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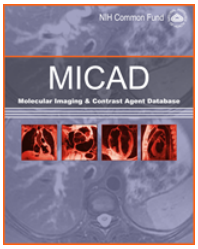

^{64}Cu-Tetraazacyclododecane-*N*,*N*',*N*'',*N*'''-tetraacetic acid-conatumumab

^{64}Cu-DOTA-conatumumab

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Chemical name:	^{64}Cu-Tetraazacyclododecane-*N*,*N*',*N*'',*N*'''-tetraacetic acid-conatumumab	
Abbreviated name:	^{64}Cu-DOTA-conatumumab	
Synonym:	^{64}Cu-DOTA-AMG 655	
Agent category:	Antibody	
Target:	Death receptor 5 (DR5), also known as TRAIL-R2 (TR2)	
Target category:	Receptor	
Method of detection:	Positron emission tomography (PET)	
Source of signal:	^{64}Cu	
Activation:	No	
Studies:	• *In vitro* • Rodents	Structure is not available in PubChem.

Background

[PubMed]

The tumor necrosis factor–related apoptosis-inducing ligand (TRAIL) receptor is a member of the tumor necrosis factor superfamily of cytokines that selectively activate a complex apoptotic pathway (caspase cascade) in tumor cells, thereby inducing apoptosis (cell death) (1, 2). There are two cell-surface TRAIL receptors (death receptor 4 [DR4] and 5 [DR5]) that are capable of inducing apoptosis and three decoy TRAIL receptors that are not capable of inducing apoptotic signals (3, 4). Conatumumab is a fully human monoclonal antibody (mAb) that acts as a human DR5 agonist antibody to tumor cells, which causes apoptosis in *in vitro* and *in vivo* studies (5, 6). Conatumumab is being evaluated in clinical trials (7, 8). Rossin et al. (9) reported the development of ^{64}Cu-tetraazacyclododecane-*N*,*N*',*N*'',*N*'''-tetraacetic acid-conatumumab (^{64}Cu-DOTA-conatumumab) for positron emission tomography (PET) imaging of DR5 in nude mice bearing tumor xenografts.

Related Resource Links:

- Chapters in MICAD (DR5)

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- Gene information in NCBI (DR5)
- Articles in Online Mendelian Inheritance in Man (OMIM) (DR5)
- Clinical trials (Conatumumab)

Synthesis

[PubMed]

2,2',2''-(10-(2-(2,5-dioxopyrrolidin-1-yloxy)-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid (DOTA-*N*-hydroxysuccinimide) was added to conatumumab (100 nmol) in phosphate-buffered saline (9). The reaction mixture was adjusted to pH 8.5 and incubated for ~2 h at room temperature. DOTA-conatumumab was purified with column chromatography. DOTA-conatumumab (0.6–1.2 nmol) was incubated with 33–222 MBq (1–6 mCi) $^{64}CuCl_2$ in ammonium acetate buffer (pH 5.5) for 1 h at 37°C. ^{64}Cu-DOTA-conatumumab was purified with column chromatography, with a radiochemical purity of >95%. The specific activities were 6 MBq/nmol (0.16 mCi/nmol) and 123 MBq/nmol (3.3 mCi/nmol) for *ex vivo* biodistribution studies and PET studies, respectively. There were approximately five DOTA molecules per antibody. ^{64}Cu-DOTA-conatumumab was stable in mouse serum for 24 h at 37°C.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Rossin et al. (9) performed competition binding experiments using a conatumumab immobilized Biacore sensor chip. DOTA-conatumumab and conatumumab inhibited the binding of huTR2-Fc (1 nM) with 50% inhibition concentration (IC_{50}) values of 0.389 nM and 0.320 nM, respectively. The potency of DOTA-conatumumab and conatumumab to induce caspase 3/7 activities was compared in Colo205 human colon tumor cells. The effective doses to induce 50% of the maximum caspase 3/7 activities were 0.135 ± 0.31 nM and 0.128 ± 0.30 nM (n = 5), respectively. These data suggest that DOTA-conatumumab and conatumumab exhibit similar immunoreactivity and agonist activity for DR5.

Animal Studies

Rodents

[PubMed]

Rossin et al. (9) performed PET and *ex vivo* biodistribution studies of 0.33 MBq (0.009 mCi) ^{64}Cu-DOTA-conatumumab (52 pmol) in nude mice (n = 4/group) bearing Colo205 tumors at 6 h and 24 h after injection. *Ex vivo* tumor accumulation values were 13.86 ± 1.19% injected dose/gram (ID/g) and 20.68 ± 3.03% ID/g at 6 h and 24 h after injection, respectively. Accumulation at 24 h after injection was highest in the spleen (42.66% ID/g), followed by the blood (18.14% ID/g), liver (10.75% ID/g), lung (9.30% ID/g), heart (6.06% ID/g), and kidney (5.99% ID/g). Co-injection of conatumumab (2 nmol) decreased the radioactivity levels in the tumors and spleen by 50%–60% at 6 h and 24 h after injection. The binding in the spleen may be because of binding of ^{64}Cu-DOTA-conatumumab to splenic Fc receptors on macrophages. Little inhibition was observed in the other normal tissues. ^{64}Cu-DOTA-conatumumab remained >98% intact in the blood at 24 h after injection.

Whole-body PET images were obtained in the tumor-bearing mice (n = 2/group) at 1, 6 and 24 h after injection of 3.7 MBq (0.1 mCi) ^{64}Cu-DOTA-conatumumab (30 pmol) (9). High levels of background radioactivity were detected at 1 h and 6 h. However, the tumors could be visualized at 6 h. The standard uptake value (SUV) of the tumors was 3.16 at 24 h. Co-injection of conatumumab (2 nmol) decreased the SUV to 1.55 with ~50% inhibition. The spleen SUV decreased from 1.73 (control) to 1.23 (blocked).

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.

NIH Support

CA86307

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