^{68}Ga-1,4,7,10-Tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid-Epidermal growth factor

^{68}Ga-DOTA-EGF

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Chemical name:	^{68}Ga-1,4,7,10-Tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid-Epidermal growth factor	
Abbreviated name:	^{68}Ga-DOTA-EGF	
Synonym:		
Agent category:	Polypeptide	
Target:	EGF receptor (EGFR, HER1)	
Target category:	Receptor	
Method of detection:	PET	
Source of signal:	^{68}Ga	
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) 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,

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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) and C225 (an anti-EGFR, chimeric, monoclonal antibody) have been labeled as ^{111}In-trastuzumab (12-14) and ^{99m}Tc-EC-C225 (15, 16) for imaging EGFR expression on solid tumors using single-photon emission computed tomography (SPECT). However, antibodies that are approximately 25-fold larger than EGF may not be easily transported to cells within solid tumors. Therefore, ^{111}In-EGF and ^{99m}Tc-HYNIC-EGF have been developed for SPECT imaging studies of tumors (17, 18). However, positron emission tomography (PET) offers better sensitivity, resolution, and quantification than SPECT (19). ^{68}Ga ($t_{1/2}$ = 68 min, 89% β^+ decay) is an attractive radionuclide for labeling EGF and is readily available from a commercial ^{68}Ge/^{68}Ga generator. Cells retain ^{68}Ga well, providing a good signal/background ratio. For evaluation as a PET imaging agent, ^{68}Ga has been attached to EGF *via* 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA) to form ^{68}Ga-DOTA-EGF (20).

Related Resource Links:

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

Synthesis

[PubMed]

Commercially available monofunctional *N*-hydroxysuccinimide ester of DOTA was used to conjugate human EGF to form DOTA-EGF, which was purified by column chromatography (20). ^{68}Ga was conjugated to DOTA-EGF under microwave heating for 1 min to 95°C. ^{68}Ga-DOTA-EGF was purified by column chromatography. The yield of ^{68}Ga-DOTA-EGF was 60–77% with a radiochemical purity >95% and specific activities of 12–20 MBq/nmol (0.32–0.54 mCi/nmol).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Velikyan et al. (20) performed cell-binding assays with ^{68}Ga-DOTA-EGF using EGFR-expressing human cervical carcinoma A431 and glioma U343 cell lines. Binding of ^{68}Ga-DOTA-EGF (approximately 0.01 μM) to both cell lines was completely blocked by EGF (approximately 1 μM). Saturation binding experiments determined that dissociation constant (K_d) values were 2.0 and 2.3 nM for A431 and U343 cells, respectively. The number of binding sites per cells was 1.9×10^6 per A431 cell and 7.8×10^5 per U343 cell. Both cell lines rapidly internalized ^{68}Ga-DOTA-EGF at 37°C.

Animal Studies

Rodents

[PubMed]

Velikyan et al. (20) studied the biodistribution of ^{68}Ga-DOTA-EGF in nude mice bearing an A431 xenograft. The organs with the highest accumulation at 30 min after ^{68}Ga-DOTA-EGF injection were the kidneys and liver (>35%ID/g), followed by the pancreas, salivary gland, small and large intestines, stomach, and spleen. The uptake of ^{68}Ga-DOTA-EGF in the A431 tumor xenograft was 1.51 ± 0.16 and 2.69 ± 0.29%ID/g for 0.016 and 0.16 nmol ^{68}Ga-DOTA-EGF, respectively ($P = 0.036$). The radiotracer had a rapid blood clearance at 30 min with tumor/blood ratios of 4.42 ± 1.81 and 4.50 ± 2.53 for 0.016 and 0.16 nmol ^{68}Ga-DOTA-EGF, respectively. Very high radioactivity was found in bile, urine, and feces. No blocking experiment was performed.

The whole-body distribution of ^{68}Ga-DOTA-EGF (2.0 MBq/mouse or 0.05 mCi/mouse) was also assessed by PET imaging from 20–30 min after injection. The highest activity concentrations were visualized in the kidneys and liver with clearance of radioactivity through the urinary bladder. The accumulation of ^{68}Ga-DOTA-EGF was clearly visible in the tumors. 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]

No publication is currently available.

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