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Comparison of bifunctional chelates for Ga radioisotopes

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Both ⁶⁷Ga (t_{1/2} 3.26 d) and ⁶⁸Ga (t_{1/2} 68 min) are radioisotopes with appropriate emissions for nuclear imaging. ⁶⁸Ga is of particular interest due to its potential availability from a ⁶⁸Ge/⁶⁸Ga generator. The short half-life of ⁶⁸Ga requires the use of targeting vectors with fast localization such as small peptides. In addition, bifunctional chelates (BFCs) that facilitate fast radiolabeling under mild conditions and produce a high specific activity (SA) product in high radiochemical yield (RCY) that does not require time-consuming post-radiolabeling purification are needed.

Two promising chelating moieties for gallium radioisotopes are Oxo (1-oxa-4,7,10-triazacyclododecane-4,7,10-triacetic acid) and PCTA (3,6,9,15-tetraazabicyclo [9.3.1]pentadeca-1(15),11,13-triene-3,6,9-triacetic acid). The radiolabeling efficiency, SA and stability of the BFCs of Oxo and PCTA were compared directly to analogous BFCs of DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) and NOTA (1,4,7-triazacyclononane-1,4,7-triacetic acid). Small animal PET imaging and biodistributions were also studied to compare the in vivo clearance of the ⁶⁸Ga radiolabeled BFCs. Advantages with respect to RCY, SA, and stability were noted for the BFCs of PCTA and NOTA.

An RGD-containing peptide was conjugated to three different BFCs, two commonly used BFCs of DOTA and NOTA and the novel BFC of PCTA. The resulting constructs were evaluated to ascertain the potential of the BFCs for ⁶⁸Ga peptide imaging. RCYs of >95% were achieved within 20 minutes using the PCTA and NOTA conjugates when the reaction was done at either room temperature or with mild heating (37℃). Further purification was not needed under these conditions. SAs of ≥0.5 mCi/nmol were achievable. The radiolabeling reaction required heating at higher temperatures (80℃) or extended reactions times at 37℃ in order to obtain equivalent RCY and SA with the DOTA conjugate. A challenge with apo-transferrin for 1 h showed that both the PCTA and NOTA Ga-radiolabeled conjugates were stable whereas the DOTA conjugate lost ~15% of Ga.

In conclusion, BFCs of PCTA and NOTA were found to have superior Ga radiolabeling and stability properties compared to the BFC of DOTA. Cell and small animal imaging studies are planned to examine the effect of the BFCs on the receptor binding and biodistribution of Ga-radiolabeled peptide conjugates.

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