Gallium labelled NOTA-based RGD-conjugates for targeting $\alpha_v\beta_3$ integrin receptor

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Introduction and Objectives : Ga(III) chelates are of high interest in the field of medical imaging.

^{68}Ga ($t_{1/2}$ = 68 min), a β^+ emitter, which can be produced from a ^{68}Ge generator system allowing easy routine manufacture in hospital facilities. The most common chelators for Ga(III) are hexadentate and, among them, triaza macrocycles are particularly suitable due to their high conformational and size selectivity, allowing a good fit of the relatively small cation in the macrocyclic cavity.

Peptides have shown to be the most effective targeting moieties known for cellular receptors, drug delivery, molecular imaging and radiotherapeutic applications. The RGD peptide sequence has emerged as one of the most efficient epitopes for targeting the $\alpha_v\beta_3$ integrin receptor. This integrin is highly expressed on activated endothelial cells in neovasculature of various tumors and it has been demonstrated that it is overexpressed on both the endothelial cells and tumor cells in melanoma, glioma, ovarian and breast cancers and the $\alpha_v\beta_3$ expression correlates well with tumor progression and invasiveness of tumors.

Methodologies and Results In this work we describe the synthesis of two conjugates based on derivatives of NOTA, in which one of the acetate pendant arms displays a α-alkyl substituent with a variable number of carbon atoms, and bearing a RGD peptide moiety. The radiolabelling of NOTAC6-GRGDG and NOTAC8-GRGDG with [67Ga] has been characterized and the stability and octanol/water partition coefficient (log P) of [^{67}Ga]NOTAC8-GRGDG was obtained. The internalization profile of the radiolabelled bioconjugates was accessed both in breast tumor and glioblastoma cell lines.