Gadolinium-1,4,7,10-tetraazacyclododecane-*N*',*N*'',*N*''',*N*''''-tetraacetic acid-Gly-Pro-D-Leu-D-Ala-NHOH

P947

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Chemical name:	Gadolinium-1,4,7,10-tetraazacyclododecane-*N*',*N*'',*N*''',*N*''''-tetraacetic acid-Gly-Pro-D-Leu-D-Ala-NHOH	
Abbreviated name:	P947	
Synonym:	Gd-DOTA-FN-439	
Agent category:	Peptide	
Target:	Matrix metalloproteinases (MMPs)	
Target category:	Enzyme	
Method of detection:	Magnetic resonance imaging (MRI)	
Source of signal/contrast:	Gadolinium	
Activation:	No	
Studies:	• *In vitro* • Rodents	Click on protein, nucleotide (RefSeq), and gene for more information about MMP.

Background

[PubMed]

Extracellular matrix (ECM) adhesion molecules consist of a complex network of fibronectins, collagens, chondroitins, laminins, glycoproteins, heparin sulfate, tenascins, and proteoglycans that surround connective tissue cells, and they are mainly secreted by

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fibroblasts, chondroblasts, and osteoblasts (1). Cell substrate adhesion molecules are considered essential regulators of cell migration, differentiation, and tissue integrity and remodeling. These molecules play an important role in inflammation and atherogenesis, but they also participate in the process of invasion and metastasis of malignant cells in the host tissue (2). Invasive tumor cells adhere to the ECM, which provides a matrix environment for permeation of tumor cells through the basal lamina and underlying interstitial stroma of the connective tissue. Overexpression of matrix metalloproteinases (MMPs) and other proteases by tumor cells allows intravasation of tumor cells into the circulatory system after degradation of the basement membrane and ECM (3). Several families of proteases are involved in atherogenesis, myocardial infarction, angiogenesis, and tumor invasion and metastasis (4-7).

Gadolinium (Gd), a lanthanide metal ion with seven unpaired electrons, has been shown to be very effective in enhancing proton relaxation because of its high magnetic moment and water coordination (8, 9). Gd-Labeled diethylenetriaminepentaacetic acid (Gd-DTPA) was the first intravenous magnetic resonance imaging (MRI) contrast agent used clinically, and a number of similar Gd chelates have been developed in an effort to further improve clinical use. However, these low molecular weight Gd chelates have short blood and tissue retention times, which limit their use as imaging agents in the vasculature and cancer. Various macromolecular Gd complexes have demonstrated superior contrast enhancement for MRI of the vasculature and carcinomas (10-12); however, these Gd complexes cannot proceed into further clinical development because of high tissue accumulation and slow excretion of toxic Gd ions. Furthermore, they are largely nonspecific. Gly-Pro-D-Leu-D-Ala-NHOH was found to be a broad-spectrum inhibitor of MMP-1, -2, -3, -8, -9, and -13 (13). Gd-1,4,7,10-tetraazacyclododecane-*N*',*N*'',*N*''',*N*''''-tetraacetic acid (DOTA)-Gly-Pro-D-Leu-D-Ala-NHOH (P947) has been developed to detect MMP activities in atherosclerotic plaques.

Synthesis

[PubMed]

P947 was prepared by coupling Gly-Pro-D-Leu-D-Ala-NHOH to DOTA (13). P947 is a Gd(III) complex of a bi-functional DOTA chelate conjugated *via* a phenylbutyric linker with a thiourea function to the tetrapeptidyl hydroxamic acid Gly-Pro-D-Leu-D-Ala-NHOH. It has a molecular weight of 1,210 Da and the r1 relaxivity value of 5.5 mM^{-1} s^{-1} in water at 1.5 T and 37°C, whereas Gd-DOTA has the r1 relaxivity value of 3.7 mM^{-1} s^{-1}.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

P947 exhibited 50% inhibition concentration (IC_{50}) values of 100 μM for MMP-14, 10 μM for MMP-3 and MMP-9, 1 μM for MMP-1, MMP-2, and MMP-13, and 0.1 μM for MMP-8 (13). Immunohistochemical measurements of human and rabbit atherosclerotic aortas revealed the presence of various MMPs in the aortas with higher P947

accumulation than Gd-DOTA. Gly-Pro-D-Leu-D-Ala-NHOH blocked P947 accumulation in the rabbit experiments.

Animal Studies

Rodents

[PubMed]

Lancelot et al. (13) used a 9.4-T MRI scanner to perform *in vivo* MRI in apolipoprotein E–deficient ($ApoE^{-/-}$) mice ($n = 8$). Injection of P947 (0.1 mmol/kg) provided strong MRI contrast enhancement in the atherosclerotic aortic wall within 1 h of injection; this enhancement was still visualized up to 22 h. The contrast enhancement was 95%, 50%, 20%, and 10% at 1, 2, 3, and 22 h after injection, respectively. On the other hand, Gd-DOTA provided only a diffuse contrast, and the atherosclerotic aortic wall was not clearly outlined with little contrast enhancement. No enhancement was observed in the aortic wall of the wild-type mice after injection of P947. *Ex vivo* biodistribution studies in $ApoE^{-/-}$ mice showed that the organ with the highest uptake was the kidney (90 nmol Gd/g), followed by the liver (18 nmol Gd/g), at 30 min after injection of P947. The liver uptake of P947 was three-fold higher than that of Gd-DOTA, whereas no differences were observed in the kidney, muscle, and plasma. The plasma half-life was 30 min for P947 and 15 min for Gd-DOTA. P947 levels in the atherosclerotic arteries were 3-fold higher than Gd-DOTA levels. 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.

NIH Support

HL78667, R01 HL71021

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