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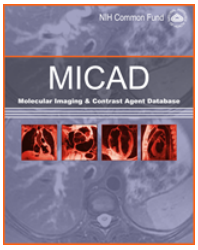

$^{111}In/^{125/131}I$-Labeled anti-mucin-1 murine, chimeric or humanized antibody hPAM4

[$^{111}In/^{125/131}I$]-hPAM4

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Chemical name:	$^{111}In/^{125/131}I$-Labeled anti-mucin-1 murine, chimeric or humanized antibody hPAM4	
Abbreviated name:	[$^{111}In/^{125/131}I$]-hPAM4	
Synonym:		
Agent Category:	Antibody	
Target:	Mucin 1 (MUC1)	
Target Category:	Antigen	
Method of detection:	Single-photon emission tomography (SPECT); gamma planar imaging	
Source of signal / contrast:	$^{111}In/^{125/131}I$	
Activation:	No	
Studies:	• Rodents • Humans	Structure not available in PubChem.

Background

[PubMed]

Mucins (MUC) are a distinct class of transmembrane glycoproteins (designated as MUC1, MUC3A, MUC3B, MUC4, etc.) that are expressed primarily by the glandular and ductal cells of the epithelium in the human body and are known to modulate the tumorigenicity, progression, and pathogenesis of different cancers (1). The structure, physiological function, and process of promoting the development of malignancies by MUCs, particularly MUC1 and MUC4, are discussed in detail by Bafna et al. (1). MUC1 has been shown to be characteristically overexpressed by pancreatic adenocarcinoma (PAC) cells and is not detectable in normal pancreatic ducts or other normal tissues, or during an incident of pancreatitis (2). Because it is detectable only in the serum of patients suffering from PAC, it was suggested recently that the MUC1 antigen can be used as a biomarker for the early detection this malignancy (3, 4).

The majority of individuals suffering from PAC do not survive for more than 1 year after diagnosis, and <1% of these patients live beyond 5 years (5). Although surgical resection of the cancer is a possible treatment for this

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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 and the tumor load in the patient is too high to warrant surgery (5). Patients with nonresectable PAC are treated either with gemcitabine or radiotherapy; however, these treatments are not curative and only prolong survival and improve the quality of life of the patient (5). The detection of this invasive cancer at an early stage would facilitate proper staging of the disease, which could be followed either by surgical resection of the tumor or the initiation of a vigorous treatment regimen that could possibly improve patient prognosis (6).

More than a decade ago, a ^{131}I-labeled murine monoclonal antibody, PAM4 ([^{131}I]-mPAM4), directed against a mucin (later identified to be MUC1 (5)) was reported to detect human xenograft PAC tumors in mice with high specificity and, compared to controls, significantly extended the survival time of the animals when used for radiotherapy of the cancer (7-9). In a preliminary study, [^{131}I]-PAM4 was demonstrated to detect the primary and the metastasized pancreatic carcinoma tumors in humans, and there was a low nonspecific uptake of the tracer in the liver, spleen, and bone marrow of the patients (10). In another study, a chimeric form of PAM4 (cPAM4) was labeled with ^{125}I and ^{111}In to obtain [^{125}I]-cPAM4 and [^{111}In]-cPAM4, respectively, and the biodistribution of these labeled mAbs was investigated in mice bearing human xenograft PAC tumors (11). Recently, Gulec et al. studied the biodistribution of ^{111}In-labeled humanized PAM4 ([^{111}In]-hPAM4) in a phase I clinical trial (2).

