

Humanized anti-type 1 insulin-like growth factor receptor monoclonal antibody conjugated to cadmium telluride quantum dots

AVE1642-QD

Arvind Chopra, PhD¹

Created: July 15, 2009; Updated: August 12, 2009.

Chemical name:	Humanized anti-type 1 insulin-like growth factor receptor monoclonal antibody conjugated to cadmium telluride quantum dots	
Abbreviated name:	AVE1642-QD	
Synonym:		
Agent Category:	Antibody	
Target:	Type 1 insulin-like growth factor receptor (IGF1R)	
Target Category:	Receptor	
Method of detection:	Near-infrared (NIR) fluorescence	
Source of signal / contrast:	Quantum dots (QD)	
Activation:	No	
Studies:	<ul style="list-style-type: none">• <i>In vitro</i>• Rodents	Structure not available in PubChem .

Background

[[PubMed](#)]

Overexpression and activation of the type 1 insulin-like growth factor receptor (IGF1R), which mediates its activity through an associated tyrosine kinase, is believed to promote the progression and metastasis of several cancers (1-3). In addition, higher than normal or overexpression of the IGF1R itself, or any of its different constituent parts, is considered to

¹ National Center for Biotechnology Information, NLM, NIH, Bethesda, MD 20894; Email: micad@ncbi.nlm.nih.gov.

NLM Citation: Chopra A. Humanized anti-type 1 insulin-like growth factor receptor monoclonal antibody conjugated to cadmium telluride quantum dots. 2009 Jul 15 [Updated 2009 Aug 12]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

indicate an aggressive or drug-resistant cancer phenotype with a poor prognosis for the patient (3). As a consequence, the IGF1R is a target of various agents, including monoclonal antibodies (mAbs) directed against it, that are under evaluation in [clinical trials](#) approved by the United States Food and Drug Administration for the treatment of cancers. Also, using xenograft tumor models, a downregulation in IGF1R expression has been shown to be accompanied by reduced tumor growth, suggesting that IGF1R levels can be used to monitor patient response to anti-cancer treatment(s) (4, 5).

The epidermal growth factor receptor (EGFR), which is known to be overexpressed in several cancers, is routinely quantified in a clinical setting with *in situ* hybridization or immunohistochemical techniques, and the data obtained from these investigations are used to select patients who are most likely to benefit from an anti-EGFR therapy (6, 7). However, no such quantification is available for IGF1R expression, which has been quantified only in cultured cells using a humanized anti-IGF1R mAb (AVE1642) conjugated to cadmium telluride quantum dots (QD) (AVE1642-QD) (8). Recently, the use of AVE1642 QD was evaluated for the detection and imaging of xenograft tumors that express IGF1R in a mouse model (9). For comparison, the investigators also evaluated the use of Alexa 680 (a near-infrared fluorescent dye with a maxima at 705 nm) covalently linked to AVE1642 (AVE1642-Alexa 680) (discussed in a separate chapter of MICAD; www.micad.nih.gov) for the detection and imaging of the tumors expressing IGF1R (9).

Synthesis

[PubMed]

The AVE1642 mAb was obtained from a commercial source, and its conjugation with the QDs was performed with a heterobifunctional cross-linker, succinimidyl-4-(*N*-maleimidomethyl)cyclohexane-1-carboxylate, as described by Zhang et al. (9). Purification of the AVE1642-QD conjugate was not described. The number of AVE1642 molecules conjugated to each QD and the stability of the complex under *in vitro* or *in vivo* conditions were not reported.

For one of the studies, an alternate method, which generated a direct-linkage between the mAb and the QDs, was used to generate the AVE1642-QDs (9). The purification, number of AVE1642 molecules linked to each QD, and stability of the complex were not reported.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The receptor binding ability of AVE1642-QD was investigated using mouse embryo fibroblast R-/IGF1R cells (R cells stably transfected with human *igf1r* DNA) that express high levels of IGF1R (9). The cells were exposed to either AVE1642-QD, QD alone (control), or an anti-CD20 antibody conjugated to the QD (negative control) for 1 h at 4°C in phosphate-buffered saline (PBS) containing 1% bovine serum albumin and 0.1% sodium azide. Binding of the fluorescent mAbs or the QDs was analyzed with

fluorescence-assisted cell sorting (FACS). Only cells exposed to AVE1642-QD were reported to show fluorescence, and no signal was obtained from cells exposed to the unconjugated QDs. R-/IGF1R cells pretreated with AVE1642 did not produce a fluorescent signal upon exposure to the QD conjugated mAb, indicating that the cells had downregulated the IGF1R levels due to prior exposure to AVE1642.

