Gadolinium-diethylenetriaminepentaacetic acid-cyclo(Cys-Asn-Gly-Arg-Cys)-Gly-Lys-quantum dots

cNGR-pQDs

Kam Leung, PhD[1]

Created: January 15, 2009; Updated: March 19, 2009.

Chemical name:	Gadolinium-diethylenetriaminepentaacetic acid-cyclo(Cys-Asn-Gly-Arg-Cys)-Gly-Lys-quantum dots	
Abbreviated name:	cNGR-pQDs, Gd-DTPA-cNGR-QDs	
Synonym:		
Agent category:	Peptide	
Target:	Aminopeptidase N (CD13)	
Target category:	Enzyme	
Method of detection:	Magnetic resonance imaging (MRI); optical, near-infrared (NIR) fluorescence imaging	
Source of signal/ contrast:	Gadolinium (Gd^{3+}), quantum dots (QDs)	
Activation:	No	
Studies:	• *In vitro* • Rodents	No structure is available in PubChem.

Background

[PubMed]

[1] National for Biotechnology Information, NLM, NIH, Bethesda, MD; Email: MICAD@ncbi.nlm.nih.gov.

Corresponding author.

NLM Citation: Leung K. Gadolinium-diethylenetriaminepentaacetic acid-cyclo(Cys-Asn-Gly-Arg-Cys)-Gly-Lys-quantum dots. 2009 Jan 15 [Updated 2009 Mar 19]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

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 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 a 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 degrading the basement membrane and ECM (3).

Tumor angiogenesis represents a continuous and important process in tumor development in which the tumor attempts to gain an independent blood supply (4). This process is driven by the tumor's overproduction of angiogenic factors, which bind to receptors on nearby vessel endothelial cells. Angiogenesis is essential for the growth of solid tumors and their metastases. Imaging angiogenesis may be useful for monitoring angiogenic treatments of tumors and cardiovascular diseases (5-7). Aminopeptidase N (APN, CD13) is a membrane bound glycoprotein with MMP activity that cleaves unsubstituted, N-terminal amino acids with neutral side chains from peptides (8). APN has been shown to play a role in tumor angiogenesis, invasion, and metastasis (9). In addition to endothelial cells of angiogenic vessels, most cells of myeloid origin, epithelial cells, fibroblasts and smooth muscle cells also express CD13 (10, 11). The tumor homing peptide cyclo(Cys-Asn-Gly-Arg-Cys)-Gly-Lys (cNGR) contains the Asn-Gly-Arg (NGR) motif that binds to APN (12). Gadolinium (Gd^{3+}), a lanthanide metal paramagnetic 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, which lead to brighter contrast images (13, 14). Fluorescent semiconductor quantum dots (QDs) are nanocrystals made of CdSe/CdTe-ZnS with a radius of 1–10 nm (15-17). They can be tuned to emit in a range of wavelengths by changing their sizes and composition, thus providing broad excitation profiles and high absorption coefficients. Oostendorp et al. (18) prepared multimodal cNGR-labeled paramagnetic QDs (cNGR-pQDs) for measurement of tumor angiogenic activity with magnetic resonance imaging.

Synthesis

[PubMed]

The cNGR peptide was synthesized using solid-phase peptide synthesis and then labeled on the resin with biotin-succinimidyl ester *via* the ε-amino group of the lysine (18). cNGR-Biotin was purified with high-pressure liquid chromatography. Streptavidin-QDs (10 streptavidin molecules/QD) were incubated with cNGR-biotin and then with biotinylated poly-lysine dendritic wedge with eight Gd-DTPA moieties in a molar ratio of

1:6:24 at room temperature. Each QD carried a maximum of 192 Gd^{3+} ions and six cNGR peptides.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The T_1 relaxivity of cNGR-pQDs was 7.1 ± 0.4 $mM^{-1}s^{-1}$ per Gd^{3+} ion at 7 T and 20°C in saline buffer (18).

Animal Studies

Rodents

[PubMed]

Oostendorp et al. (18) performed magnetic resonance imaging (7 T) in nude mice (n = 7) bearing human colorectal adenocarcinoma LS174T tumors after intravenous injection of 525 ng cNGR-pQDs or pQDs alone. The changes in R_1 were spatially heterogeneous and most pronounced at the tumor rim for both cNGR-pQDs and pQDs. The R_1 changes induced by cNGR-pQDs and pQDs were 0.3 s^{-1} and 0.1 s^{-1}, respectively. The two-fold increase in contrast was confirmed by a two-fold better localization of cNGR-pQDs to tumor endothelial cells than pQDs with *ex vivo* two-photon laser scanning microscopy. The contrast in the tumor rim was ~50-fold greater than in the tumor core or muscle (<0.05 s^{-1}). Administration of excess cNGR (0.525 mg/mouse) 10 min after injection of cNGR-pQDs decreased the contrast by ~80% in the tumor rim. Both contrast agents accumulated primarily and similarly in the spleen, heart, liver, and kidneys.

