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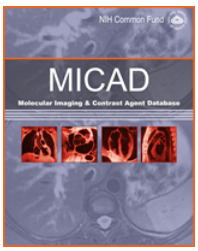

^{86}Y-CHX-A"-Diethylenetriamine pentaacetic acid-cetuximab

^{86}Y-CHX-A''-DTPA-cetuximab

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Chemical name:	^{86}Y-CHX-A"-Diethylenetriamine pentaacetic acid-cetuximab	
Abbreviated name:	^{86}Y-CHX-A"-DTPA-cetuximab	
Synonym:	^{86}Y-CHX-A"-DTPA-erbitux	
Agent category:	Chimeric monoclonal antibody	
Target:	Epidermal growth factor receptor (EGFR, HER1)	
Target category:	Receptor	
Method of detection:	Positron emission tomography (PET)	
Source of signal:	^{86}Y	
Activation:	No	
Studies:	• *In vitro* • Rodents	Click on protein, nucleotide (RefSeq), and gene for more information about EGF.

Background

[PubMed]

Epidermal growth factor (EGF) is a 53-amino acid cytokine (6.2 kDa) that is secreted by ectodermic cells, monocytes, kidneys, and duodenal glands (1). EGF stimulates growth of epidermal and epithelial cells. EGF and at least seven other growth factors and their transmembrane receptor kinases play important roles in cell proliferation, survival, adhesion, migration, and differentiation. The EGF receptor (EGFR) family consists of four transmembrane receptors, including EGFR (HER1/erbB-1), HER2 (erbB-2/neu), HER3 (erbB-3), and HER4 (erbB-4) (2). HER1, HER3, and HER4 comprise three major functional domains: an extracellular ligand-binding domain, a hydrophobic transmembrane domain, and a cytoplasmic tyrosine kinase domain. No ligand has been clearly identified for HER2; however, HER2 can be activated as a result of ligand binding to other HER receptors with the formation of receptor homodimers and/or heterodimers (3). HER1 as well as HER2 are overexpressed on many solid tumor cells such as breast, non–small-cell lung, head and neck, and colon cancers (4-6). The high levels of HER1 and HER2 expression on cancer cells are associated with a poor prognosis (7-10).

Trastuzumab, a humanized immunoglobulin G_1 (IgG_1) monoclonal antibody against the extracellular domain of recombinant HER2 (11), was labeled as ^{111}In-trastuzumab (12-14). C225, an anti-EGFR (HER1), mouse-human

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chimeric, monoclonal IgG_1 antibody, also known as erbitux and cetuximab, was labeled as ^{99m}Tc-EC-C225 (15, 16) for imaging EGFR expression on solid tumors using single-photon emission computed tomography (SPECT). For evaluation as a positron emission tomography (PET) imaging agent for EGFR, ^{86}Y has been attached to cetuximab *via* CHX-A"-diethylenetriamine pentaacetic acid (CHX-A"-DTPA) to form ^{86}Y-CHX-A"-DTPA-cetuximab (17).

Related Resource Links:

- Chapters in MICAD
- Gene information in NCBI (EGFR).
- Articles in OMIM
- Clinical trials (Trastuzumab, cetuximab)
- Drug information in FDA (Trastuzumab, cetuximab)

Synthesis

[PubMed]

Bifunctional CHX-A"-DTPA was used to conjugate cetuximab to form CHX-A"-DTPA-cetuximab (~150 kD), which was purified with column chromatography (17). DTPA per antibody was determined to be 2.3. Next, ^{86}Y solution (140–170 MBq (3.8–4.6 mCi)) was added to CHX-A"-DTPA-cetuximab (0.33 nmol) in ammonium acetate buffer (pH 5–6). The reaction mixture was incubated for 30 min at room temperature, and ^{86}Y-CHX-A"-DTPA-cetuximab was purified with column chromatography. The yield of ^{86}Y-CHX-A"-DTPA-cetuximab was 55%–75% with a specific activity of ~300 MBq/nmol (8.1 mCi/nmol).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Nayak et al. (17) performed cell-binding assays with ^{86}Y-CHX-A"-DTPA-cetuximab using the EGFR-expressing human glioblastoma U87MG cell line. Binding of ^{86}Y-CHX-A"-DTPA-cetuximab under excess antigen conditions indicated that the immunoreactivity was 65%–75%, suggesting that the majority of the accessible lysine residues were some distance from the EGFR-binding region of cetuximab. ^{86}Y-CHX-A"-DTPA-cetuximab was stable for up to 24 h in buffer at 4°C.

Animal Studies

Rodents

[PubMed]

Nayak et al. (17) performed *ex vivo* biodistribution studies of 0.5 MBq (0.014 mCi) ^{86}Y-CHX-A"-DTPA-cetuximab in nude mice (n = 5) bearing human colorectal carcinoma LS-174T tumors at 1–4 d after injection. Accumulation into LS-174T tumors was high, with 21.2 ± 1.0% injected dose/gram (ID/g) at 1 d and 27.4 ± 3.6% ID/g at 4 d after injection. On the other hand, normal tissues exhibited gradual declines in radioactivity from 1 d (<10% ID/g) to 4 d (<5% ID/g) after injection. Radioactivity declined by 70% in the blood and by 60% in the liver from 1 d to 4 d after injection. The tumor/blood ratio increased from 1.5 at 1 d to 6.8 at 4 d after injection. Co-injection of 1.3 nmol cetuximab inhibited the tumor accumulation by ~78% at 3 d after injection. By contrast, little inhibition was observed in the non-tumor tissues.

Nayak et al. (17) studied the whole-body distribution of 4 MBq (0.11 mCi) ^{86}Y-CHX-A"-DTPA-cetuximab with microPET imaging in six xenograft (EGFR-positive) tumor models in mice with static scans at various time

points (1–3 d). The tumor uptake reached a plateau at 2 d after injection. The accumulation of ^{86}Y-CHX-A''-DTPA-cetuximab was clearly visible in all tumors at 1–3 d after injection. The mean tumor residence times were similar in all six tumors (2.1–2.5 d). Co-injection of 1.3 nmol cetuximab inhibited accumulation of radioactivity in the LS-174T tumors by 76% at 3 d after injection. There was a good correlation (r^2 = 0.9) between the tracer accumulation measured with microPET and that measured with *ex vivo* biodistribution studies.

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

Intramural research program

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