antagonist expressed in the context of the Fc fragment of murine IgG2a or human IgG1 (OVV-CXCR4-A-Fc) is capable of mediating complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC) of tumor cells.
- No systemic toxicity or mobilization of CXCR4-expressing hematopoietic stem and progenitor cells was observed after intravenous injection of OVV-CXCR4-A-Fc to mice.
- A systematic delivery of the armed virus after resection of the primary tumor further reduces the development of spontaneous metastasis resulting in increased tumor-free survival.

Development Status: Patent Status: Provisional Patent Pending

Inventor: Dr. Danuta Kozbor, PhD

Additional References:

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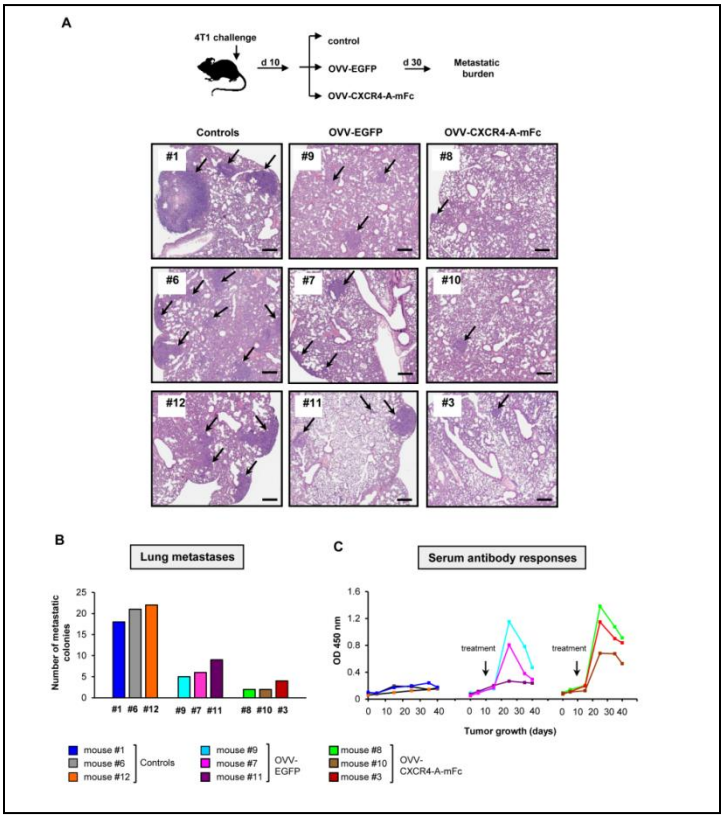
Diagram:

Inhibition of spontaneous metastasis in a breast cancer model



Inhibition of peritoneal metastasis in an ovarian cancer model