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.

References

1. Bosman F.T., Stamenkovic I. *Functional structure and composition of the extracellular matrix.* J Pathol. 2003;200(4):423–8. PubMed PMID: 12845610.
2. Jiang W.G., Puntis M.C., Hallett M.B. *Molecular and cellular basis of cancer invasion and metastasis: implications for treatment.* Br J Surg. 1994;81(11):1576–90. PubMed PMID: 7827878.
3. Albelda S.M. *Role of integrins and other cell adhesion molecules in tumor progression and metastasis.* Lab Invest. 1993;68(1):4–17. PubMed PMID: 8423675.
4. Folkman J. *Angiogenesis in cancer, vascular, rheumatoid and other disease.* Nat Med. 1995;1(1):27–31. PubMed PMID: 7584949.
5. Sinusas A.J. *Imaging of angiogenesis.* J Nucl Cardiol. 2004;11(5):617–33. PubMed PMID: 15472646.
6. Carmeliet P. *Manipulating angiogenesis in medicine.* J Intern Med. 2004;255(5):538–61. PubMed PMID: 15078497.
7. Miller J.C., Pien H.H., Sahani D., Sorensen A.G., Thrall J.H. *Imaging angiogenesis: applications and potential for drug development.* J Natl Cancer Inst. 2005;97(3):172–87. PubMed PMID: 15687360.
8. Riemann D., Kehlen A., Langner J. *CD13--not just a marker in leukemia typing.* Immunol Today. 1999;20(2):83–8. PubMed PMID: 10098327.
9. Sato Y. *Role of aminopeptidase in angiogenesis.* Biol Pharm Bull. 2004;27(6):772–6. PubMed PMID: 15187415.
10. Corti A., Curnis F., Arap W., Pasqualini R. *The neovasculature homing motif NGR: more than meets the eye.* Blood. 2008;112(7):2628–35. PubMed PMID: 18574027.
11. Curnis F., Arrigoni G., Sacchi A., Fischetti L., Arap W., Pasqualini R., Corti A. *Differential binding of drugs containing the NGR motif to CD13 isoforms in tumor vessels, epithelia, and myeloid cells.* Cancer Res. 2002;62(3):867–74. PubMed PMID: 11830545.
12. Arap W., Pasqualini R., Ruoslahti E. *Cancer treatment by targeted drug delivery to tumor vasculature in a mouse model.* Science. 1998;279(5349):377–80. PubMed PMID: 9430587.
13. Brasch R.C. *New directions in the development of MR imaging contrast media.* Radiology. 1992;183(1):1–11. PubMed PMID: 1549653.
14. Runge V.M., Gelblum D.Y. *Future directions in magnetic resonance contrast media.* Top Magn Reson Imaging. 1991;3(2):85–97. PubMed PMID: 2025435.
15. Zheng G., Li H., Yang K., Blessington D., Licha K., Lund-Katz S., Chance B., Glickson J.D. *Tricarbocyanine cholesteryl laurates labeled LDL: new near infrared fluorescent probes (NIRFs) for monitoring tumors and gene therapy of familial hypercholesterolemia.* Bioorg Med Chem Lett. 2002;12(11):1485–8. PubMed PMID: 12031325.
16. Gao X., Nie S. *Quantum dot-encoded beads.* Methods Mol Biol. 2005;303:61–71. PubMed PMID: 15923675.

17. Pinaud F., Michalet X., Bentolila L.A., Tsay J.M., Doose S., Li J.J., Iyer G., Weiss S. *Advances in fluorescence imaging with quantum dot bio-probes.* Biomaterials. 2006;27(9):1679–87. PubMed PMID: 16318871.
18. Oostendorp M., Douma K., Hackeng T.M., Dirksen A., Post M.J., van Zandvoort M.A., Backes W.H. *Quantitative molecular magnetic resonance imaging of tumor angiogenesis using cNGR-labeled paramagnetic quantum dots.* Cancer Res. 2008;68(18):7676–83. PubMed PMID: 18794157.