^{89}Zr-*N*-Succinyldesferrioxamine-DN30

^{89}Zr-DN30

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Chemical name:	^{89}Zr-N-Succinyldesferrioxamine-DN30	
Abbreviated name:	^{89}Zr-DN30	
Synonym:		
Agent category:	Antibody	
Target:	MET, also known as the tyrosine kinase receptor for hepatocyte growth factor	
Target category:	Receptor	
Method of detection:	Positron emission tomography (PET)	
Source of signal:	^{89}Zr	
Activation:	No	
Studies:	• *In vitro* • Rodents	Structure is not available in PubChem.

Background

[PubMed]

MET is a proto-oncogene that encodes a protein MET, also known as c-Met or hepatocyte growth factor receptor (HGFR) (1). MET is a membrane receptor that is essential for embryonic development and wound healing. Hepatocyte growth factor (HGF) is the only known ligand of MET. MET is normally expressed by stem cells, progenitor cells and cells of epithelial origin, whereas expression of HGF is restricted to cells of mesenchymal origin. Upon HGF stimulation, MET induces several biological responses that lead invasive growth (2). Abnormal MET activation in cancer correlates with poor prognosis, where de-regulated MET triggers tumor growth, induces angiogenesis, and activates

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metastasis (3). MET is deregulated in many types of human malignancies, including cancers of kidney, liver, stomach, breast, and brain (2, 4, 5). Monoclonal antibody DN30 is directed against the extracellular domain of MET with a K_d of 2.64 nM (6). Inhibition of HGFR function with DN30 has been shown to inhibit pathological angiogenesis as well as tumor growth and metastasis. Perk et al. (7) prepared ^{89}Zr-*N*-succinyldesferrioxamine-DN30 (^{89}Zr-DN30) for imaging MET expression in tumors.

Related Resource Links:

- Chapters in MICAD (c-Met)
- Gene information in NCBI (c-Met).
- Articles in Online Mendelian Inheritance in Man (OMIM) (c-Met)
- Clinical trials (c-Met)
- Drug information in FDA (c-Met)

Synthesis

[PubMed]

N-Succinyldesferrioxamine (*N*-sucDf) B-tetrafluorphenol-Fe and DN30 were incubated in sodium carbonate buffer (pH, 9.5) for 30 min at room temperature (7). To the mixture, an EDTA solution was added and the mixture was incubated for 30 min at 35°C. *N*-sucDf-DN30 was isolated from the incubation mixture with a PD-10 column. There was ~1 chelate group per antibody. *N*-sucDf-DN30 was mixed with ^{89}Zr-oxalate. The mixture was incubated for 45 min at room temperature. ^{89}Zr-DN30 had a radiochemical purity of >95% and a specific activity 8.2-10.6 MBq/nmol (0.22-0.29 mCi/nmol) with a labeling yield of >70%.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Radioimmunoreactivity of ^{89}Zr-DN30 for MET was determined by measuring of ^{89}Zr-DN30 binding to GTL-16 cells to be >95% at infinite antigen excess (7).

Animal Studies

Rodents

[PubMed]

Perk et al. (7) performed biodistribution studies of 0.28 MBq (0.008 mCi,) ^{89}Zr-DN30 (0.66 nmol) in nude mice bearing human gastric carcinoma cell line GTL-16 (high MET expression) or the HNSCC cell line FaDu (low MET expression) xenografts. GTL-16 tumor uptake values were 12.2% ID/g (percentage injected dose per gram) at 1 d, 17.3% ID/g at 2 d, 18.1% ID/g at 3 d, and 19.6% ID/g at 5d. The radioactivity level in the blood was 17.1, 13.3, 10.6 and 8.8% ID/g at 1, 2, 3, and 5 d, respectively. The organs with the

highest uptake were the liver (8.4% ID/g), spleen (7.9% ID/g), lung (4.5% ID/g), and kidneys (3.5% ID/g) with the lowest radioactivity in the muscle (1.2% ID/g) at 3 d after injection. The tumor/muscle ratio was 15. On the other hand, the FaDu tumor uptake was lower than GTL-16 tumor with only 7.8% ID/g and the tumor/muscle ratio of 7 at d 3. PET imaging revealed that GTL-16 tumors as small as 11 mg were readily visualized as early as 1 d and up to 4 d after injection. The liver and spleen were also visualized. FaDu tumors were less pronounced than the GTL-16 tumors. Immunohistochemistry with DN30 was performed on GTL-16 and FaDu xenografts showed that the expression of MET was higher in the GTL-16 tumor sections than that of FaDu tumor sections. No blocking experiments 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.

References

1. Boccaccio C., Comoglio P.M. *Invasive growth: a MET-driven genetic programme for cancer and stem cells.* Nat Rev Cancer. 2006;6(8):637–45. PubMed PMID: 16862193.
2. Di Renzo M.F., Olivero M., Giacomini A., Porte H., Chastre E., Mirossay L., Nordlinger B., Bretti S., Bottardi S., Giordano S.et al. *Overexpression and amplification of the met/HGF receptor gene during the progression of colorectal cancer.* Clin Cancer Res. 1995;1(2):147–54. PubMed PMID: 9815967.
3. Lengyel E., Prechtel D., Resau J.H., Gauger K., Welk A., Lindemann K., Salanti G., Richter T., Knudsen B., Vande Woude G.F., Harbeck N. *C-Met overexpression in node-positive breast cancer identifies patients with poor clinical outcome independent of Her2/neu.* Int J Cancer. 2005;113(4):678–82. PubMed PMID: 15455388.
4. Smith H.S., Stern R., Liu E., Benz C. *Early and late events in the development of human breast cancer.* Basic Life Sci. 1991;57:329–37. PubMed PMID: 1814293.
5. Di Renzo M.F., Olivero M., Serini G., Orlandi F., Pilotti S., Belfiore A., Costantino A., Vigneri R., Angeli A., Pierotti M.A.et al. *Overexpression of the c-MET/HGF receptor in human thyroid carcinomas derived from the follicular epithelium.* J Endocrinol Invest. 1995;18(2):134–9. PubMed PMID: 7629381.

6. Petrelli A., Circosta P., Granziero L., Mazzone M., Pisacane A., Fenoglio S., Comoglio P.M., Giordano S. *Ab-induced ectodomain shedding mediates hepatocyte growth factor receptor down-regulation and hampers biological activity.* Proc Natl Acad Sci U S A. 2006;103(13):5090–5. PubMed PMID: 16547140.
7. Perk L.R., Stigter-van Walsum M., Visser G.W., Kloet R.W., Vosjan M.J., Leemans C.R., Giaccone G., Albano R., Comoglio P.M., van Dongen G.A. *Quantitative PET imaging of Met-expressing human cancer xenografts with (89)Zr-labelled monoclonal antibody DN30.* Eur J Nucl Med Mol Imaging. 2008;35(10):1857–67. PubMed PMID: 18491091.