ISOTOPES BOUND TO AN INNATE IMMUNE RESPONSE MOLECULE

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Introduction

Sn-117m with its 14-day $t_{1/2}$ emits apoptosis-inducing theranostic conversion electrons (CE) that distribute tissue doses out to 300µm. Sn-117m, has been used therapeutically in inflammatory models. We describe a 12 amino acid (AA) molecule chelated to Sn-117m that binds to the receptor for advanced glycation end-product (RAGE). AGE is an innate immune response molecule and RAGE is implicated in immune cell disruption, peripherally in diabetes and CNS inflammation.

Description of the Work

The Aβ peptide 8 AA chain fragment sequence 16 through 23 was selected based on the binding affinity to RAGE shown by Gospodarska[1]. The aminobenzyl-DOTA (ABD) chelating agent was bound to Sn-117m and then linked to a 4 AA binding segment to provide additional solubility and spacing from the critical 88 AA segment that was subsequently attached (i.e., [Sn-117m]-ABD-4AA-8AA; Figure 1). Purity of the conjugate was assessed by HPLC. Both Lu-177 and Sn-117m were chelated to the conjugate in high yields as per HPLC. Biodistribution in mice was measured after systemic injection of [Lu-177]-ABD-4AA-8AA at 2 and 24 hours. The gamma photons from Lu-177 were measured in each organ. The radio trace of a HPLC for the Lu-177m chelate chromatograph shows two peaks consistent with two conformations for the chelate and no free Lu-177. Similar results were obtained for the Sn-117m chelate.

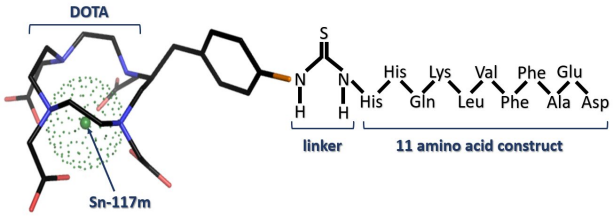

Figure 1: Construct of [Sn-117m]-ABD-4AA-8AA molecule

Incubation of Lu-177-ABD-4AA-8AA with a solution of RAGE showed a slight decrease in the retention time of the mixture in a gravity fed size exclusion column, consistent with affinity of the chelate to RAGE. Initial indications show this molecule is stable and with favorable BD in mice.

Conclusions

Sn-117m-ABD-4AA-8AA is a candidate for trials in neuroinflammatory disorders to produced CE induced apoptosis in microglia by anchoring it to RAGE.

Reference

1. Gospodarska E, et al. Binding sites of truncated variants of the Aβ peptide to the V-domain of the RAGE receptor reveal Aβ residues responsible for binding, Biochimica et Biophysica Acta 1814 (2011) 592-609.