IMPROVING ONCOLYTIC HERPES SIMPLEX VIRUS FOR METASTATIC BREAST CANCER

The primary objective of this study is to establish a novel treatment strategy for metastatic breast cancer, for which there is a dire need for innovative new therapies. It is likely that oHSV will be effective against metastatic breast cancer when combined with HDAC inhibitors (HDI). oHSV has been shown to be safe in multiple clinical trials, but significant potency has yet to be observed in most patients. HDI are undergoing clinical trials for a variety of malignancies and vorinostat, romidepsin, and belinostat have been FDA approved for T-cell lymphoma. We hypothesize that HDI significantly increase the replication of oHSV in metastatic breast cancer cells and synergistically improve antitumor efficacy. Two specific aims are proposed to test this hypothesis.

Aim 1: Enhancement of oHSV antitumor efficacy with HDAC inhibitors

The completion of this aim will demonstrate whether HDI increase oHSV replication and antitumor efficacy *in vivo*. It will also provide the necessary pre-clinical studies to enable translational studies using this combination therapy.

Aim 2: Elucidation of mechanisms responsible for enhanced replication of oHSV

These experiments will allow us to identify better targeted approaches of enhancing oHSV. Mechanistic studies are designed to reveal why certain combinations are more effective than others, allowing the identification of specific pathways that can be targeted in future studies to further enhance therapy.

PROGRESS

Experiments have proceeded on schedule during the first year of the funding period. We have performed oHSV replication studies *in vitro* and *in vivo* with treatment of HDI. We published our *in vitro* studies in PLOS One (Cody, Markert, and Hurst, *PLOS One* 2014 Mar 20;9(3):e92919) and proceeded with the *in vivo* animal models. The replication of oHSV significantly increased in orthotopic tumor xenografts using athymic mice upon treatment with the HDI panobinostat or SAHA. We evaluated efficacy for inhibition of orthotopic tumor growth by comparing oHSV only and combination of oHSV with HDI. Both treatments resulted in significant inhibition of tumor growth and no change was noted between the oHSV only *versus* combination treatment on overall survival. We decided to shift our focus due to the disappointing clinical trial results with HDI for solid tumors including breast cancer. There are inherent problems with the current design of HDI and we proposed a new strategy to improve specificity by targeting the HDAC activity associated specifically with one chromatin complex. We submitted applications to NIH (R21) and to DoD (BCRP Breakthrough) for this new strategy titled “Targeting histone deacetylase activity specifically associated with SIN3 chromatin complexes”. In addition, we are currently in the process of submitting an NIH R01 application to further probe the mechanisms of this HDAC chromatin complex that regulates breast cancer metastasis (Feb 5, 2015 submission) titled “Regulation of breast cancer metastasis by SIN3 chromatin modification complexes”. Two of my students will be presenting their work regarding this project at the 2015 AACR annual meeting. Additionally, I have presented this work as an invited seminar at the following: Department of Pharmacology at Penn State College of Medicine, Department of Chemistry and Biochemistry at the College of Charleston, and Department of Pathology at the University of Alabama at Birmingham. We are also preparing a manuscript for the *Journal of Oncolytic Virotherapy* as an invited review article. Overall, although we have shifted our focus slightly to probe mechanisms of HDAC complexes that regulate breast cancer metastasis in more detail to better understand possible reasons for the clinical trial results with HDI, we continue to make progress towards the proposed specific aims.