^{125}I-Labeled chimeric monoclonal antibody, ch806, targeting the epidermal growth factor receptor deletion variant de2-7 (EGFRvIII)

[^{125}I]-ch806

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Chemical name:	^{125}I-Labeled chimeric monoclonal antibody, ch806, targeting the epidermal growth factor receptor deletion variant de2-7 (EGFRvIII)	
Abbreviated name:	[^{125}I]-ch806	
Synonym:		
Agent Category:	Antibody	
Target:	Epidermal growth factor receptor deletion variant de2-7 (EGFRvIII)	
Target Category:	Receptor	
Method of detection:	Single-photon emission tomography (SPECT); gamma planar imaging	
Source of signal / contrast:	^{125}I	
Activation:	No	
Studies:	• *In vitro* • Rodents	Structure not available in PubChem.

Background

[PubMed]

The biological characteristics, activating ligands, and functioning of the different members of the transmembrane epidermal growth factor receptor (EGFR) family are

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described elsewhere (1-3). The EGFR receptors are known to regulate the growth, survival, differentiation, and migration of cells through the activation of an associated intracellular tyrosine kinase (TK) signal transduction pathway, and they are overexpressed in many malignant epithelial tumors (1, 2). Overexpression of the EGFR in tumors has been attributed to gene amplification, and this phenomenon is believed to introduce mutations in the receptor (2, 4). Also, overexpression of the EGFR usually indicates a poor clinical prognosis for the patient (4). The most common mutation observed in the EGFR receptor is the deletion of a segment of the extracellular domain, including the ligand-binding region, which results in the generation of a variant known as the de2-7 EGFR or EGFRvIII (2, 4). The generation, structure, functions, and role of the EGFRvIII in tumor malignancy have been reviewed by Gan et al. (5). Although the EGFRvIII is nonresponsive to the ligand, it is constitutively active with a constantly operating downstream TK signaling pathway that appears to promote the development of a neoplastic phenotype, particularly for glioblastomas and to some extent for other cancers such as those of the prostate and the breast (2, 6).

Because the EGFR promotes and helps maintain the cancerous state of cells, several antibodies that inhibit the receptor activity and small molecules that block the downstream TK signaling pathway have been developed and have been approved by the United States Food and Drug Administration (FDA) for the treatment of certain cancers (2). The antibodies are directed toward the extracellular domain of the receptor, block ligand binding, and inhibit activation of the TK signal transduction pathway, which ultimately results in downregulation of the EGFR on the cell surface. However, because the EGFRvIII lacks the ligand-binding region on the extracellular domain, these antibodies cannot obstruct the constitutive mutant receptor activity (2). As a consequence, the monoclonal antibody (mAb) 806, which specifically targets the EGFRvIII, was generated and characterized in preclinical studies (7, 8). Subsequently, a chimeric form of the mAb (chAb), designated as ch806, was developed (9) and evaluated in a phase I clinical trial with patients having cancerous tumors overexpressing the EGFRvIII (4). Results obtained from this trial indicated that ch806 could be a good biotherapeutic agent for the treatment of cancers expressing the ch806 antigen (4). In addition, several other clinical trials approved by the FDA are in progress to evaluate the targeting of EGFRvIII as a treatment against various cancers.

The internalization, intracellular trafficking, and biodistribution (in nude mice bearing xenograft human epidermoid carcinoma cell tumors) of mAb806 labeled with ^{125}I and ^{111}In, respectively, have been investigated by Perera et al. (8) and are described separately in MICAD (www.micad.nih.gov) (10, 11). The characterization and biodistribution (in nude mice bearing xenograft human glioblastoma cell tumors) of ch806 labeled with ^{125}I ([^{125}I]-ch806) or ^{111}In ([^{111}In]-ch806) have been investigated by Panousis et al. (9). The use of ^{124}I-labeled ch806 for the detection of EGFRvIII-expressing xenograft human glioblastoma tumors in nude mice with an immuno–positron emission tomography (PET) technique was investigated by Lee et al. (6) and is described in another chapter in MICAD (12). This chapter describes the studies performed with [^{125}I]-ch806. Studies performed with [^{111}In]-ch806 are described separately in MICAD (13).

