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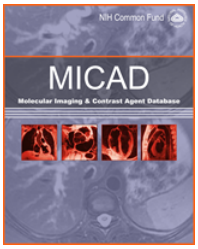

^{99m}Tc-Ac-Lys(DTPA)-Tyr-Lys(DTPA)-Lys(thiosemicarbazonyl-glyoxyl-cysteinyl-)-NH2 (IMP-192)

[^{99m}Tc]-IMP-192

Arvind Chopra, PhD[1]

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Chemical name:	[^{99m}Tc]-Labeled Ac-Lys(DTPA)-Tyr-Lys(DTPA)-Lys(thiosemicarbazonyl-glyoxyl-cysteinyl-)-NH_2 (IMP-192)	
Abbreviated name:	[^{99m}Tc]-IMP-192	
Synonym:		
Agent Category:	Compound	
Target:	Bispecific PAM4 antibody	
Target Category:	Antibody	
Method of detection:	Single photon emission computed tomography (SPECT); gamma planar imaging	
Source of signal / contrast:	^{99m}Tc	
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 fewer than 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 usually by the time that 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). The detection of this cancer at an early stage can 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

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

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 of limited utility to visualize cancerous lesions due to their large size (~150 kDa) and 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 a higher signal-to-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 elsewhere (9, 10).

Cardillo et al. developed a bispecific F(ab')$_2$ mAb (bsPAM4; bsmAb) by cross-linking a PAM4 Fab' fragment (binds the MUC-1 antigen) to a murine anti-indium-diethylenetriaminepentaacetic acid (DTPA) mAb Fab' fragment (binds the peptide heptan antigen) and used the unlabeled bsmAb to pretarget human CaPan-1 cell xenograft PAC tumors in nude mice (4). After the bsmAb was cleared from blood circulation the animals were injected with a radiolabeled peptide heptan to visualize the PAC lesions with whole body scintigraphy. To confirm the tumor targeting specificity and delivery of bsPAM4 to the tumor (the pretargeting bsmAb) the biodistribution of this bsmAb was investigated in mice bearing human PAC tumors using ^{125}I-labeled bsPAM4 ([^{125}I]-bsPAM4) (4). Subsequently two groups of animals pretargeted with bsPAM4 were separately injected with 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), that specifically bind the anti-indium-DTAP mAb Fab' arm of the bsmAb and the biodistribution of these radiolabeled peptides was investigated in the tumor bearing rodents. This chapter describes the biodistribution characteristics of [^{99m}Tc]-IMP-192. The biodistribution of radioiodinated bsPAM4 in non-pretargeted mice (11) and the biodistribution and imaging studies performed with [^{111}In]-IMP-156 in mice pretargeted with bsPAM4 (12) 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 of bsPAM4 and another bsmAb, bispecific retuximab (bsRIT; for use as a control) has been described by Cardillo et al. (4). The cross-linked bsmAbs were purified by size-exclusion chromatography (SEC) and the ratio of each Fab' fragment in the complex was determined to be 1:1 with high performance liquid chromatography. The two bsmAbs were labeled with ^{125}I using the chloramine-T method to obtain [^{125}I]-bsPAM4 and [^{125}I]-bsRIT as described elsewhere (4). [^{125}I]-bsPAM4 and [^{125}I]-bsRIT were reported to have a specific activity (SA) of 492.2 MBq/mg (11.6 mCi/mg) and 403.3 MBq/mg (10.9 mCi/mg), respectively. The radiochemical purity and yield of both the radioiodinated bsmAbs was not reported.

IMP-192 was obtained from a commercial source and labeled with ^{99m}Tc as described elsewhere (4). The number of Tc atoms bound to each molecule of IMP-192 (that has two DTPA sites within the structure as described above) was not reported. The SA of [^{99m}Tc]-IMP-192 was reported to be 77.7 MBq/nmol (2.1 mCi/nmol) and the radiolabeled peptide was reported to contain no aggregates and <2% unbound radioactivity as

determined by instant thin layer chromatography. In an earlier study the radiochemical yield of the ^{99m}Tc-labeled peptide was reported to be 94-99% and had a SA of up to 67.7 GBq/mmol (1.83 Ci/mmol).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Karacay et al. reported that IMP-192 can be stored in a freeze dried form at -20^{o} C for prolonged periods (13). The *in vitro* stability of [^{99m}Tc]-IMP-192 in normal saline (0.9% sodium chloride), 1% human serum albumin and 10 mM cysteine was 96%, 96% and 89%, respectively, as determined by reversed-phase high performance liquid chromatography (13).

To investigate the bsmAb binding characteristics of [^{99m}Tc]-IMP-192, 0.15 pmol of the labeled peptide was mixed with 10 pmol bsPAM4 in presence of excess MUC1 (200 µg) and the mixture was incubated at 37^{o} C for 1 h (4). Subsequently size-exclusion chromatography of the mixture revealed that 81% of the tracer bound to bsPAM4 and of the total bsmAb bound fraction 85% of the label was in the MUC1 fraction, 11% in the non-MUC1-reactive bsPAM4 fraction and 4% of the radiocompound bound nonspecifically to the MUC1 antigen.

Animal Studies

Rodents

[PubMed]

The biodistribution of [^{99m}Tc]-IMP-192 was investigated in athymic *nu/nu* mice bearing human PAC CaPan-1 cell tumors (n = 14 mice/group) that were pretargeted with either [^{125}I]-bsPAM4 or [^{125}I]-bsRIT (control bsmAb) (4). A group of animals was injected with 10 µCi (150 pmol) [^{125}I]-bsPAM4 and another other group received 10 µCi (150 pmol) of [^{125}I]-bsRIT. Two other groups of animals received the labeled peptides alone. After 40 h the mice were injected with 28 µCi (15 pmol) [^{99m}Tc]-IMP-192 and the animals were euthanized at 3 and 24 h post injection (p.i.; i. e. 43 and 64 h after administration of the bsmAbs). All organs of interest, including the tumors, were removed from the mice and the amount of radioactivity in the various tissues was determined. Data obtained from this study was presented as percent of injected dose per gram tissue (%ID/g).

At 3 h after injecting the radiolabeled peptide the amount of radioactivity in the tumor from animals pretreated with bsPAM4 was reported to be 16.8 ± 4.8%ID/g (P < 0.0005) compared to 1.1 ± 0.2%ID/g in tumors of the bsRIT pretreated animals (4). Similarly, at 24 h after the treatment with [^{99m}Tc]-IMP-192 mice pretreated with bsPAM4 had an accumulation of 12.9 ± 4.2%ID/g (P < 0.0008) compared to 0.4 ± 0.03%ID/g in animals pretreated with bsRIT. Animals injected with the labeled peptide alone showed negligible uptake of radioactivity at both the time points (0.2 ± 0.05%ID/g, P < 0.0004, and 0.06 ± 0.02%ID/g, P < 0.0002 at 3 h and 24 h after treatment, respectively). At 24 h after treatment the tumor-to-nontumor ratios with [^{99m}Tc]-IMP-192 for all tissues were higher than the ratios obtained from animals treated with [^{125}I]-bsPAM4 alone. In animals pretreated with bsPAM4 the tumor-to-blood ratio with the ^{99m}Tc-labeled peptide was 80:1 compared to a ratio of 4:1 obtained with the non-pretargeted mice injected with [^{125}I]-bsPAM4 alone (P<0.0002).

From these studies the investigators concluded that [^{99m}Tc]-IMP-192was suitable to target PAC xenograft tumors in rodents pretargeted with bsPAM4 in rodents (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.

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