^{125}I-Labeled anti-mucin 1 bispecific antibody bsPAM4

[^{125}I]-bsPAM4

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Created: June 22, 2011; Updated: July 26, 2011.

Chemical name:	[^{125}I]-Labeled anti-mucin 1 bispecific antibody bsPAM4	
Abbreviated name:	[^{125}I]-bsPAM4	
Synonym:		
Agent Category:	Antibody	
Target:	Mucin 1 (MUC1)	
Target Category:	Antigen	
Method of detection:	Single-photon emission computed tomography (SPECT); gamma planar imaging	
Source of signal / contrast:	^{125}I	
Activation:	No	
Studies:	• *In vitro* • Rodents	Structure not available in PubChem.

Background

[PubMed]

The majority of 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

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NLM Citation: Chopra A. ^{125}I-Labeled anti-mucin 1 bispecific antibody bsPAM4. 2011 Jun 22 [Updated 2011 Jul 26]. In: Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2013.

of the two; however, these treatments are not curative because they only prolong survival and improve the quality of life of the patient (2). The detection of this invasive cancer at an early stage 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 to detect neoplastic tumors with scintigraphy in patients having pancreatic malignancies (4). However, intact radiolabeled antibodies are known to have limited tumor penetration due to their large size (~150 kDa) and are of limited utility to visualize cancerous lesions with different imaging modalities (primarily positron emission tomography and single-photon emission computed tomography) due to their long circulating half-life (5). To amplify the signal obtained from an imaging agent that can be used to detect malignant tumors noninvasively, investigators have developed and evaluated a variety of strategies in preclinical studies in animals, such as pretargeting the cancer lesion with a suitable mAb (or its derivative) followed by exposing the animals to an appropriate radiolabeled, small molecular weight ligand that targets the mAb or its derivative. This technique has been shown to generate higher signal/noise ratios during imaging compared to ratios obtained with a directly labeled mAb alone (6-8). Use of the pretargeting technique for the imaging and therapy of cancer has been discussed in detail elsewhere (9, 10).

Cardillo et al. developed bsPAM4 (or bsmAb), a bispecific F(ab')$_2$ mAb fragment, by cross-linking a PAM4 Fab' fragment to a murine anti—indium-diethylenetriamine pentaacetic acid (DTPA) mAb Fab' fragment and using the unlabeled bsPAM4 to pretarget human CaPan-1 cell xenograft PAC tumors in nude mice (4). The animals were exposed to two radiolabeled peptide haptens, ^{111}In-labeled Ac-Phe-Lys(DTPA)-Tyr-Lys(DTPA)-NH_2 ([^{111}In]-IMP-156) and ^{99}Tc-labeled Ac-Lys(DTPA)-Tyr-Lys(DTPA)-Lys(thiosemicarbazonyl-glyoxyl-cysteinyl-)-NH_2 ([^{99m}Tc]-IMP-192), respectively, that bind specifically to the anti-indium-DTPA mAb Fab' fragment arm of the bsmAb. To confirm the tumor-targeting specificity of bsPAM4, the biodistribution of ^{125}I-labeled bsPAM4 ([^{125}I]-bsPAM4) was investigated in a group of mice bearing human PAC tumors and the results are presented in this chapter (4). The biodistribution studies performed with [^{111}In]-IMP-156 (11) and [^{99m}Tc]-IMP-192 (12) in mice bearing human PAC tumors pretargeted with bsPAM4 are discussed in separate chapters of MICAD (www.micad.nih.gov).

Other Sources of Information

Peptide haptens [PubMed]

Clinical trials with bispecific antibodies

Application of multivalent antibodies [PubMed]

Synthesis

[PubMed]

The synthesis methods for bsPAM4 and bispecific rituximab (bsRIT) for use as a control were described by Cardillo et al. (4). The cross-linked bsmAbs were purified with size-exclusion chromatography (SEC), and the ratio of each Fab' fragment in the complex was determined with high-performance liquid chromatography to be 1:1. The bsmAbs were labeled with ^{125}I (bsPAM4) or ^{131}I (bsRIT) with the chloramine-T method to obtain [^{125}I]-bsPAM4 and [^{131}I]-bsRIT (4). [^{125}I]-bsPAM4 and [^{131}I]-bsRIT were reported to have specific activities of 488 MBq/mg (13.2 mCi/mg) and 103 MBq/mg (2.8 mCi/mg), respectively. The radiochemical purity and yield of the radioiodinated bsmAbs were not reported.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Both bsPAM4 and bsRIT were reported to be stable in mouse serum and showed no aggregation or degradation for at least 5 days (incubation temperature not provided) as determined with SEC (4).

Animal Studies

Rodents

[PubMed]

The biodistribution of [^{125}I]-bsPAM4 was investigated in athymic *nu/nu* mice bearing human PAC CaPan-1 cell tumors (4). The animals (n = 5 mice/group) were coinjected with 370 kBq/150 pmol (10 μCi/150 pmol) [^{125}I]-bsPAM4 or 1.3 MBq/150 pmol (35 μCi/150 pmol) [^{131}I]-bsRIT and euthanized at predetermined time points varying from 4 h to 72 h postinjection (p.i.). All organs of interest, including the tumors, were removed, and the amount of radioactivity accumulated in the various tissues was determined. Data obtained from this study were presented as percent of injected dose per gram tissue (% ID/g).

The amount of radioactivity in the tumor from [^{125}I]-bsPAM4 was reported to be significantly higher (P = 0.0320–0.0098) than that from [^{131}I]-bsRIT at all time points (4). With [^{125}I]-bsPAM4, the amount of radioactivity detected in the tumor was 6.43 ± 1.50% ID/g and 5.37 ± 2.38% ID/g at 36 h and 48 h p.i., respectively, which was significantly higher than the accumulation with the ^{131}I-labeled control bsmAb (0.65 ± 0.33% ID/g and 0.47 ± 0.19% ID/g, at 36 h and 48 h p.i., respectively) (P = 0.0180 and 0.0098 at the respective time points). Although the blood clearance rates of both the radioiodinated bsmAbs were for the most part very similar, the uptake of label from [^{125}I]-bsPAM4 in the non-tumor tissues was significantly higher than that observed with [^{131}I]-bsRIT; e.g.,

at 24 h p.i., uptake in the spleen was 0.66 ± 0.06% ID/g with [^{125}I]-bsPAM4 *versus* 0.52 ± 0.02% ID/g ($P = 0.0412$) with [^{131}I]-bsRIT, and uptake in the muscle at the same time point was 0.30 ± 0.04% ID/g for [^{125}I]-bsPAM4 *versus* 0.19 ± 0.02% ID/g ($P = 0.0169$) with [^{131}I]-bsRIT, etc.

From these studies, the investigators concluded that bsPAM4 was suitable to target PAC xenograft tumors in rodents and could be used for the pretargeting studies with [^{111}In]-IMP-156 and [^{99m}Tc]-IMP-192 (4).

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.

NIH Support

Studies described in this chapter were supported by National Institutes of Health grants CA-54425 and CA92723.

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