Characterization of RGD-Glu-(^{90}Y-DOTA)-6-Ahx-RM2 for targeting prostate cancer

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Background

When treating cancer, early and accurate tumor detection is vitally important. For example, prostate cancer is second only to skin cancer as the most common cancer of men but must be differentiated from benign disease that presents with similar signs and symptoms. Developing compounds that improve positron emission tomography (PET) or single-photon emission computed tomography (SPECT) can potentially improve tumor cell visualization on imaging. Agents that bind to multiple receptors that are overexpressed on prostate cancer cells accomplish this goal by increasing the density of bound conjugate. The compound developed in this study binds to both Gastrin Releasing Peptide receptor (GRPr) and $\alpha_v\beta_3$ integrin receptor.

Methods

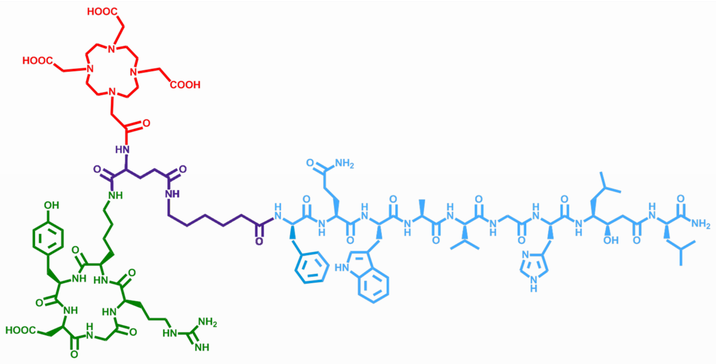

Figure 1. The chemical structure of the RGD-Glu-DOTA-6-Ahx-RM2 conjugate. In green, RGD (Arg-Gly-Asp), a nonregulatory peptide that targets $\alpha_v\beta_3$ integrin receptor; in red, DOTA (1,4,7,10-tetraazacyclotetradodecane-1,4,7,10-tetraacetic acid), a chelating agent; in purple, Glu (glutamic acid) and 6-Ahx (6-amino hexanoic acid), linkers; and in blue, RM2 (D-Phe-Gln-Trp-Ala-Val-Gly-His-Sta-Leu-NH2) an antagonist that targets GRPr.

^{nat}Y and ^{90}Y Labeling and Characterization

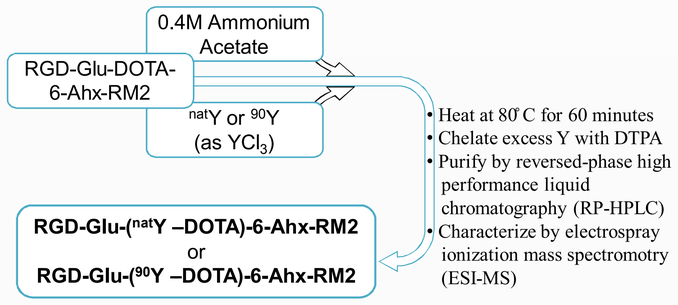

Figure 2. Schematic depicting the process by which RGD-Glu-DOTA-6-Ahx-RM2 is metallated with either ^{nat}Y or ^{90}Y.

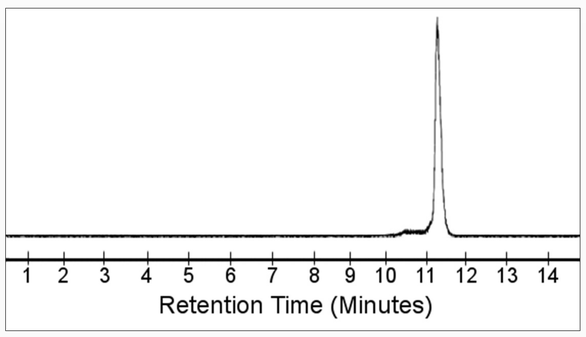

Figure 3. Chromatogram generated via RP-HPLC for RGD-Glu-(^{90}Y-DOTA)-6-Ahx-RM2 immediately after metallation depicting the compound's retention time (t_R) of 11.3 minutes.

