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NLM Citation: Chopra A. [^{111}In]Labeled-(NAc-dD-CHA-F-dS-dR-Y-L-W-S-βAla)$_2$-K-K(DOTA). 2010 Apr 1 [Updated 2010 May 27]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.
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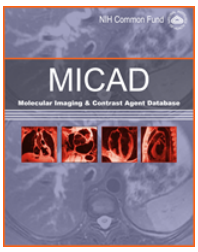

[^{111}In]Labeled-(NAc-dD-CHA-F-dS-dR-Y-L-W-S-βAla)$_2$-K-K(DOTA)

[^{111}In]Anti-uPA peptide

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Created: April 1, 2010; Updated: May 27, 2010.

Chemical name:	[^{111}In]Labeled-(NAc-dD-CHA-F-dS-dR-Y-L-W-S-βAla)$_2$-K-K(DOTA)	
Abbreviated name:	[^{111}In]Anti-uPAR peptide	
Synonym:		
Agent Category:	Compound	
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 / contrast:	^{111}In	
Activation:	No	
Studies:	• *In vitro* • Rodents	Structure not available in PubChem.

Background

[PubMed]

The urokinase-type plasminogen activator (uPA) is a serine protease that mediates its activity through a receptor (uPAR) and has an important role in several physiological processes such as matrix remodeling, inflammation, fibrinolysis, and cancer tumor angiogenesis, invasion, and metastasis (1). In addition, uPA activity is modulated by two specific inhibitors known as uPAI-1 and uPAI-2. The structure and functioning of uPA and its receptor is discussed in detail by Ploug (2). The uPA, uPAR, and the two inhibitors comprise the uPA system (uPAS), and any one or a combination of the uPAS components is known to be overexpressed in various malignant tumors, indicating a strong correlation of uPAS component overexpression to a poor prognostic outcome for the cancer patient (3). Therefore, investigators are interested in developing and evaluating agents that can be used non-invasively for the detection (e.g., by imaging techniques) and therapy (e.g., by radiotherapy with nuclide-containing uPAR ligands) of cancers that overexpress components of the uPAS. Li et al. recently reported the use of a linear, high-affinity uPAR antagonist, ^{64}Cu-labeled peptide for the visualization of uPAR expression under preclinical conditions (4). In another study, Knor et al. evaluated and successfully used an α-emitting nuclide-conjugated peptide targeting the uPAR for the therapy of advanced ovarian cancer tumors in a mouse model (5).

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In a continued effort to develop and evaluate possible imaging agents for the visualization uPAR-expressing cancers, Liu et al. (6) synthesized and characterized a ^{111}In-labeled (NAc-dD-CHA-F-dS-dR-Y-L-W-S-βAla)$_2$-K-K(DOTA) peptide ([^{111}In]anti-uPAR peptide; referred to as Test peptide from here on) under *in vitro* conditions and in mice bearing human breast cancer cell xenograft tumors.

Synthesis

[PubMed]

Synthesis of the Test peptide has been discussed in detail by Liu et al. (6). The radiochemical yield, purity, and stability of the labeled compound were not reported. The specific activity of the Test peptide was reported to be 1.85–3.70 MBq/μg (50–100 μCi/μg).

A scrambled [^{111}In]anti-uPAR peptide (referred to as Scrambled peptide from here on) was also synthesized for use as a negative control during the biodistribution studies. The radiochemical yield, purity, specific activity, and stability of the Scrambled peptide were not reported.

A ^{125}I-labeled amino terminal fragment of uPA ([^{125}I]ATF) that binds to the uPAR was also synthesized by the investigators for comparison with the Test peptide (6). However, the radiochemical yield, purity, specific activity, and stability of [^{125}I]ATF were not reported.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

To determine the binding affinity of the Test peptide, MDA-MB-231 human breast cancer cells were allowed to bind [^{125}I]ATF in presence of increasing concentrations of the non-radioactive competitor peptides (6). Based on this study, the half maximal inhibitory concentration (IC_{50}) of the Test peptide was reported to be 240 ± 125 nM, which was 300- to 600-fold higher than non-radioactive uPA or ATF (the IC_{50} values for uPA and ATF were 0.75 ± 0.01 and 0.44 ± 0.02 nM, respectively). This indicated that the anti-uPAR peptide had a lower affinity for uPAR than either uPA or ATF.

In another study, the investigators showed that cells obtained from the MDA-MB-231 xenograft tumors had a four- to five-fold lower uPAR occupancy compared to cells that had been stripped of the endogenous uPA using appropriate buffers (6). Using siRNA that inhibited the expression of uPA in MDA-MB-231 cells, the investigators showed that the specific binding of [^{125}I]ATF to these cells was increased by ~4.4-fold ($P < 0.01$), and this increase in binding correlated well with the decrease observed in uPA mRNA and protein expression as determined with reverse transcriptase polymerase chain reaction and Western blot analysis, respectively (6). On the basis of these results, the investigators suggested that the high IC_{50} value observed for the anti-uPAR peptide (see above) could be due to receptor binding of the endogenous uPA. However, they did not explain why the IC_{50} values for uPA or ATF were lower than that of the Test peptide, given that the binding studies for all these peptides were performed under the same experimental conditions.

Animal Studies

Rodents

[PubMed]

Biodistribution patterns of the Test peptide, the Scrambled peptide, and, for comparison, the [^{125}I]ATF peptide were studied in severe combined immunodeficient mice bearing MDA-MB-231 xenograft tumors (6). The animals (n = 3 mice/time point per labeled compound) were injected with the respective radiochemicals *via* the

tail vein and euthanized at 1, 4, and 24 h postinjection (p.i.) to determine the amount of radioactivity accumulated in the various organs, including the tumors. Both the Scrambled and the Test peptides had a rapid clearance from blood circulation, primarily through the urinary route. At 4 h p.i., the amount of radioactivity from the Test peptide that was accumulated in the blood, muscle, and the tumor was 0.06 ± 0.02% injected dose per gram tissue (% ID/g), 0.12 ± 0.06% ID/g, and 0.53 ± 0.11% ID/g, respectively. At the same time point, the amount of radioactivity in the blood, muscle, and the tumor from the Scrambled peptide was 0.15 ± 0.04% ID/g, 0.12 ± 0.02% ID/g, and 0.36 ± 0.05% ID/g, respectively. The accumulation of label in the tumor from the Test peptide was significantly ($P < 0.05$) higher than that from Scrambled peptide. No blocking studies were reported for the Test peptide. The accumulation of radioactivity from [^{125}I]ATF in the tumor was not significantly higher than that of blood at all time points except at 24 h p.i. (0.26 ± 0.06% ID/g and 0.29 ± 0.06% ID/g in the blood and tumor, respectively). Also, co-injection of [^{125}I]ATF with non-radioactive ATF was reported to reduce uptake of the label from this radiochemical significantly ($P < 0.05$) by 24 h p.i. in all organs, including the tumors (accumulation of radioactivity other time points was not reported).

The investigators report ongoing studies to determine the correlation between uPAR occupation by endogenous uPA and uptake of the radiotracer under *in vivo* conditions (6).

Other Non-Primate Mammals

[PubMed]

No references are currently available.

Non-Human Primates

[PubMed]

No references are currently available.

Human Studies

[PubMed]

No references are currently available.

Supplemental Information

[Disclaimers]

No information is currently available.

NIH Support

Some of the studies reported here were funded by National Cancer Institute Center grant I P50 CA103130-01.

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