Other Sources of Information

Other anti-MUC1 antibody chapters in MICAD

Chapters on radiolabeled antibodies in MICAD

Chimeric antibodies [PubMed]

Humanized antibodies [PubMed]

Protein and mRNA sequence of human MUC1, transcript variant 1

MUC1 in Online Mendelian Inheritance in Man database (OMIM)

Information regarding MUC1 in Genetic Association Database

Gene information of MUC1 (Gene ID: 4582)

MUC1 related Clinical trials

Synthesis

[PubMed]

The mPAM4 (8), cPAM4 (11), and hPAM4 (2) used in the different investigations were obtained from a commercial source.

mPAM4 was labeled with ^{131}I using the chloramine-T method, and the specific activity (SA) of the labeled antibody was reported to be 259–444 kBq/μg (7–12 μCi/μg) (7). The [^{131}I]-mPAM4 preparation contained <3% free ^{131}I and no aggregates as determined with thin-layer chromatography (TLC). Gold et al. labeled mPAM4 with ^{131}I using the Iodo-Gen procedure (5). The labeling efficiency of this method was reported to be 90%; the SA of the labeled mAb was 370–555 MBq/mg (10–15 mCi/mg), and the final preparation contained <5% unbound radioactivity as determined with high-performance liquid chromatography (HPLC) (5).

cPAM4 was labeled with ^{125}I using the chloramine-T procedure as described above (11). The labeled mAb had a SA of 365.6–455 kBq/μg (9.88–12.3 μCi/μg) and contained <5% unbound ^{125}I and <8% aggregates.

cPAM4 was labeled with ^{111}In after conjugation of the mAb to 1,4,7,10-tetraazacyclododecane-*N*,*N*',*N*",*N*"'-tetraacetic acid (DOTA) (11), and the DOTA:cPAM4 ratio of the conjugate was reported in another publication to be 3.3 (12). The SA of [^{111}In]-cPAM4 was reported to vary from 200 kBq/µg (5.41 µCi/µg) to 48.1–133.2 MBq/mg (1.3–3.6 mCi/mg) and contained <1.7% unbound radionuclides and <1% aggregates (5, 11, 12).

The biodistribution and tumor targeting of [^{111}In]-hPAM4 was investigated in patients suffering from pancreatic cancer in a phase I clinical trial (2). Although the [^{111}In]-hPAM4 preparation used in the clinical investigation was reported to contain <10% free radionuclide as determined with instant TLC, the SA of the labeled antibody was not reported.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

No publication is currently available.

Animal Studies

Rodents

[PubMed]

The biodistribution of [^{131}I]-mPAM4 was investigated in *nu/nu* mice bearing xenograft orthotopic CaPan-1 cell tumors as described by Alisauskus et al. (7). The mice (n = 5–8 animals/group) were injected with 25 µCi [^{131}I]-mPAM4 (route of injection was not reported) and euthanized at various time points from 1 d to 14 d postinjection (p.i.). All major organs were removed from the animals, and the amount of accumulated radioactivity in the tissues was determined. Data obtained from this study were presented as the percentage of injected dose per gram tissue (% ID/g). The amount of radioactivity in the tumor was shown to decrease steadily from ~15% ID/g at day 1 p.i. to ~4% ID/g at day 14 p.i. In all other organs, the accumulation of radioactivity was between ~2% ID/g (kidneys) and ~5% ID/g (both spleen and blood) on day 1 p.i., and accumulation reduced to <1% ID/g by day 14 p.i. in all the organs. *Ex vivo* microautoradigraphy of 5-µm tumor sections showed that the radioactivity was confined within the tumors and no tracer was detected in the surrounding normal tissues (7). No blocking studies were reported.

In another study, Cardillo et al. investigated the biodistribution of [^{125}I]-cPAM4 in athymic mice bearing CaPan-1 cell tumors (11). The biodistribution pattern of the ^{125}I-labeled chimeric mAb was shown to be similar to that of [^{131}I]-mPAM4 as described above.

