125I-Labeled trivalent, bispecific monoclonal antibody construct TF10 that targets mucin-1 and is reactive against a histamine-succinyl-glycine hapten IMP-288

[^{125}I]-TP10

Arvind Chopra, PhD[1]

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Chemical name:	^{125}I-Labeled trivalent, bispecific monoclonal antibody construct TF10 that targets mucin-1 and is reactive against a histamine-succinyl-glycine hapten IMP-288	
Abbreviated name:	[^{125}I]-TP10	
Synonym:		
Agent Category:	Antibody	
Target:	Mucin-1	
Target Category:	Antigen	
Method of detection:	Single-photon emission computed tomography (SPECT); gamma planar imaging	
Source of signal / contrast:	125I	
Activation:	No	
Studies:	• *In vitro* • Rodents	Structure not available in PubChem.

Background

[PubMed]

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

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Most individuals suffering from pancreatic adenocarcinoma (PAC) do not survive for more than 1 year after diagnosis, and <1% of these patients live beyond 5 years (1). Although surgical resection of the cancer is a possible intervention for this disease, only 10%–25% of the patients are considered suitable for this treatment because, by the time that the neoplasm is detected, the malignancy has metastasized to other organs and the tumor load in the patient is too high to warrant surgery (2). Patients with nonresectable PAC are treated either with gemcitabine or radiotherapy or a combination of the two; however, these treatments are not curative because they only prolong survival and improve the quality of life of the patient (2). Early detection of this invasive cancer would facilitate proper staging of the disease so that a suitable treatment regimen can be initiated to possibly improve patient prognosis (3).

In this regard, the monoclonal antibody (mAb) PAM4, which specifically targets mucin 1 (MUC1), a glycoprotein that is overexpressed only in PAC tumors, was developed, radiolabeled with ^{131}I or ^{111}In, and shown with scintigraphy to detect neoplastic tumors in patients with pancreatic malignancies (4). However, intact radiolabeled antibodies (5) are known to have incomplete tumor penetration due to their large size (~150 kDa), and they are of limited utility to visualize cancerous lesions with different imaging modalities because they have a long blood circulating half-life and usually generate a low signal/noise (S/N) ratio (5). To amplify the signal obtained from an imaging agent so that it can be used to detect malignant tumors noninvasively, investigators have developed and evaluated a variety of strategies in preclinical studies with animals. One such strategy involves the pretargeting of cancer lesions with a suitable mAb (or its derivative), allowing some time for the pretargeting Ab to bind to the cancerous tissue and clear from blood circulation; the animals subsequently are injected with an appropriate radiolabeled small molecular weight ligand that binds to the pretargeting mAb or its derivative. This technique has been shown to generate higher S/N ratios during imaging compared to ratios obtained with a directly labeled mAb alone (6-8). Use of the pretargeting technique with multivalent (i.e., containing more than one antigen binding site), multispecific (i.e., can bind more than a single type of antigen) Abs for the imaging and therapy of cancer has been discussed in detail elsewhere (9, 10).

Cardillo et al. developed bsPAM4 (or bsmAb), a divalent, bispecific F(ab')$_2$ mAb, by cross-linking a PAM4 Fab' fragment to a murine anti–In-diethylenetriamine pentaacetic acid (In-DTPA) mAb Fab' fragment and used the unlabeled bsPAM4 to pretarget human CaPan-1 cell xenograft PAC tumors in nude mice (4). The animals were then exposed to a radiolabeled peptide hapten that bound to the In-DTPA binding mAb Fab'; imaging showed that this technique generated higher S/N ratios compared to the directly labeled bsmAb alone. From this study, the investigators concluded that the peptide was suitable for use with scintigraphy to target and visualize human xenograft PAC tumors in nude mice (4). In an effort to further improve the S/N ratio that can be obtained with the pretargeting technique, Gold et al. generated a recombinant trivalent (i.e., three binding sites) bsmAb, designated TF10, and evaluated its use with scintigraphy for the visualization of xenograft PAC tumors in mice (1). The TF10 bsmAb is divalent for binding to MUC1 and monovalent for binding to a histamine-succinyl-glycine (HSG)

