^{89}Zr-*N*-Succinyldesferal-anti-CD44v6 chimeric monoclonal antibody U36

^{89}Zr-*N*-SucDf-cMAb U36

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Chemical name:	^{89}Zr-*N*-Succinyldesferal-anti-CD44v6 chimeric monoclonal antibody U36	
Abbreviated name:	^{89}Zr-*N*-SucDf-cMAb U36, ^{89}Zr-U36	
Synonym:		
Agent category:	Antibody, chimeric monoclonal	
Target:	CD44v6	
Target category:	Antigen	
Method of detection:	Positron emission tomography (PET)	
Source of signal:	^{89}Zr	
Activation:	No	
Studies:	• *In Vitro* • Rodents • Humans	Click on protein, nucleotide (RefSeq), and gene for more information about CD44.

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

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considered essential regulators of cell migration, differentiation, and tissue integrity and remodeling. These molecules play a role in inflammation, 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 by tumor cells allows intravasation of tumor cells into the circulatory system after degrading the basement membrane and ECM (3).

The splice variant v6 of the cell membrane glycoprotein CD44 (CD44v6) is expressed only in a few normal epithelial tissues (e.g., thyroid and prostate gland). CD44 binds to ECM and is associated with cell adhesion, lymphocyte activation, and tumor cell metastases (4, 5). Elevated levels of CD44v6 have been found in epithelial tumors, which are associated with a poor prognosis for cancer patients (5). Anti-CD44v6 chimeric (mouse/human) monoclonal antibody (cMAb) U36 was found not bind to follicles or C cells from normal human thyroid (6). CD44v6 is generally highly expressed in thyroid carcinoma (7). ^{124}I-cMAb U36 was developed for imaging of CD44v6 expression in thyroid carcinoma and other epithelial tumors (8, 9). However, production of ^{124}I is too expensive for routine clinical application. Verel et al. (10) explored the use of ^{89}Zr positron emitter (half-life, 3.27 days) to radiolabel cMAb U36. ^{89}Zr was conjugated to a bifunctional derivative of desferrioxamine B (Df) to cMAB U36 for positron emission tomography (PET) imaging of CD44v6 expression in tumors. ^{89}Zr-*N*-Succinyldesferal-cMAb U36 (^{89}Zr-*N*-SucDf-cMAb U36) has been studied in tumor-bearing mice and humans (11, 12).

Related Resource Links:

- Chapters in MICAD
- Gene information in NCBI (CD44).
- Articles in OMIM
- Clinical trials (CD44)

Synthesis

[PubMed]

cMAb U36 was coupled with *N*-SucDf *via* an amide linkage and labeled with ^{89}Zr (10). ^{89}Zr-*N*-SucDf-cMAb U36 was purified with gel filtration. ^{89}Zr-Labeling yields were >80%. The radiochemical purity was >97% with >90% immunoreactivity. Maximum specific activity was 83.3 MBq/nmol. There is only one lysine group per antibody molecule. ^{89}Zr-*N*-SucDf-cMAb U36 showed no loss of ^{89}Zr after incubation in human serum for 24 h at 37°C.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Fortin et al. (8) reported that high-affinity ^{125}I-cMAb U36 binding sites (B_{max} = 570,000 ± 30,000 sites/cell; K_d = 11 ± 2 nM) were found on the cell surfaces of KAT-4 human anaplastic thyroid carcinoma cells lacking the sodium iodide symporter. Furthermore, 20% of ^{125}I-cMAb U36 accumulated in the cells after incubation for 24 h at 37°C. Accumulation was reduced to 1% with excess cMAb U36. The labeled cells retained 29% of the radioactivity after incubation in tracer-free medium alone for another 24 h at 37°C.

Animal Studies

Rodents

[PubMed]

Verel et al. (10) performed *ex vivo* biodistribution studies and *in vivo* PET imaging studies of ^{89}Zr-*N*-SucDf-cMAb U36 in nude mice (n = 4/group) bearing HNX-OE human head and neck tumors at 24, 48, and 72 h after injection. ^{89}Zr-*N*-SucDf-cMAb U36 uptake in the tumors was 14.1 ± 1.0%, 22.0 ± 2.0%, and 26.0 ± 1.9% injected dose per gram (ID/g) at 24, 48, and 72 h, respectively. The blood level of ^{89}Zr-*N*-SucDf-cMAb U36 decreased from 14.6% at 24 h to 12.3% ID/g at 72 h. Most nontarget organs exhibited ~5% ID/g. Selective tumor uptake was confirmed with PET imaging at 24, 48, and 72 h, detecting 12 of 12 tumors (as small as 19 mg). Only the blood pool in the heart and liver was visible. The results of these studies were similar to those reported for ^{124}I-cMAb U36 in the same tumor model (9). No blocking experiment was performed.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

Borjesson et al. (11) performed PET imaging with 75 MBq (2 mCi) ^{89}Zr-*N*-SucDf-cMAb U36 in 20 cancer patients with head and neck squamous cell carcinoma (HNSCC) at 1, 24, 72, and 144 h after injection. All primary tumors, lymph node metastases in 18 of 25 positive levels (sensitivity 72%) and in 11 of 15 positive sides (sensitivity 73%) were observed. Interpretation of the PET data was correct in 112 of 121 operated levels with 93% accuracy and in 19 of 25 operated sides with 76% accuracy. For CT/MRI, sensitivities of 60% and 73% and accuracies of 90% and 80% were observed per level and side,

respectively. In the six patients with seven tumor-involved neck levels and sides, ^{89}Zr-*N*-SucDf-cMAb U36 PET and [^{18}F]fluoro-2-deoxy-D-glucose PET yielded comparable diagnostic results.

Borjesson et al. (12) performed radiation dosimetry of ^{89}Zr-*N*-SucDf-cMAb U36 in 20 cancer patients with HNSCC. PET scans were performed at 1, 24, 72, and 144 h after injection of 75 MBq (2.0 mCi) ^{89}Zr-*N*-SucDf-cMAb U36. For men, the highest absorbed doses were in the liver (1.25 ± 0.27 mSv/MBq), thyroid (0.91 ± 0.27 mSv/MBq), kidneys (0.82 ± 0.15 mSv//MBq), spleen (0.67 ± 0.11 mSv//MBq), and lungs (0.63 ± 0.20 mSv//MBq). The effective dose was 0.53 ± 0.03 mSv/MBq. For women, the absorbed doses in these organs were ~10–20% higher than those for men with an effective dose of 0.66 ± 0.03 mSv/MBq. ^{89}Zr-*N*-SucDf-cMAb U36 accumulation in tumors increased over time, whereas accumulation in most organs decreased over time. The mean tumor accumulation was 0.019 ± 0.010% ID/g at 168 h after injection as assessed with biopsies.

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