Gold et al. studied the biodistribution of [^{111}In]-cPAM4 (used as a surrogate for immunotherapeutic ^{90}Y-labeled cPAM4) in athymic mice bearing similarly sized CaPan-1 cell tumors (5). The animals (n = at least 8 mice/group) were injected with 25 µCi labeled cPAM4 for a total of 25 µg protein/animal, and the preparation also contained the unlabeled chimeric antibody. The mice were euthanized on days 1, 4 and 7 p.i., and all major organs were removed to determine the amount of accumulated radioactivity. The uptake of radioactivity by the tumor was ~25% ID/g on day 1 p.i., increased to ~40% ID/g by day 4 p.i., and decreased to ~25% ID/g on day 7 p.i. During the same period, the accumulation of the tracer in all major organs was between ~2% ID/g (normal pancreas) and ~10% ID/g (blood) on day 1 p.i., and between 2% ID/g (blood) and ~7% ID/g (liver) on day 7 p.i. The amount of tracer in the liver remained constant during the entire period of the study, indicating that the radioactivity was excreted primarily through the hepatobiliary route. The estimated potential radiation dose received by the tumor, the tumor/blood radiation ratio, and the maximum tolerated dose of [^{90}Y]-cPAM4 for the animals were described elsewhere (5). Other investigators reported a similar biodistribution pattern for [^{111}In]-cPAM4 in athymic *nu/nu* mice bearing CaPan-1 cell tumors (11).

In another study, mice bearing subcutaneous CaPan-1 cell tumors were injected with [^{111}In]-cPAM4, and whole-body immunoscintigraphic images were acquired from the animals (n = 2 mice) at various time points as described by Cardillo et al. (12). At 24 h p.i., high background levels of the tracer were observed in the thoracic and abdominal areas of the animals, and the tumors on the animals became visible clearly only at 48 h p.i., indicating a slow clearance of radioactivity from the mice (12). In another part of the same study (n = 14 animals), the tumor/blood, tumor/liver, tumor/kidney, and tumor/normal pancreas radioactivity uptake ratios were reported to be 2.4 ± 1.0, 3.5 ± 1.6, 5.9 ± 1.3, and 18.6 ± 8.2, respectively.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

Two patients with histologically confirmed metastatic pancreatic cancer were injected with [^{131}I]-mPAM4; one patient received 270 MBq (7.3 mCi) [^{131}I]-mPAM4 in a protein dose of 0.6 mg, and the other patient received 315 MBq (8.5 mCi) [^{131}I]-mPAM4 in a protein dose of 0.6 mg (5). Blood samples taken from the two patients showed that the clearance of radioactivity from this tissue was biexponential. The circulating half-life of the tracer in the early component of the curve was 1.9 h in the patient with the smaller dose and 4.6 h in the patient with the larger dose; in the late component the half-life values were 28.6 h and 39.2 h, respectively. HPLC analysis of the plasma obtained from these patients at 24 h p.i. showed the presence of 66%–78% ^{131}I in the small molecular weight fraction, indicating that mPAM4 was catabolized in the blood within 24 h p.i. Scintigraphy was performed on a patient injected with [^{131}I]-mPAM4 (the patient had previously undergone chemotherapy and radiotherapy for the treatment of PAC), and clear uptake of the tracer was observed in tumors on the left hepatic lobe and in the mid-abdomen area of the patient (5). Similarly, tumors were also detected in posterior and anterior planar images acquired from a second patient injected with the radioiodinated mAb (5). From this study, the investigators concluded that mPAM4 specifically targeted pancreatic cancer tumors in the patients.

In a phase I clinical study to evaluate the efficacy of [^{90}Y]-hPAM4 for the treatment of PAC, 21 patients (4 patients with stage III, locally advanced disease; 17 patients with stage IV metastatic disease) were administered a slow intravenous injection of [^{111}In]-hPAM4 to investigate the biodistribution of the tracer (a surrogate for the ^{90}Y-labeled homolog) in the individuals (2). The patients received 3–5 mCi of the label, and the total protein content of each dose, including the unlabeled hPAM4, was 10 mg (for 6 patients) and 100 mg (for 16 patients). Starting at 4 h p.i., repeat whole-body planar scintigraphic images were acquired from the patients over 7 days. Pancreatic tumors were clearly visible at 24 h p.i. (only a representative image was presented (2)), and the visibility was progressively prominent on the subsequent images. From a review of the various images obtained from this study, the investigators concluded there was no qualitative difference was apparent in the biodistribution of [^{111}In]-hPAM4 at the two doses (10 and 100 mg total hPAM4), the humanized mAb showed a normal biodistribution in the patients suffering from PAC and was suitable for the scintigraphic visualization of PAC tumors in humans (2).

Supplemental Information

[Disclaimers]

No information is currently available.

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