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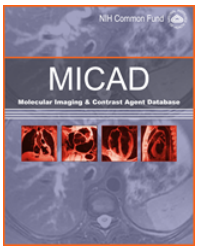
NLM Citation: Leung K. ^{68}Ga-1,4,7-Triazacyclononane,1-glutaric acid-4,7-acetic acid-Asp-cyclohexylalanine-Phe-D-Ser-D-Arg-Tyr-Leu-Trp-Ser-NH_2 (AE105-NH_2). 2012 May 20 [Updated 2012 Aug 23]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/



^{68}Ga-1,4,7-Triazacyclononane,1-glutaric acid-4,7-acetic acid-Asp-cyclohexylalanine-Phe-D-Ser-D-Arg-Tyr-Leu-Trp-Ser-NH_2 (AE105-NH_2)

^{68}Ga-NODAGA-AE105-NH_2

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Created: May 20, 2012; Updated: August 23, 2012.

Chemical name:	^{68}Ga-1,4,7-Triazacyclononane,1-glutaric acid-4,7-acetic acid-Asp-cyclohexylalanine-Phe-D-Ser-D-Arg-Tyr-Leu-Trp-Ser-NH_2 (AE105-NH_2)	
Abbreviated name:	^{68}Ga-NODAGA-AE105-NH_2, ^{68}Ga-NODAGA-D-Cha-F-s-r-Y-L-W-S-NH_2	
Synonym:		
Agent category:	Peptide	
Target:	Urokinase-type plasminogen activator receptor (uPAR)	
Target category:	Receptor	
Method of detection:	Single-photon emission computed tomography (SPECT), gamma planar imaging	
Source of signal:	^{68}Ga	
Activation:	No	
Studies:	• *In vitro* • Rodents	Click on protein, nucleotide (RefSeq), and gene for more information about uPAR.

Background

[PubMed]

Extracellular matrix (ECM) adhesion molecules consist of a complex network of fibronectins, collagens, chondroitins, laminins, glycoproteins, heparin sulfate, tenascins, and proteoglycans that surround connective tissue cells, and they are mainly secreted by fibroblasts, chondroblasts, and osteoblasts (1). Cell substrate adhesion molecules are considered essential regulators of cell migration, differentiation, and tissue integrity and remodeling. These molecules play an important role in inflammation and atherogenesis, but they also participate in the process of invasion and metastasis of malignant cells in the host tissue (2). Invasive tumor cells adhere to the ECM, which provides a matrix environment for permeation of tumor cells through the basal lamina and underlying interstitial stroma of the connective tissue. Overexpression of matrix metalloproteinases (MMPs) and

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other proteases by tumor cells allows intravasation of tumor cells into the circulatory system after degradation of the basement membrane and ECM (3). Several families of proteases are involved in atherogenesis, myocardial infarction, angiogenesis, and tumor invasion and metastasis (4-7).

Urokinase-type plasminogen activator (uPA) is a serine protease (8, 9). The uPA/uPA receptor (uPAR) system is responsible for tissue degradation after plasminogen activation to plasmin, which leads to a cascade of proteolysis or thrombolysis, depending on the physiological conditions. uPA also directly activates MMPs, vascular endothelial growth factor, and human growth factor (10). Malignant tumors often express high levels of uPA and uPAR (11); therefore, the uPA/uPAR system is linked to vascular diseases and cancer. The synthetic peptide Asp-cyclohexylalanine-Phe-D-Ser-D-Arg-Tyr-Leu-Trp-Ser (AE105) has been identified to have a high affinity for human uPAR (dissociation constant (K_d) = 0.4 nM) (12), and AE105 has been labeled with ^{64}Cu ($T_{1/2}$ = 12.7 h, β^+ = 17.8%) as ^{64}Cu-1,4,7,10-tetraazacyclododecane-*N*,*N*′,*N*″,*N*‴-tetraacetic acid-AE105 (^{64}Cu-DOTA-AE105) and ^{64}Cu-DOTA-AE105-NH_2 for use in positron emission tomography (PET) imaging of uPAR expression in tumors (13, 14). Persson et al. (15) also prepared ^{68}Ga-1,4,7-triazacyclononane,1-glutaric acid-4,7-acetic acid-AE105-NH_2 (^{68}Ga-NODAGA-AE105-NH_2) and ^{68}Ga-DOTA-AE105-NH_2 for evaluation as alternative PET agents (^{68}Ga: $T_{1/2}$ = 68 min, β^+ = 89%).

