Oncostatin M Receptor as a Therapeutic Target of Radioimmune Therapy in Metastatic Synovial Sarcoma
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Abstract
Synovial sarcoma is a soft tissue malignancy of the muscle that primarily affects adolescents. Due to its low incidence, little advancement has been made in the treatment of this cancer. With an overall survival rate of roughly 40%, the need for new treatments for synovial sarcoma is evident. Oncostatin M Receptor (OSMR) is a type I cytokine receptor and is overexpressed in metastatic synovial sarcoma. OSMR does not have high expression in normal tissues, making it an ideal target for cancer therapy. We hypothesize that by using an anti-OSMR monoclonal antibody conjugated to a radioactive Copper67 isotope, synovial sarcoma can be targeted at both primary and metastatic locations through systemic therapy. Cu67 is a beta radiation emitting isotope that is tissue damaging and able to induce cell death in cancer cells. By conjugating the chelating molecule p-SCN-Bn-NOTA to an anti-OSMR antibody, Cu67 was able to be captured to the antibody. Capture efficiency of Cu67 was measured after TLC separation and found to be 80% efficient when compared to the chelator alone. This data suggests that targeting OSMR through radioimmunotherapy (RIT) is a viable treatment and indicates further testing in animal models.

Introduction
Synovial sarcoma is a soft-tissue malignancy with a predilection for adolescents and young adults. It is a well-established translocation sarcoma and is defined by the presence of the t(X;18)(p11.2;q11.2) translocation, involving the SS18 (formerly SYT) gene on chromosome 18 and one of several synovial sarcoma X (SSX) genes on chromosome X (usually SSX1 or SSX2) (1). Patients diagnosed with synovial sarcoma share the fate of many other translocation positive sarcomas; the mutation for this cancer is known, yet means to target the fusion protein SS18-SSX directly exists. Currently, the treatment for synovial sarcoma consists of surgery, possibly in combination with doxorubicin and cyclophosphamide based therapies based on the extent of disease. Unfortunately, no advancements have been made in the treatment of this disease in decades (2). The low mutational burden of this disease makes targeted therapies more difficult to develop, and renders immune therapies ineffective (3). Oncostatin M receptor (OSMR), a growth-regulating cytokine, is known to be overexpressed in multiple cancers and lead to a more aggressive phenotype (4-6). This makes the cell surface receptor a viable therapeutic target.

Recently, there has been an increase in the use of radio-labeled ligands in the treatment of cancers including bone, breast and prostate cancers, and radioimmunotherapy (RIT) has been successful in the treatment of non-Hodgkin lymphoma as well as other malignancies (7). We hypothesize that an anti-OSMR antibody radio-labelled with Cu67 isotope can treat synovial sarcoma systemically.

Results
Using genetically engineered mouse models of metastatic and non-metastatic synovial sarcoma, it was determined that OSMR protein was present in malignant tissue. RNA-seq data of metastatic vs non-metastatic mouse synovial sarcoma suggested that the protein would be a viable target for therapy in metastatic disease, and immunohistochemistry confirmed Western blotting of protein in tumors (Figure 1). Western blotting further confirmed that OSMR is present in high concentrations compared to that of normal tissue muscle, making it ideal for targeted therapy (Figure 2). Based on this data, we began our synthesis of OSMR targeting therapy (Figure 3). First, a monoclonal anti-OSMR antibody was purified to eliminate the presence of contaminants and ions with a yield of 61%. Next, the antibody was conjugated to the chelator p-SCN-Bn-NOTA resulting in a yield of 57% (Figure 4a). To confirm successful conjugation, mass spectrometry was performed and conjugation confirmed (Figure 4c). Finally, Cu67 was captured by the chelating moiety, and capture confirmed through Thin Layer Chromatography (TLC) (Figure 4b) confirming that our conjugate was able to capture Cu67 with acceptable efficiency, although some capture capability was lost when compared to that of the NOTA chelator alone (Figure 4d). We also noted that, due to the antibody having multiple binding locations for the NOTA chelator, Cu67 capture was greater than 1:1.

Conclusion
The unique expression of OSMR in synovial sarcoma makes it an ideal target for RIT. Here, we show that OSMR is expressed at significant levels through both RNAseq data and Western blot protein detection, and is absent in non-malignant tissue. We have also shown that targeting this protein through RIT is possible, and that a chelating moiety can be conjugated to an anti-OSMR monoclonal antibody and used to capture beta radiation emitting Cu67 with acceptable efficiency and yield. Finally, we have found that the NOTA chelator binds to multiple sites in the anti-OSMR monoclonal antibody, allowing for a higher capture concentration of Cu67. Further research is indicated to determine if this conjugate is effective at treating primary and secondary synovial sarcoma tumors, and to assess its potential toxicities.

Citations