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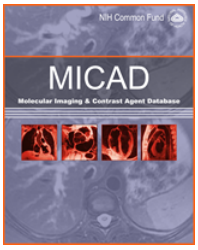

^{111}In-Diethylenetriamine pentaacetic acid-NAVPNLRGDLQVLAQKVART

^{111}In-DTPA-A20FMDV2

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Chemical name:	^{111}In-Diethylenetriamine pentaacetic acid-NAVPNLRGDLQVLAQKVART	
Abbreviated name:	^{111}In-DTPA-A20FMDV2	
Synonym:		
Agent category:	Peptide	
Target:	Integrin $\alpha_v\beta_6$	
Target category:	Receptor	
Method of detection:	Single-photon emission computed tomography (SPECT), gamma planar imaging	
Source of signal:	^{111}In	
Activation:	No	
Studies:	• *In vitro* • Rodents	Structure is not available in PubChem.

Background

[PubMed]

Integrins are a family of heterodimeric glycoproteins on cell surfaces that mediate diverse biological events involving cell–cell and cell–matrix interactions (1). Integrins consist of an α and a β subunit and are important for cell adhesion and signal transduction. $\alpha_v\beta_3$ integrin is the most prominent receptor affecting tumor growth, tumor invasiveness, metastasis, tumor-induced angiogenesis, inflammation, osteoporosis, and rheumatoid arthritis (2-7). Expression of $\alpha_v\beta_3$ integrin is strong on tumor cells and activated endothelial cells, whereas expression is weak on resting endothelial cells and most normal tissues. $\alpha_v\beta_3$ antagonists are being studied as antitumor and antiangiogenic agents, and the agonists are being studied as angiogenic agents for coronary angiogenesis (6, 8, 9). A tripeptide sequence consisting of Arg-Gly-Asp (RGD) has been identified as a recognition motif used by extracellular matrix proteins (vitronectin, fibrinogen, laminin, and collagen) to bind to a variety of integrins, including $\alpha_v\beta_3$ and $\alpha_v\beta_6$. Various radiolabeled antagonists have been introduced for imaging of tumors and tumor angiogenesis (10).

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The $\alpha_v\beta_6$ integrin plays an important role in the development of epithelial cells and is nearly undetectable on normal adult tissues. However, the levels of $\alpha_v\beta_6$ integrin can be upregulated during tissue remodeling and wound healing (11). On the other hand, $\alpha_v\beta_6$ integrin is strongly expressed on tumor cells of the oral cavity, pancreas, breast, ovary, colon, and stomach (12-14). $\alpha_v\beta_6$ integrin affects tumor growth, tumor invasiveness, and metastasis (13). $\alpha_v\beta_6$ binds to the RGD motif in fibronectin, tenascin, and the viral protein 1 (VP1) of the foot-and-mouth disease virus (FMDV) (15). FMDV binds to cells through the RGD motif of the GH loop of the VP1. The consensus $\alpha_v\beta_6$-binding motif DLXXL was identified with the use of phage display screening, with minimal binding to $\alpha_v\beta_3$, $\alpha_{IIb}\beta_3$, and $\alpha_v\beta_5$ (16). A 20-amino acid peptide, NAVPNLRGDLQVLAQKVART (A20FMDV2), was identified as a ligand binding to $\alpha_v\beta_6$ integrin (15). A20FMDV2 was radiolabeled with *N*-succinimidyl 4-[^{18}F]fluorobenzoate ([^{18}F]SFB) to study *in vivo* biodistribution of the tracer in tumor-bearing mice (17). [^{18}F]FB-A20FMDV2 was found to have specific accumulation in $\alpha_v\beta_6$-positive tumors. For single-photon emission computed tomography (SPECT), Saha et al. (18) prepared ^{111}In-diethylenetriamine pentaacetic acid-A20FMDV2 (^{111}In-DTPA-A20FMDV2) for *in vivo* imaging of $\alpha_v\beta_6$-positive tumors.