motif containing hapten (DOTA-D-Tyr-D-Lys(HSG)-D-Glu-D-Lys(HSG)-NH_2 (IMP-288, HSG hapten)), and was generated by linking two PAM4 Fab fragments to an anti-HSG hapten mAb Fab fragment as described elsewhere (1). The biodistribution of ^{125}I-labeled TF10 ([^{125}I]-TF10) was studied in mice bearing PAC tumors and is discussed in this chapter. The biodistribution of ^{111}In-labeled IMP-288 ([^{111}In]-IMP-288) and the visualization of PAC tumors in mice with this labeled hapten is discussed in a separate chapter of MICAD (www.micad.nih.gov) (11).

Related Resource Links

Peptide haptens [PubMed]

Clinical trials with bispecific antibodies

Application of multivalent antibodies [PubMed]

Synthesis

[PubMed]

The recombinant synthesis of TF10 with the "dock-and-lock" method and the ^{125}I labeling of the bsmAb with the Iodogen procedure have been described by Gold et al. (1). The specific activity of [^{125}I]-TF10 was reported to be 14.8 kBq/pmol (0.4 μCi/pmol). Although the purity of the radiolabeled bsmAb was not reported, it was ascertained with size-exclusion high-performance liquid chromatography, and the amount of free isotope in the preparation was determined with instant thin-layer chromatography. The radiochemical yield of the final product was not reported.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The binding of TF10 to the MUC1 antigen was investigated with an ELISA assay and compared to the binding of the PAM4 and PAM4 F(ab')$_2$ mAbs (1). These mAbs exhibited similar binding curves, and the half-maximal binding values of the mAbs were estimated to be 1.42 ± 0.10, 1.31 ± 0.12, and 1.83 ± 0.16 nmol/L, respectively (P = 0.05 for all). In comparison, bsPAM4 had a half-maximal binding of 30.61 ± 2.05 nmol/L (P = 0.0379), indicating that TF10 bound the antigen in a divalent manner (1). The immunoreactivity of ^{125}I-TF10 to the MUC1 antigen was reported to be 87%, with 9% remaining unbound and 3% free ^{125}I, as determined with low-pressure size-exclusion chromatography.

Animal Studies

Rodents

[PubMed]

The biodistribution of [^{125}I]-TF10 was investigated in athymic nude mice bearing subcutaneous human xenograft pancreatic adenocarcinoma CaPan-1 cell tumors (1). The animals (n = 5 mice /group) were injected with the radioiodinated bsmAb (10 μCi (40 μg)) and euthanized at predetermined time points to determine the amount of radioactivity that accumulated in the various organs, including the tumors. Data obtained from this study were presented as a percent of injected dose per gram tissue (% ID/g).

Rapid clearance of radioactivity from the blood was observed with [^{125}I]-TF10, decreasing from 21.03 ± 1.93% ID/g at 1 h postinjection (p.i.) to 0.13 ± 0.2% ID/g at 16 h p.i. and 0.03 ± 0.01% ID/g at 72 h p.i. Accumulation of the label in the lungs, liver, kidneys, and spleen ranged from ~6% ID/g (lungs) to ~12% ID/g (spleen) at 1 h p.i. and decreased to ~0.10% ID/g (kidneys) and ~0.17% ID/g (lungs and spleen) at 16 h p.i. Tumor uptake of the tracer peaked at 6 h p.i. (7.17 ± 1.10% ID/g) and decreased to 3.47 ± 0.66% ID/g at 16 h p.i. and 1.34 ± 0.24% ID/g at 72 h p.i. The biodistribution of [^{125}I]-TF10 in the major organs of normal athymic nude mice (without tumors) was reported to be the same as mentioned above (data not presented), indicating that the tumors had no effect on the tissue-binding characteristics of the radioiodinated trivalent bsmAb (1). No blocking studies were reported.

From this study, the investigators concluded that TF10 was suitable to pretarget human xenograft tumors in mice (1).

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.

Supplemental Information

[Disclaimers]

No information is currently available.

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