

Clayton Butcher

Major: Biochemistry

University: University of Missouri-Columbia

Faculty Mentor: Dr. Thomas Quinn

Mentor Department: Biochemistry

Funded by: Molecular Imaging Program

Optimization of metal-cyclization of alpha-MSH peptide analogs used in the treatment and detection of melanoma

Clayton Butcher, Fabio Gallazzi and Thomas Quinn

Over the past few years Dr. Quinn and his lab have made significant progress in the development of a melanoma treatment drug. Based upon peptide analogs of the alpha-melanocyte stimulating hormone, A-MSH, Dr. Quinn has developed a metal cyclized drug that shows very promising results in therapy as well as early detection/imaging of melanoma tumors. The cyclization of the peptide around a metal core was shown to greatly increase the affinity of the peptide for its target. There are slight problems with the cyclization process that needed to be resolved or limited in order to make the synthesis of the drug as efficient as possible. The primary problem with the cyclization of the peptide is the fact that two main products are produced. One of these products is caused by the histidine residue swinging down and binding with the metal core. Histidine is one of the four amino acids directly involved with receptor recognition and thus this product's tumor uptake is at least 50% lower.

Three variables were explored in hopes of reducing this second unwanted product. A new and simpler process developed by Fridkin et. al.¹ was first considered. HPLC was used to purify the two major products and their identities were confirmed using mass spectrometry. The new procedure proved to be slightly more effective as the old procedure. With the old procedure roughly 32.3% of the two major products were of the undesired compound, however, using this new procedure this was reduced to 23.4%. A variation of the new procedure was then tried. Instead of dissolving the linear peptide in water, as the procedure called to do, the peptide was dissolved using DMF. This modification showed a significant change in the percentage of the two products. Of the two major products only 12.8% of the total was of the unwanted product thus producing 87.2% of the desired cyclized peptide. Finally an addition of an extra amino acid residue near the beginning of the sequence was tried in hopes of moving the histidine residue far enough away from the metal core in order to limit their interaction. Current tests are still being performed to determine whether or not this will be successful.

(1) Fridkin, G., Bonsera, T.A., Litman, P., and Gilon, C. Nucl. Med Biol 32, 39-50, 2005.