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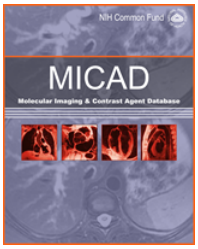

Quantum dot-prostate-specific membrane antigen antibody J591

QD655-J591

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Chemical name:	Quantum dot-prostate-specific membrane antigen antibody J591	
Abbreviated name:	QD655-PMSA, QD655-J591	
Synonym:		
Agent category:	Antibody	
Target:	Prostate-specific membrane antigen (PSMA), folate hydrolase	
Target category:	Antibody-antigen binding	
Method of detection:	Optical, near-infrared fluorescence (NIR)	
Source of signal:	Quantum dot (QD)	
Activation:	No	
Studies:	• *In vitro* • Rodents	Click on protein, nucleotide (RefSeq), and gene for more information about PSMA.

Background

[PubMed]

Optical fluorescence imaging is increasingly used to monitor biological functions of specific targets in small animals (1-3). However, the intrinsic fluorescence of biomolecules poses a problem when visible light (350-700 nm) absorbing fluorophores are used. Near-infrared (NIR) fluorescence (700-1000 nm) detection avoids the background fluorescence interference of natural biomolecules, providing a high contrast between target and background tissues. NIR fluorophores have wider dynamic range and minimal background as a result of reduced scattering compared with visible fluorescence detection. They also have high sensitivity, resulting from low infrared background, and high extinction coefficients, which provide high quantum yields. The NIR region is also compatible with solid-state optical components, such as diode lasers and silicon detectors. NIR fluorescence imaging is becoming a non-invasive alternative to radionuclide imaging in small animals (4).

Fluorescent semiconductor quantum dots (QDs) are nanocrystals made of CdSe/CdTe-ZnS with radii of 1-10 nm (5-7). They can be tuned to emit in a range of wavelengths by changing their sizes and composition, thus

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providing broad excitation profiles and high absorption coefficients. They have narrow and symmetric emission spectra with long, excited-state lifetimes, 20-50 ns, as compared with 1-10 ns of fluorescent dyes. They process good quantum yields of 40-90% and high extinction coefficients. They are more photo-stable than conventional organic dyes. They can be coated and capped with hydrophilic materials for additional conjugations with biomolecules, such as peptides, antibodies, nucleic acids, and small organic compounds, which were tested *in vitro* and *in vivo* (7-11). Although many cells have been labeled with QDs *in vitro* with little cytotoxicity, there are only limited studies of long-term toxicity of QDs in small animals (12-20). However, little is known about the toxicity and the mechanisms of clearance and metabolism of QDs in humans.

Prostate-specific membrane antigen (PSMA) is a cell-surface glycoprotein with a molecular weight of ~100 kDa. It is a unique, type II, transmembrane-bound glycoprotein that is overexpressed on prostate tumor cells and in the neovasculature of most solid prostate tumors, but not in the vasculature of normal tissues (21, 22). This unique expression of PSMA makes it an important biomarker as well as a large extracellular target of imaging agents (23, 24). PSMA has also been detected in other tissues such as the kidneys, the proximal small intestine, and the salivary glands (2). PSMA was found to have *N*-acetyl α-linked acidic dipeptidase (NAALADase) or glutamate carboxypeptidase II activity (3). PSMA may play an important role in the progression of prostate cancer and glutamatergic neurotransmission, as well as in the absorption of folate (4). In the central nervous system, PSMA metabolizes *N*-acetyl-aspartyl-glutamate, and in the proximal small intestine it removes γ-linked glutamates from poly-γ-glutamate folate and folate hydrolase (2). PSMA can be used as a marker for the detection of metastatic cancers with imaging agents. Although a commercially available monoclonal antibody (^{111}In-labeled Capromomab pendetide (^{111}In-CYT-356)) is in clinical use for the detection of prostate cancer, the results obtained with this antibody are not entirely reliable (5). In addition, this antibody has limited access to tumors and may produce low signal/noise ratios because the target is the intracellular domain of PSMA (6, 7). J591, a monoclonal antibody against the extracellular domain of PSMA (25), was conjugated to QD655 (QD655-J591) and accumulated in a human prostate cancer cell line *in vitro* and in nude mice (15).