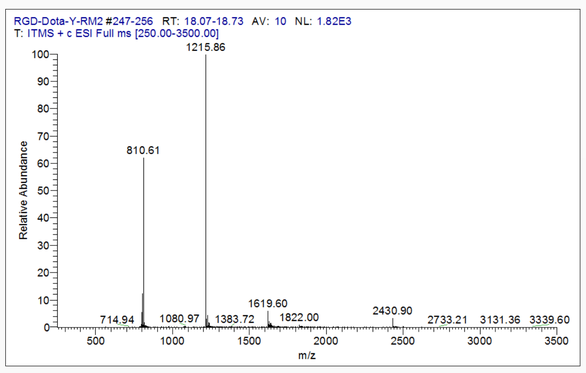

Figure 4. Mass spectrum generated via ESI-MS depicting peaks for RGD-Glu-(^{nat}Y-DOTA)-6-Ahx-RM2 at 810.61 m/z and 1215.86 m/z.

Results

RGD-Glu-(^{90}Y-DOTA)-6-Ahx-RM2 is stable in bovine serum albumin (BSA)

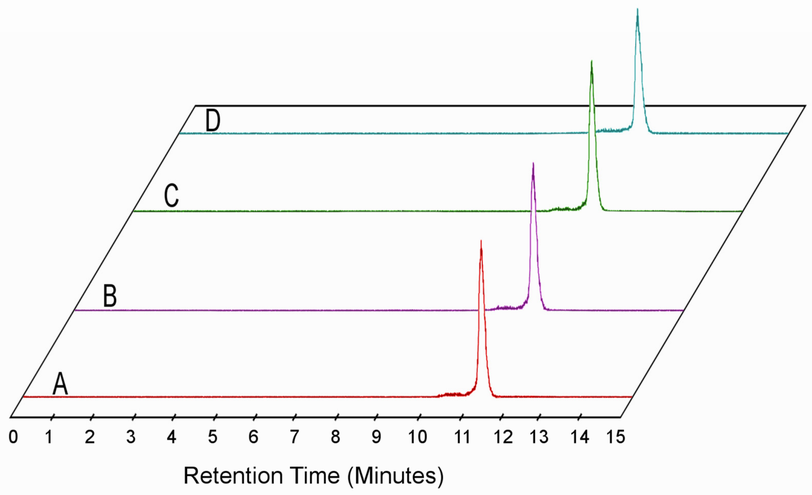

Figure 5. Chromatograms generated via RP-HPLC, with t_R of 11.3 minutes, demonstrating the stability of RGD-Glu-(^{90}Y-DOTA)-6-Ahx-RM2 in BSA at 2 (A), 4 (B), 6 (C), and 24 (D) hours after metallation.

RGD-Glu-(^{nat}Y-DOTA)-6-Ahx-RM2 has a high binding affinity for GRPr and $\alpha_v\beta_3$

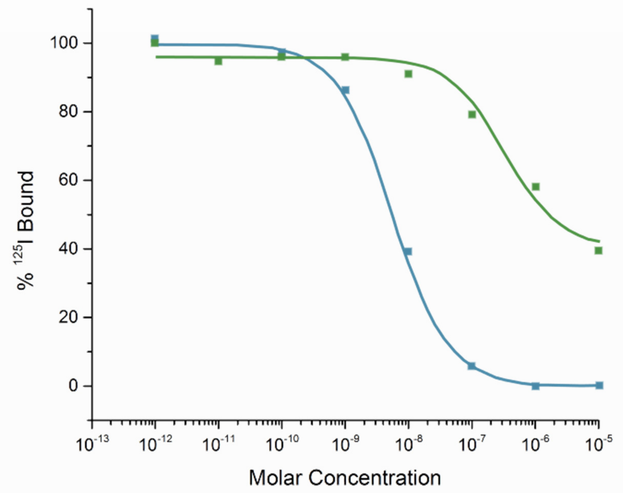

Figure 6. Graph depicting the inhibitory concentration half maximum (IC_{50}) of RGD-Glu-(^{nat}Y)-6-Ahx-RM2 for GRPr (blue) and $\alpha_v\beta_3$ integrin receptor (green), determined by competitive binding assay against the displacement radioligand ^{125}I-[Tyr^4]-bombesin and ^{125}I-echistatin respectively.