Related Resource Links

- Chapters in MICAD (uPAR)
- Gene information in NCBI (uPAR, uPA)
- Articles in Online Mendelian Inheritance in Man (OMIM) (uPAR, uPA)

Synthesis

[PubMed]

Persson et al. (15) performed NODAGA chelation of the N-terminus of AE105-NH_2*via* solid-phase synthesis. A mixture of AE105-NH_2 and NODAGA-tris(tBu)ester in a molar ratio of 1:3 was incubated for 24–48 h at room temperature. The NODAGA-AE105-NH_2 conjugate was purified with high-performance liquid chromatography (HPLC). The number of NODAGA molecules per peptide was ~1 as determined with mass spectroscopy. For radiolabeling, NODAGA-AE105-NH_2 (5 nmol) was added to $^{68}GaCl_3$ diluted in 0.1 M sodium acetate buffer (pH 5.0). The reaction mixture was incubated for 15 min at 25°C. ^{68}Ga-NODAGA-AE105-NH_2 was purified with a Sep-Pak column (>95% radiochemical purity). ^{68}Ga-DOTA-AE105-NH_2 was prepared similarly. The specific activities of ^{68}Ga-NODAGA-AE105-NH_2 and ^{68}Ga-DOTA-AE105-NH_2 were ~20 GBq/μmol (0.54 Ci/μmol) at the end of synthesis. Total synthesis time and yields for both tracers were not reported. The log *P* values were –1.15 ± 0.1 and –1.75 ± 0.1 for ^{68}Ga-NODAGA-AE105-NH_2 and ^{68}Ga-DOTA-AE105-NH_2, respectively. Both tracers were >98% intact in both saline buffer and mouse plasma for 60 min at 37°C.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Persson et al. (15) performed binding experiments with AE105-NH_2, NODAGA-AE105-NH_2, and DOTA-AE105-NH_2 with the use of a Biacore sensor chip immobilized with pro-uPA. The IC_{50} values for inhibiting the binding of 0.5 nM uPAR to pro-uPA were 7.6 ± 2.0 nM, 3.4 ± 0.4 nM, and 6.7 ± 0.9 nM for AE105-NH_2, NODAGA-AE105-NH_2, and DOTA-AE105-NH_2, respectively. Cellular accumulation of ^{68}Ga-NODAGA-AE105-NH_2 and ^{68}Ga-DOTA-AE105-NH_2 was assessed by incubating the agents with U87MG human glioblastomas (uPAR-positive) cells for 120 min at 37°C. Both tracers reached a plateau accumulation at 60 min after incubation, with 1.46 ± 0.1% and 1.37 ± 0.1% incubation dose, respectively.

Animal Studies

Rodents

[PubMed]

Persson et al. (15) performed dynamic PET imaging studies for 60 min after injection of 5–7 MBq (0.135–0.189 mCi, 0.5 nmol) ^{68}Ga-NODAGA-AE105-NH$_2$ or ^{68}Ga-DOTA-AE105-NH$_2$ in mice (n = 3/group) bearing U87MG tumors in the left and right flanks. The tumors and kidneys were visualized for both tracers at 10–60 min. Region of interest (ROI) analysis showed that the tumor accumulation values of ^{68}Ga-NODAGA-AE105-NH$_2$ were 2.5% injected dose per gram (ID/g), 2.0% ID/g, and 2.0% ID/g at 10, 30, and 60 min after injection. The tumor/blood, tumor/muscle, and tumor/liver ratios at 60 min were 1, 5, and 1, respectively. The tumor accumulation values of ^{68}Ga-DOTA-AE105-NH$_2$ were 2.2% ID/g, 1.3% ID/g, and 1.0% ID/g at 10, 30, and 60 min after injection, respectively. The tumor/blood, tumor/muscle, and tumor/liver ratios at 60 min were 1, 3, and 1, respectively. ^{68}Ga-NODAGA-AE105-NH$_2$ and ^{68}Ga-DOTA-AE105-NH$_2$ exhibited lower tumor accumulation and a lower tumor/muscle ratio than ^{64}Cu-DOTA-AE105-NH$_2$ (4.8% ID/g and 16) at 60 min after injection, as reported previously in the same tumor model. No blocking studies and *ex vivo* biodistribution studies were performed with either tracer.

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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