Related Resource Links:

- Chapters in MICAD (PSMA)
- Gene information in NCBI (PSMA).
- Articles in Online Mendelian Inheritance in Man (OMIM) (PSMA)
- Clinical trials (J591)
- Drug information in FDA (J591)

Synthesis

[PubMed]

Core shell CdSe-ZnS QDs were coated with tri-*n*-octylphosphine oxide (TOPO), a triblock amphiphilic copolymer, and polyethylene glycol (PEG) (15). The bioconjugation efficiency of J591 using ethyl-3-dimethyl(aminopropyl)carbodiimide to the QD655 was 40-50%. The assembled QDs have a hydrodynamic radius of 10-15 nm, as measured by dynamic light scattering. Each QD655-J591 contains 200 TOPO molecules, 4 to 5 triblock copolymers, 5 to 6 PEG molecules, and 5 to 6 J592 antibody molecules, as estimated by fluorescence-tagged molecules. Transmission electron microscopy indicated that the QD655-J591 consisted of single particles with little aggregation. QD655-J591 emits light at the NIR fluorescence range of 655 nm.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

LNCaP human prostate cancer cells were reported to have a K_d of 1.83 nM with ^{131}I-labeled J591 and a B_{max} of 600,000-800,00 sites/cell in a saturation binding assay (25). Binding studies of QD655-J591 and QD655-PEG were performed using human prostate cancer cell lines C4-2 (PSMA positive, a subclone of LNCaP) and PC-3 (PSMA negative) (15). QD655-J591 but not QD655-PEG was shown to bind to C4-2 cells. No fluorescence was detected on the cell surface of PC-3 cells with QD655-J591. QD655-J591 binds specifically to C4-2 cells, given that PC-3 cells without PSMA showed no binding by QD655-J591.

Animal Studies

Rodents

[PubMed]

Tumor imaging studies of QD655-J591 were evaluated in nude mice bearing a C4-2 subcutaneous xenograft model (15). Whole-body small animal images by reflectance planar fluorescence were obtained after injection of QD655-J591, QD655 coated with surface carboxylic acid groups (QD655-COOH), and QD655-PEG. Intense tumor signals were obtained with QD655-J591 (0.4 nmol/mouse) at 2 h after injection (active targeting by specific antibody-antigen recognition). Weak tumor fluorescence signals were obtained with QD655-PEG (6 nmol/mouse) at 6 h (passive targeting by enhanced vascular permeability of tumor). No tumor fluorescence signals were obtained with QD655-COOH (6 nmol/mouse) at 24 h. However, QD655-J591 has suboptimal tissue penetration and autofluorescence from the skin. No negative control (QD655 conjugated with nonspecific antibody) or blocking experiments (unconjugated J591) were performed in these studies.

The biodistribution of QD655-J591, QD655-PEG, and QD655-COOH was studied in C4-2 tumor-bearing mice by *ex vivo* tissue fluorescence intensity measurements (15). QD655-J591 uptake in tumors was high, followed to a lesser extent by QD65-PEG. The uptake of QD655-COOH in the tumor was not detectable. QD655-J591, QD655-PEG, and QD655-COOH were all markedly retained in the liver and spleen as nonspecific uptake by the reticuloendothelial system, with little or no accumulation in the brain, heart, kidney, or lung.

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. Achilefu S. *Lighting up tumors with receptor-specific optical molecular probes.* . Technol Cancer Res Treat. 2004;3(4):393–409. PubMed PMID: 15270591.
2. Becker A., Hessenius C., Licha K., Ebert B., Sukowski U., Semmler W., Wiedenmann B., Grotzinger C. *Receptor-targeted optical imaging of tumors with near-infrared fluorescent ligands.* . Nat Biotechnol. 2001;19(4):327–31. PubMed PMID: 11283589.