Related Resource Links:

- Chapters in MICAD (knot peptide, RGD, A20FMDV2)
- Gene information in NCBI (α_v integrin, β_6 integrin)
- Articles in Online Mendelian Inheritance in Man (OMIM) (α_v integrin, β_6 integrin)
- Clinical trials (RGD)
- Drug information in FDA (RGD)

Synthesis

[PubMed]

DTPA-NAVPNLRGDLQVLAQKVART (DTPA-A20FMDV2) was prepared with solid-phase peptide synthesis, with the addition of DTPA at the N-terminus (18). A mixture of 1–30 MBq (0.027–0.81 mCi) $^{111}InCl_3$ and DTPA-A20FMDV2 was incubated in ammonium acetate buffer (pH 5.5) for 30 min at room temperature. ^{111}In-DTPA-A20FMDV2 was found to have a radiochemical purity of >98%. The specific activity of ^{111}In-DTPA-A20FMDV2 was not reported. ^{111}In-DTPA-A20FMDV2 remained >95% intact after incubation in phosphate-buffered saline for 24 h at 37°C, but it remained only 50% intact in mouse serum for 4 h at 37°C.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

A receptor-binding assay with biotinylated A20FMDV2 using human A375Ppuro ($\alpha_v\beta_6$-negative) and A375Pβ6 ($\alpha_v\beta_6$-positive) cell lines was analyzed with flow cytometry (18). $\alpha_5\beta_1$, $\alpha_v\beta_3$, $\alpha_v\beta_5$, and $\alpha_v\beta_8$ integrins were present on both cell lines. A20FMDV2 bound well at 1–10,000 nM to A375Pβ6 cells but not to A375Ppuro cells, suggesting that A20FMDV2 is highly selective for $\alpha_v\beta_6$. DTPA-A20FMDV showed similar binding to these cells as A20FMDV2. Saturation binding assays of ^{111}In-DTPA-A20FMDV2 with A375Pβ6 cells exhibited an affinity constant (K_d) of 1.73 ± 0.46 nM. Internalization assays showed that 50% of total bound radioactivity internalized into A375Pβ6 cells within 20 min and reached 89%–96% by 60 min. On the other hand, neither binding nor internalization was observed in A375Ppuro cells. Confocal microscopy showed binding of A20FMDV2 to the cell membrane of A375Pβ6 cells initially, and most of the peptide was internalized into the cytoplasm by 30 min.

Animal Studies

Rodents

[PubMed]

Saha et al. (18) performed *ex vivo* biodistribution studies with 1 MBq (0.027 mCi) ^{111}In-DTPA-A20FMDV2 in nude mice (n = 3/group) bearing A375Ppuro and A375Pβ6 xenografts on opposite flanks in the shoulder region at 1 h after injection. ^{111}In-DTPA-A20FMDV2 exhibited tumor accumulation of 2.1% injected dose (ID)/g in A375Pβ6 tumors at 1 h and only 0.3% ID/g in A375Ppuro tumors. The highest radioactive concentration was found in the kidneys (98% ID/g), followed by the intestine (2.2% ID/g), gallbladder (1.7% ID/g), lung (1.3% ID/g), and stomach (1.2% ID/g). The spleen, muscle, blood, and liver showed low levels of radioactivity (<0.3% ID/g). Co-injection of 100-fold excess DTPA-A20FMDV2 markedly inhibited accumulation of radioactivity by ~70% in the $\alpha_v\beta_6$-positive tissues, such as the intestine, stomach gallbladder, and A375Pβ6 tumors, but there was little inhibition in the $\alpha_v\beta_6$-negative tissues, such as the spleen, liver, and A375Ppuro tumors. There was ~50% inhibition in the kidney, but this was determined to be non-specific because 100-fold excess of the non-labeled scrambled peptide (DTPA-A20FMDV2ran) showed similar inhibition in the kidney, with no inhibition in other tissues or in either tumor.

SPECT/computed tomography imaging was performed in nude mice bearing both A375Ppuro and A375Pβ6 xenografts at 1 h after injection of 10–20 MBq (0.27–0.54 mCi) ^{111}In-DTPA-A20FMDV2 (18). The kidneys, urinary bladder, intestine, and A375Pβ6 tumors were clearly visualized, whereas little radioactivity was observed in the A375Ppuro tumors. SPECT imaging studies were also performed in nude mice bearing human breast carcinoma cells (MCF10A.DCIS.COM and MCF10A.CA1a) with endogenous expressed $\alpha_v\beta_6$ integrin. The tumors were clearly visualized with >2% ID/g. No blocking studies were performed.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

No publication is currently available.

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