^{111}In-1,4,7,10-Tetraazacyclododecane-*N*,*N*′,*N*″,*N*‴-tetraacetic acid-cyclo(D-diaminobutyric acid-Arg-Phe-Phe-D-Trp-Lys-Thr-Phe)

^{111}In-KE88

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Chemical name:	^{111}In-1,4,7,10-Tetraazacyclododecane-*N*,*N*′,*N*″,*N*‴-tetraacetic acid-cyclo(D-diaminobutyric acid-Arg-Phe-Phe-D-Trp-Lys-Thr-Phe)	
Abbreviated name:	^{111}In-KE88, ^{111}In-DOTA-cyclo(dDab-RFFwKTF)	
Synonym:		
Agent category:	Peptide	
Target:	Somatostatin receptors (SSRs)	
Target category:	Receptor	
Method of detection:	Single-photon emission computed tomography (SPECT), planar gamma imaging	
Source of signal:	^{111}In	
Activation:	No	
Studies:	• *In vitro* • Rodents	Click on protein, nucleotide (RefSeq), and gene for more information about somatostatin.

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Background

[PubMed]

Somatostatin (SST) is an inhibitor of the release of somatotropin, glucagon, insulin, gastrointestinal hormones, and other secretory proteins (1). SST is also known as somatotropin release-inhibiting factor (SRIF). SST is a cyclic polypeptide with two biologically active isoforms, SRIF-14 and SRIF-28, of 14 and 28 amino acids, respectively. SRIF has a short plasma half-life of <3 min (2). SST receptors (SSTRs) (G-protein–coupled) have been found on a variety of neuroendocrine tumors and cells of the immune system, and five individual subtypes (sst_1–sst_5) have been identified and subsequently cloned from animal and human tissues (3, 4). SST also inhibits cell proliferation and promotes apoptosis through binding to specific cell-surface SSTRs (5).

^{111}In-Labeled diethylenetriaminepentaacetic acid-octreotide ((^{111}In-DTPA-OCT) is an SSTR analog that, over the last decade, has remained the most widely used radiopharmaceutical for the scintigraphic detection and staging of primary and metastatic neuroendocrine tumors bearing SSTRs with single-photon emission computed tomography (SPECT) (5). It has also showed promising results in peptide-receptor radionuclide therapy (6). ^{111}In-DTPA-OCT binds with high affinity to SSTR subtypes 2 and 5 (sst_2 and sst_5) and to sst_3 to a lesser degree, but it does not bind to sst_1 or sst_4 (7). Currently used targeting SSTR peptides mainly have affinity for sst_2. However, sst_1, sst_3, sst_4, and sst_5 are also expressed in different tumors. Therefore, there is a need for pansomatostatin radioligands (8). Ginj et al. (9) has developed a series of pansomatostatin ligands. One of them, 1,4,7,10-tetraazacyclododecane-*N*,*N*′,*N*″,*N*‴-tetraacetic acid-cyclo(D-diaminobutyric acid-Arg-Phe-Phe-D-Trp-Lys-Thr-Phe) (KE88) was found to be an agonist to all sst subtypes. For evaluation as a SPECT imaging agent for all sst subtypes, ^{111}In has been attached to KE88 *via* 1,4,7,10-tetraazacyclododecane-*N*,*N*′,*N*″,*N*‴-tetraacetic acid (DOTA) to form ^{111}In-KE88.

Synthesis

[PubMed]

DOTA-tris(tert-butylester) was used to conjugate the N-terminal amino acid to form KE88 after standard solid-phase peptide synthesis of KE88 (9). KE88 was purified with high-performance liquid chromatography. $^{111}InCl_3$ was conjugated to KE88 with a radiochemical yield of >95%. ^{111}In-KE88 had a >97% radiochemical purity and a specific activity of ~37 GBq/μmol (1 Ci/μmol).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Ginj et al. (9) showed that KE88 exhibited an agonistic effect on forskolin-stimulated cAMP accumulation in CCL39 cells expressing sst_1–sst_5 with effective concentrations of

7.35, 9.73, 1.92, 0.47, and 2.66 nM, respectively. ^{111}In-KE88 internalization into HEK-sst_2, HEK-sst_3, and HEK-sst_5 cells was performed after 4 h of incubation at 37°C with <0.5, 32.2, and <0.1%, respectively.

Animal Studies

Rodents

[PubMed]

Ginj et al. (9) performed *ex vivo* biodistribution studies with ^{111}In-KE88 in nude mice (*n* = 3/group) bearing xenografts of HEK-sst_2 tumor cells on one flank and HEK-sst_3 tumors on the other flank. The accumulation of ^{111}In-KE88 in the HEK-sst_3 tumors was 15.2% injected dose per gram (% ID/g) at 15 min, 22.9% ID/g at 1 h, 23.2% ID/g at 4 h, and 14.9% ID/g at 24 h after injection, whereas the accumulation in the HEK-sst_2 tumors was 18.5, 13.6, 3.7, and 1.1% ID/g at the time points, respectively. Therefore, the sst_3 tumors exhibited a higher ^{111}In-KE88 accumulation and slower washout than the sst_2 tumors. The kidney was the only organ that had a higher accumulation at 1 h after injection than the tumors with 64% ID/g, followed by the pituitary (9% ID/g) and liver (2.7% ID/g). Accumulation of radioactivity in the other tissues was low at I h after injection. The concentration in the blood was only 0.1% ID/g at 4 h after injection, with tumor/blood ratios of 232 for the sst_3 tumors and 37 for the sst_2 tumors. Co-injection with DOTA-TATE (sst_2-selective ligand) reduced the accumulation of the radioactivity by 90% in the sst_2 tumors at 1 h after injection. Co-injection with ^{111}In-DTPA-TATE and KE88 reduced the accumulation of the radioactivity by 84% in the sst_3 tumors. Whole-body SPECT imaging visualized the sst_3 tumor as early as 1 h after ^{111}In-KE88 injection with a strong radioactivity signal in the kidneys. In contrast, the sst_2 tumor was barely visualized. By 4 h, only the sst_3 tumor and kidneys were visible.

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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