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Improving the synthesis and effectiveness of future melanoma drugs

Melanoma is the 6th most commonly diagnosed cancer in the United States and its incidence is still on the increase. Early detection and prompt surgical excision are crucial for long term survival. Once melanoma becomes metastatic and disseminated, the survival rates for those suffering from the cancer drop significantly to as low as 3-6%. With no significant advances in therapies or survival rates of patients with advanced melanoma in the past 30 years new techniques are desperately needed. This study examined the synthesis and characterization of a specific class of radiolabeled cyclic melanocyte stimulating hormone (MSH) peptide analogs that target melanoma tumors. Our goal is to improve the production efficiency and tumor targeting properties of the radiolabeled MSH peptides to increase their melanoma imaging and therapy potential. Two potential drug candidates were considered in this study. The conjugation of a novel chelator of one of the candidates, CBTE2A-CCMSH(Arg11), was modified by researchers at Washington University to allow for better coordination of copper-64. This modification allows the drug to be used for positron emission tomography. Our goal was to cyclized this peptide around rhenium to allow for maximum tumor uptake. Addition of norleucine to the receptor binding loop of the cyclic peptide, Dota-Re-CC-Nle-MSH, was also examined for its ability to improve tumor cell binding and increase peptide stability. The metal cyclized peptides were purified by reverse phase high performance liquid chromatography. The identities of the purified products were confirmed by LC-mass spectrometry. After purification each candidate was radiolabled with indium-111 or copper-64 and evaluated for their radiochemical stabilities and abilities to image tumors in melanoma bearing mice using single-photon emission tomography or positron emission tomography. Current tests show that the addition of the norleucine was unsuccessful in improving cyclization yield and our imaging study was inconclusive because of poor radiolabeling, but more tumor binding tests need to be performed. 64Cu-CBTE2A-Re-CCMSH(Arg11) has, however, shown great initial results in MicroPET trials and may be one of the best candidates for future clinical trials.

This project was completed to fulfill a Capstone requirement.