

Targeting Alzheimer’s Disease Microglia With A Radioisotope Linked To The V-domain of RAGE

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BACKGROUND	METHODS	RESULTS	CONCLUSIONS
- Microglia (MG) are partially responsible for events leading to deposition of beta amyloid (Aβ) and tau in AD. - Tin-117m (Sn-117m) is a therapeutic conversion electron (CE) and imageable γ emitting theranostic radioisotope with a maximum CE tissue penetration of 290 μm. Lutetium-177 (Lu-177) is a β emitting isotope. - Amino acid (AA) residues attached by click chemistry to an isotope chelating agent may be designed to link to the V-domain of the receptor for advance glycation end-products (RAGE) on MG¹ as a therapeutic and imaging agent. - Improving water solubility, reducing steric hindrance, and improving its production yield enhances this molecule’s suitability for targeting pro-inflammatory (PI) microglia and macrophages.	This MG targeting agent is a truncated portion of the Aβ1-40 peptide AA chain identified as critical in binding to RAGE expressed by PI microglia. The 8 AA segment composed of the 16th to 23rd AA (KLVFFAED) was selected based on the binding affinity to βA. ² A 3 AA (HHG) spacer was added to reduce steric hindrance and increase water solubility. A linking azide was added to the AA sequence HHGKLVFFAED to allow for click chemistry. The radioisotope Lu-177 was chelated into a water-soluble cyclooctyne-DOTA (COD) molecule. The COD was then connected to the 11 AA sequence via DCBO-azide aqueous click chemistry to produce the final molecule. Purity of the conjugate was assessed by HPLC.	DOTA bound Lu-177 successfully connected to the 11 AA chain. The additional 3 AA spacer enhanced water solubility and should reduce steric interference when binding to RAGE. The final molecule (i.e., [Lu-177]-COD-3AA-8AA) is shown on the Figure, with a molecular weight of ~2.4 kDa. Water solubility and high yield of production was confirmed. The purity of the final molecule was verified using HPLC. The HPLC demonstrated that the final product was easily purified by separation from other biproducts.	This AD microglia RAGE targeting molecules’ unique characteristics include: - Water solubility - Reduced steric hinderance - Ease of production due to click-chemistry methods of formulation - High (100%) yield of production compared to other conjugation methods. - Suitability for both therapeutic and imaging applications targeting pro-inflammatory microglia in AD using Sn-117m (CE, γ-photons), Lu-177 (β-particles, γ-photons) and potentially other isotopes. - Switching from Lu-177 to Sn-117m will provide therapeutic and imaging CE to induce apoptosis in AD-associated inflammatory MG^{3, 4} and macrophages.
		REFERENCES "Isotopes Bound to an Innate Immune Response Molecule", GR Gonzales <i>et al.</i>, abstract presentation at SNMMI, June 24-27, 2023, Chicago, IL "Binding Studies of Truncated Variants of the Aβ Peptide to the V-Domain of the RAGE Receptor Reveal Aβ Residues Responsible for Binding", Gospodarska, Emilia, <i>et al.</i> <i>Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics</i>, vol. 1814, no. 4, 2011, pp. 592–609 "Human brain dosimetry in disrupted blood brain barrier using [Sn-117m]-DOTA-Annexin V (SnDAV): A model for targeting aged microglia in Alzheimer's disease", GR Gonzales, <i>et al.</i>, poster presentation at Alzheimer's "Targeting of vulnerable plaque using [tin-117m]-DOTA-annexin", HW Strauss, <i>et al.</i>, Society of Nuclear Medicine and Molecular Imaging, June 8-12, 2013, Vancouver, BC, Canada	CONTACT Please send questions to: ggonzales@neurosn.com