W. Hans Meisen
PhD Candidate

“Improving Oncolytic Viral Therapy for Brain Tumors”

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1984 ................................. Born – Stafford, VA

2007 ................................. B.S. Biology; University of Virginia

2009 ................................. M.S. Microbiology; Georgetown University

2010 ................................. Ph.D, Candidate; Biomedical Sciences; Ohio State University

COMMITTEE MEMBERS

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ABSTRACT

Oncolytic viruses [OVs] are an exciting cancer immunotherapy which has received considerable attention in recent years. OVs are viruses designed to specifically destroy cancer cells and promote anti-tumor immune responses. Promising phase 3 clinical trial data in melanoma patients suggests FDA approval for OV therapy may soon be a reality. Despite successes in cancers like melanoma, the efficacy of these viruses in central nervous system [CNS] cancers has been limited. While these viruses have proved safe in early phase clinical trials, durable responses have not been achieved. The unique brain tumor microenvironment and restrictive blood brain barrier make these cancers a therapeutic challenge for researchers and clinicians. The goal of these studies was to develop novel strategies to improve OV therapy for CNS cancers.

In part one of this dissertation we examined the therapeutic efficacy of a targeted OV for breast cancer [BC] brain metastases. The 2 year survival rate of patients with this disease is less than 2%. Treatment options for BC brain metastases are limited and there is an unmet need to identify novel therapies for this disease. Brain angiogenesis inhibitor 1 [BAI1] is a G-protein coupled receptor involved in tumor angiogenesis, invasion, phagocytosis, and synaptogenesis. Here, we found BAI1 expression was significantly reduced in BC and higher expression was associated with better patient survival. Nestin is an intermediate filament whose expression is up-regulated in several cancers. We found higher Nestin expression significantly correlated with BC lung and brain metastases. These findings suggested both BAI1 and Nestin could be therapeutic targets for this disease. We then demonstrated the ability of an OV, 34.5ENVE, to target and kill high nestin expressing cells and deliver therapeutic Vstat120 [extracellular fragment of BAI1]. Finally, we demonstrated 34.5ENVE could extend the survival of mice in two models of BC brain metastases.
In the context of OV therapy, the immune response is a double-edged sword. While it has the potential to generate long-term anti-tumor immune responses, early innate immune responses to viral infection reduce OV replication, tumor destruction, and efficacy. In part two of this dissertation, we characterized the antiviral effects of macrophages and microglia on OV therapy for glioblastoma. Glioblastoma is one of the most common and deadly types of primary brain tumors, and patients diagnosed with these tumors have a median survival of only 15 months. We identified microglia/macrophage secreted tumor necrosis factor α [TNFα] as a major factor which reduces OV replication through the induction of apoptosis in infected tumor cells. We demonstrated that the transient inhibition of TNFα could significantly enhance OV replication and anti-tumor efficacy in vivo. The results of these studies suggest FDA approved TNFα inhibitors may significantly enhance patient outcomes in OV clinical trials for glioblastoma.

One of the challenges to creating novel therapeutics, such as OVs, for CNS cancers is developing animal models and non-invasive imaging modalities in which to evaluate them. Live animal imaging is particularly challenging in brain tumor models because the skull significantly limits options for monitoring tumor growth and treatment responses. Bioluminescent imaging [BLI] and magnetic resonance imaging [MRI] are two non-invasive imaging modalities which can significantly enhance intracranial tumor studies. These imaging modalities allow real time measurements of tumor volume, cancer cell viability, and therapeutic responses, but they vary in the information they can provide. In part three of this dissertation we evaluated BLI and MRI in three murine glioblastoma models. We found BLI and MRI output was significantly affected by tumor necrosis, hemorrhaging, tumor depth, extra-cranial growth, and animal positioning. In synthesizing the data from this study, we created a multi-modality imaging paradigm for analyzing changes in tumor growth and biology while reducing cost-prohibitive and time consuming MRI for preclinical brain tumor studies.
RECENT ABSTRACTS AND PRESENTATIONS

ORAL PRESENTATIONS:

2014  Meisen W.H. Vstat120 tempers the microglia innate inflammatory response to oncolytic viral therapy. 16th Annual Meeting of the Translational Research Cancer Centers Consortium: Immune Suppression and the Tumor Microenvironment, Seven Springs, PA.

2013  Meisen WH. Vstat120 modulates immune responses to oncolytic viral treatment and enhances efficacy for GBM. The 7th International Meeting On Replicating Oncolytic Virus Therapeutics, Quebec, Canada.


2012  Meisen W.H. Vstat120 tempers the microglia innate inflammatory response to oncolytic viral therapy. 14th Annual Meeting of the Translational Research Cancer Centers Consortium: Immune Suppression and the Tumor Microenvironment, Seven Springs, PA.

POSTER PRESENTATIONS:


treatment and enhances efficacy for GBM. 17th Annual Meeting for the American Society of Gene and Cell Therapy, Washington, DC.


**RECENT PUBLICATIONS**

**REVIEWS/EDITORIALS**


AWARDS AND HONORS

2014  Ohio State University Presidential Fellowship, Columbus, Ohio.

2014  Ohio State University Board of Trustees Student Recognition Award, Columbus, Ohio.

2014  Outstanding Poster Presentation Award, 17th Annual Meeting for the American Society of Gene and Cell Therapy. Washington, DC.

2014  Travel Award, The Seventh International Meeting On Replicating Oncolytic Virus Therapeutics. Quebec, Canada.

2013  Travel Award, 12th Annual OSUWMC (OSU Wexner Medical Center) Trainee Research Day. The Ohio State University, Columbus, OH.

2010-13 College of Medicine Systems and Integrative Biology Fellowship, Sponsored by National Institute of General Medical Sciences and the OSU College of Medicine, Columbus, Ohio.

FUTURE PLANS

I will pursue a post doctoral research position in cancer research.