In another study, MCF-7 cells, a breast cancer cell line that constitutively expresses high levels of the IGF1R, were shown with FACS analysis to bind AVE1642-QD but not QDs alone (9).

From these studies the investigators concluded that AVE1642-QD was able to detect the expression of IGF1R under *in vitro* conditions (9). These observations were similar to those obtained with the AVE1642-Alexa680 conjugate (9).

Animal Studies

Rodents

[PubMed]

Zhang et al. used athymic mice bearing xenograft tumors generated with R-/IGF1R cells to investigate the *in vivo* specificity of AVE1642-QD (9). The mice were injected with 0.1 nmol of the QD-conjugated mAb through the tail vein (control animals were injected with PBS alone), and blood was drawn from the animals at predesignated time points (the number of animals used per time point was not reported) to determine the QD fluorescence by imaging. The QD fluorescence of blood was reported to diminish very rapidly, and by 2 h after treatment no fluorescence was detectable in this organ. On the basis of this observation, for subsequent work, whole-body imaging of the animals was performed only at 2 and 24 h after mAb-QD conjugate injection. By 2 h after the conjugate treatment, QD fluorescence was observed primarily in organs that contain the reticuloendothelial system (RES) and are rich in phagocytic cells (e.g., liver, bone marrow, lymph nodes, and spleen). The high nonspecific uptake of QDs by these organs was reported to mask the fluorescent signal from the tumors in the animals. *Ex vivo* imaging of the tumors revealed that the fluorescent signal was present in the middle of tumors obtained from the animals injected with either the QDs alone or the animals injected with the QD-conjugated mAb. In addition, there was little difference between the fluorescence obtained from the tumors of both animal groups. Pretreatment of the animals with AVE1642 before injection with AVE1642-QD did not reduce the fluorescence in tumors from either group. From these observations the investigators concluded that, although the QDs and the AVE1642-QDs accumulated in the tumors, the uptake of these agents was nonspecific and independent of IGF1R expression (9).

Ex vivo imaging of tumors performed with the QDs and with the mAb-QD complex generated by an alternate method (see the Synthesis section above for details) yielded results similar to those detailed above (9). This confirmed that the tumor uptake of

AVE1642-QD was due to nonspecific binding of the complex to the cells and did not depend on the level of IGF1R expressed by the cells.

Toluidine blue staining of liver sections obtained from animals treated with AVE1642-QD showed that the mAb-QD complex was localized in the liver sinusoids at 2 and 24 h after treatment of the animals (9). Staining of the liver sections with an antibody directed specifically against the monocytes and the macrophages (MOMA-2) showed that the AVE1642-QD fluorescence was co-localized with the MOMA-2 staining of the sections. Treatment of the animals with clodronate liposomes, which are known to deplete macrophages from the RES of the organs, did not prevent the uptake of AVE1642-QD by the liver cells. This indicated that uptake of the mAb-QD complex in the liver was independent of macrophage accumulation in RES of the organ.

From these studies the investigators concluded that AVE1642-QD performed well only under *in vitro* conditions, but could not be used *in vivo* for the detection and quantification of IGF1R in a rodent model (9). In comparison, AVE1642-Alexa680 was shown to be a suitable imaging agent to detect and quantify IGF1R under *in vivo* conditions (9).

Other Non-Primate Mammals

[PubMed]

No references are currently available.

Non-Human Primates

[PubMed]

No references are currently available.

Human Studies

[PubMed]

No references are currently available.

Supplemental Information

[Disclaimer]

No information is currently available.

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