RGD-Glu-(^{111}In-DOTA)-6-Ahx-RM2 and RGD-Glu-(^{177}Lu-DOTA)-6-Ahx-RM2 preferentially bind to prostate cancer cells in PC-3 tumor-bearing SCID mice

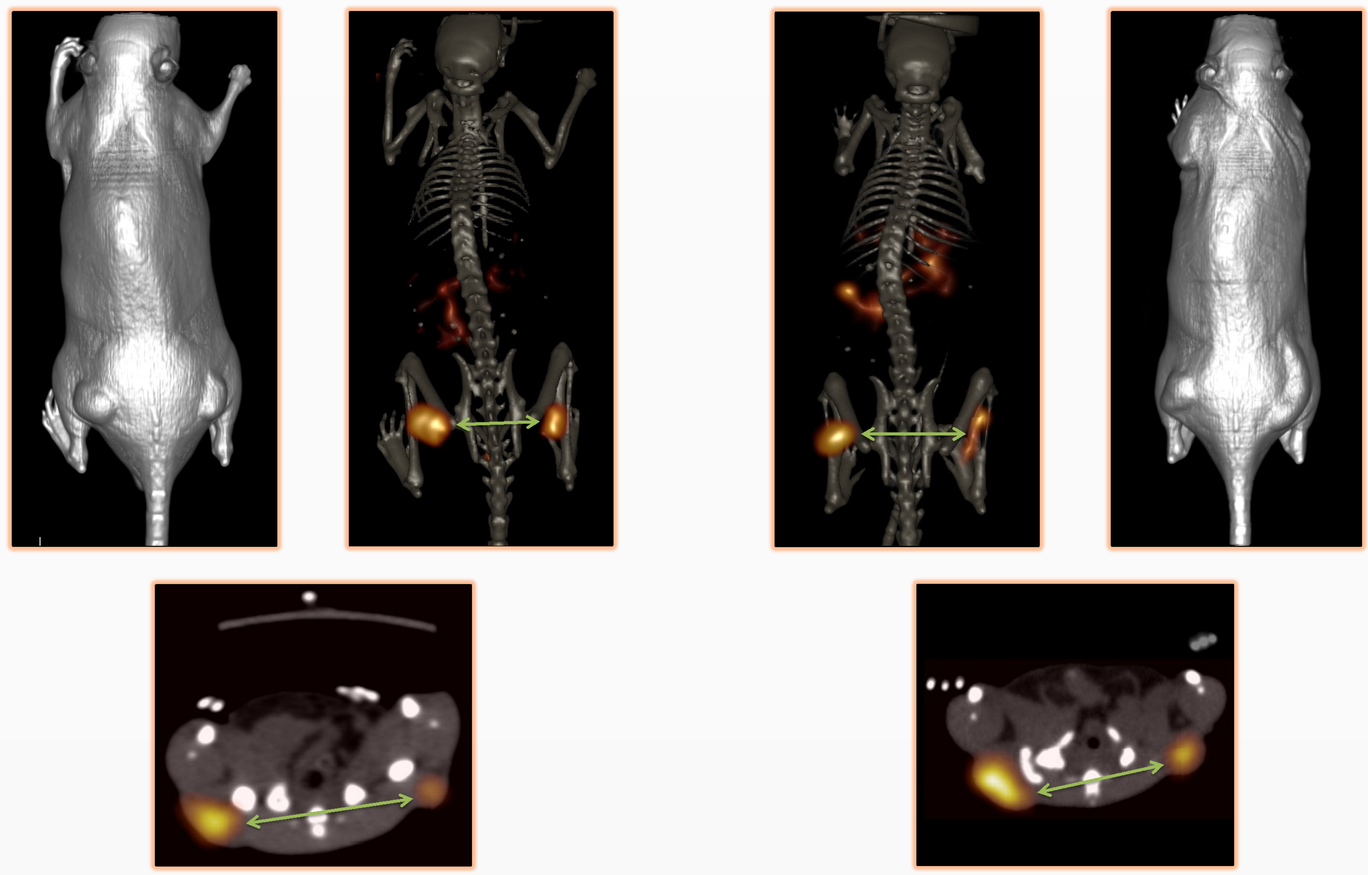

Figure 7. MicroSPECT images demonstrating RGD-Glu-(^{111}In-DOTA)-6-Ahx-RM2 (left) and RGD-Glu-(^{177}Lu-DOTA)-6-Ahx-RM2 (right) uptake on prostate cancer cells in PC-3 tumor-bearing SCID mice 24 hours after injection. Tumor location is indicated by green arrows. As a pure β^- emitting radionuclide, ^{90}Y cannot be visualized on SPECT; however, the same conjugate radiolabeled with either ^{111}In or ^{177}Lu (both gamma emitting radionuclides) demonstrates the compound's in vivo distribution in tissue. As the β^- radiation from ^{90}Y only penetrates a small distance in human tissue (about 2.4 mm), it may be useful as a targeted treatment option for prostate cancer.

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