Contribution ID: **52** Type: **not specified**

Evaluation of 225Ac-anti-VLA-4 for targeted α-therapy for treatment of metastatic melanoma

Background.
Very late antigen 4 (VLA-4; also called integrin α4β1) is overexpressed in melanoma tumors with an active role in tumor growth, angiogenesis, and metastasis. This makes VLA-4 an ideal antigenic target for targeted alpha therapy. The expression of VLA-4 on primary melanomas in human correlates with the development of metastasis and has been associated with high risk of metastasis and tumor progression. Furthermore, up-regulation of VLA-4 in melanoma is associated with a more aggressive, metastatic phenotype. Here in we evaluated an 225Ac-anti-VLA-4 conjugate as well as its 111In-labeled companion imaging agent for targeted radiotherapy in an aggressive mouse melanoma model.

Methods.
An anti-VLA-4 antibody was conjugated to DOTA for 225Ac-labeling and DTPA for 111In-labeling. The resulting agents, 225Ac- or 111In-labeled anti-VLA-4 were evaluated in vitro, including binding affinity, internalization, and clonogenic assays as well as in vivo biodistribution studies. Furthermore, the therapeutic efficacy of 225Ac-anti-VLA-4 was evaluated in a subcutaneous and disseminated disease mouse model of melanoma.

Results.
111In-DTPA-anti-VLA-4 demonstrated high affinity for VLA-4 in B16F10 cells, having a Kd of 0.18 ± 0.05 nM and approximately 20% internalized at 8 hours. For delivery of an α-emitting radionuclide to VLA-4 positive tumor cells, the DOTA conjugate was labeled with 225Ac with specific activity of 3.5 MBq/nmol and >95% radiochemical purity, and demonstrated selective uptake in VLA-4 positive B16F10 cells. Clonogenic assays demonstrated a decrease in the surviving fraction of B16F10 cells treated with 225Ac-DOTA-anti-VLA-4 compared to controls. Biodistribution studies demonstrated uptake in the VLA-4 positive tumor in addition to VLA-4 rich organs. A blocking dose highlighted the potential of blocking uptake in VLA-4 rich organs without a significant impact on tumor uptake. Therapeutic efficacy studies demonstrated significant increases survival in mice treated with 225Ac-DOTA-anti-VLA-4 compared to saline and cold antibody controls. In addition, a single mouse (subcutaneous model) remained tumor-free until the study end-point, 6-months post-treatment.

Conclusion.
111In- and 225Ac-labeled anti-VLA-4 antibody conjugates are capable of selectively delivering radionuclides for SPECT imaging and targeted alpha therapy to melanoma tumor cells that overexpresses VLA-4. The biodistribution studies highlighted the uptake in VLA-4 rich organs, including the spleen and bone, could be potentially reduced without significantly impacting the uptake in the tumor. The agents presented here with future dose optimization have the potential to identify and treat patients who have metastatic melanoma.

Acknowledgments.
The 225Ac used in this research was supplied by the Isotope Program within the Office of Nuclear Physics in the Department of Energy's Office of Science.

Email Address

jnedrow1@jhmi.edu

Presentation Type

Contributed Oral

Primary authors: CORTEZ, Angel (Johns Hopkins University); Dr NEDROW, Jessie (Johns Hopkins University)

Co-authors: SHTEKLER, Abigail (Johns Hopkins University); RAO, Akhila (Johns Hopkins University); Dr JOSEFSSON, Anders (Johns Hopkins University); Dr SGOUROS, George (Johns Hopkins University); Dr HOBBS, Robert (Johns Hopkins University); AUSTIN, Zachery (Johns Hopkins University)

Presenter: Dr NEDROW, Jessie (Johns Hopkins University)

Track Classification: Preclinical