Other sources of information

Human EGFR Gene (Gene ID: 1956)

Protein and mRNA sequence of human EGFR variant 1

EGFR in OMIM (Online Mendelian Inheritance in Man)

EGFR signaling pathways (NCI-Nature Pathways Interactive Database)

Anti-EGFR antibodies in PubMed

EGFR tyrosine kinase inhibitors in PubMed

Related chapters in MICAD

Synthesis

[PubMed]

The production and ^{125}I labeling of ch806 to obtain [^{125}I]-ch806 was done using a modified chloramine-T method and is described elsewhere (9). The radiochemical purity of the [^{125}I]-chAb was reported to be >98.6% as determined with instant thin-layer chromatography. The specific activity of [^{125}I]-ch806 was reported to be ~0.040 MBq/6.6 pmol (~166.7 Ci/mmol). The final formulation and storage conditions of the radiolabeled chAb were not reported.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The stability of [^{125}I]-ch806 was determined in healthy human donor serum at 37°C and was reported to maintain a radiochemical purity of 95% for up to 7 days (9). Under the same storage conditions and duration, immunoreactivity of the labeled chAb with U87MG.de2-7 cells (a human glioma cell line generated to overexpress the EGFRvIII) was determined to be >65%. Using various cell lines expressing or overexpressing the EGFRvIII or the wild-type EGFR, respectively, it was shown that ch806 and the parental mAb806 had a similar receptor-binding profile.

The receptor association constant for [^{125}I]-ch806 was reported to be 1.90×10^9 M^{-1} compared with 1.1×10^9 M^{-1} for the parental mAb806 as determined with the Lindmo assay using U87MG.de2-7 cells (9). The number of [^{125}I]-ch806 molecules bound per cell was reported to be 4.7×10^5 compared with 6.0×10^5 for [^{111}In]-ch806 (9).

Animal Studies

Rodents

[PubMed]

The biodistribution patterns of [^{125}I]-ch806 and [^{111}In]-chb806 were studied in BALB/c nude mice respectively bearing xenograft U87MB.de2-7 and A431 cell tumors (of human epidermoid carcinoma origin; overexpress the EGFR and do not express the EGFR, respectively) (9). Nude mice bearing FaDu xenograft tumors (of human squamous cell carcinoma origin) were used as controls for this study. The animals (n = 3–5 animals/time point) were injected with the respectively labeled chAb through the tail vein and euthanized at predetermined time points ranging from 4 h to 312 h post-injection (p.i.) for the collection of tumors and all major organs (9). All data of radioactivity accumulated in the various organs were presented as percent of injected dose per gram tissue (% ID/g). In general, the uptake and retention of label by the tumors was significantly ($P < 0.001$) lower at all time points with [^{125}I]-ch806 (peaking at ~7.0% ID/g at 24 h) than with [^{111}In]-chAb806 (peaking at ~31.0% ID/g at 48 h). With [^{125}I]-ch806, the accumulation of radioactivity in the xenografts from 72 h to 168 h p.i. was more than six times lower than the uptake with [^{111}In]-ch806 in the same period (9). During the entire study period, the accumulation of radioactivity from [^{125}I]-ch806 and [^{111}In]-ch806 in all major organs was ~10.0% ID/g, except for the kidneys and blood. The accumulation of radioactivity in these organs correlated to the level of tracer present in the blood pool of the animals. Lower uptake of the label and similar tracer biodistribution patterns were observed in all of the tissues from animals bearing the A431 or the FaDu xenograft tumors. No blocking studies using unlabeled ch806, mAb806, or another suitable anti-EGFR mAb were reported.

The half-life times of [^{125}I]-ch806 and [^{111}In]-chAb806 were determined to be 2.85 ± 0.24 h and 3.42 ± 0.92 h, respectively, using serum samples obtained from the tracer-injected animals (9). The total serum clearance for [^{125}I]-ch806 was reported to be 0.063 ± 0.0003 ml/h; total serum clearance for [^{111}In]-chAb806 was 0.045 ± 0.005 ml/h.

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.

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