3. Ntziachristos V., Bremer C., Weissleder R. *Fluorescence imaging with near-infrared light: new technological advances that enable in vivo molecular imaging.* . Eur Radiol. 2003;13(1):195–208. PubMed PMID: 12541130.
4. Tung C.H. *Fluorescent peptide probes for in vivo diagnostic imaging.* . Biopolymers. 2004;76(5):391–403. PubMed PMID: 15389488.
5. Chan W.C., Maxwell D.J., Gao X., Bailey R.E., Han M., Nie S. *Luminescent quantum dots for multiplexed biological detection and imaging.* . Curr Opin Biotechnol. 2002;13(1):40–6. PubMed PMID: 11849956.
6. Gao X., Nie S. *Quantum dot-encoded beads.* . Methods Mol Biol. 2005;303:61–71. PubMed PMID: 15923675.
7. Michalet X., Pinaud F.F., Bentolila L.A., Tsay J.M., Doose S., Li J.J., Sundaresan G., Wu A.M., Gambhir S.S., Weiss S. *Quantum dots for live cells, in vivo imaging, and diagnostics.* . Science. 2005;307(5709):538–44. PubMed PMID: 15681376.
8. Alivisatos A.P., Gu W., Larabell C. *Quantum dots as cellular probes.* . Annu Rev Biomed Eng. 2005;7:55–76. PubMed PMID: 16004566.
9. Hilger I., Leistner Y., Berndt A., Fritsche C., Haas K.M., Kosmehl H., Kaiser W.A. *Near-infrared fluorescence imaging of HER-2 protein over-expression in tumour cells.* . Eur Radiol. 2004;14(6):1124–9. PubMed PMID: 15118831.
10. Medintz I.L., Uyeda H.T., Goldman E.R., Mattoussi H. *Quantum dot bioconjugates for imaging, labelling and sensing.* . Nat Mater. 2005;4(6):435–46. PubMed PMID: 15928695.
11. Smith A.M., Gao X., Nie S. *Quantum dot nanocrystals for in vivo molecular and cellular imaging.* . Photochem Photobiol. 2004;80(3):377–85. PubMed PMID: 15623319.
12. Akerman M.E., Chan W.C., Laakkonen P., Bhatia S.N., Ruoslahti E. *Nanocrystal targeting in vivo.* . Proc Natl Acad Sci U S A. 2002;99(20):12617–21. PubMed PMID: 12235356.
13. Braydich-Stolle L., Hussain S., Schlager J.J., Hofmann M.C. *In vitro cytotoxicity of nanoparticles in mammalian germline stem cells.* . Toxicol Sci. 2005;88(2):412–9. PubMed PMID: 16014736.
14. Frangioni J.V., Hajjar R.J. *In vivo tracking of stem cells for clinical trials in cardiovascular disease.* . Circulation. 2004;110(21):3378–83. PubMed PMID: 15557385.
15. Gao X., Cui Y., Levenson R.M., Chung L.W., Nie S. *In vivo cancer targeting and imaging with semiconductor quantum dots.* . Nat Biotechnol. 2004;22(8):969–76. PubMed PMID: 15258594.
16. Han M., Gao X., Su J.Z., Nie S. *Quantum-dot-tagged microbeads for multiplexed optical coding of biomolecules.* . Nat Biotechnol. 2001;19(7):631–5. PubMed PMID: 11433273.
17. Lovric J., Bazzi H.S., Cuie Y., Fortin G.R., Winnik F.M., Maysinger D. *Differences in subcellular distribution and toxicity of green and red emitting CdTe quantum dots.* . J Mol Med. 2005;83(5):377–85. PubMed PMID: 15688234.
18. Ohnishi S., Lomnes S.J., Laurence R.G., Gogbashian A., Mariani G., Frangioni J.V. *Organic alternatives to quantum dots for intraoperative near-infrared fluorescent sentinel lymph node mapping.* . Mol Imaging. 2005;4(3):172–81. PubMed PMID: 16194449.
19. Shiohara A., Hoshino A., Hanaki K., Suzuki K., Yamamoto K. *On the cyto-toxicity caused by quantum dots.* . Microbiol Immunol. 2004;48(9):669–75. PubMed PMID: 15383704.
20. Soltesz E.G., Kim S., Laurence R.G., DeGrand A.M., Parungo C.P., Dor D.M., Cohn L.H., Bawendi M.G., Frangioni J.V., Mihaljevic T. *Intraoperative sentinel lymph node mapping of the lung using near-infrared fluorescent quantum dots.* . Ann Thorac Surg. 2005;79(1):269–77. PubMed PMID: 15620956.
21. Feneley M.R., Jan H., Granowska M., Mather S.J., Ellison D., Glass J., Coptcoat M., Kirby R.S., Ogden C., Oliver R.T., Badenoch D.F., Chinegwundoh F.I., Nargund V.H., Paris A.M., Britton K.E. *Imaging with prostate-specific membrane antigen (PSMA) in prostate cancer.* . Prostate Cancer Prostatic Dis. 2000;3(1):47–52. PubMed PMID: 12497162.
22. Ghosh A., Heston W.D. *Tumor target prostate specific membrane antigen (PSMA) and its regulation in prostate cancer.* . J Cell Biochem. 2004;91(3):528–39. PubMed PMID: 14755683.
23. Nanus, D.M., M.I. Milowsky, L. Kostakoglu, P.M. Smith-Jones, S. Vallabahajosula, S.J. Goldsmith, and N.H. Bander, *Clinical use of monoclonal antibody HuJ591 therapy: targeting prostate specific membrane antigen.* J Urol, 2003**170**(6 Pt 2): p. S84-8; discussion S88-9.

24. Nargund V., Al Hashmi D., Kumar P., Gordon S., Otitie U., Ellison D., Carroll M., Baithun S., Britton K.E. *Imaging with radiolabelled monoclonal antibody (MUJ591) to prostate-specific membrane antigen in staging of clinically localized prostatic carcinoma: comparison with clinical, surgical and histological staging.* . BJU Int. 2005;95(9):1232–6. PubMed PMID: 15892807.
25. Smith-Jones P.M., Vallabahajosula S., Goldsmith S.J., Navarro V., Hunter C.J., Bastidas D., Bander N.H. *In vitro characterization of radiolabeled monoclonal antibodies specific for the extracellular domain of prostate-specific membrane antigen.* . Cancer Res. 2000;60(18):5237–43. PubMed PMID: 11016653.