# Radioiodinated anti-CEA monoclonal antibody NP-4 F(ab´)$_2$ fragment

$^{123}$I/$^{131}$I/$^{125}$I-NP-4 F(ab´)$_2$

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| **Chemical name:** | Radioiodinated anti-CEA monoclonal antibody NP-4 F(ab´)$_2$ fragment | |
| **Abbreviated name:** | $^{123}$I/$^{131}$I/$^{125}$I-NP-4 F(ab´)$_2$ | |
| **Synonym:** | $^{131}$I-NP-4 F(ab´)$_2$ anti-CEA monoclonal antibody, $^{125}$I-NP-4 F(ab´)$_2$ anti-CEA monoclonal antibody, $^{123}$I-NP-4 F(ab´)$_2$ anti-CEA monoclonal antibody, $^{131}$I-NP-4 F(ab´)$_2$ MAb, $^{125}$I-NP-4 F(ab´)$_2$ MAb, $^{123}$I-NP-4 F(ab´)$_2$ MAb | |
| **Agent Category:** | Antibody F(ab´)$_2$ fragment | |
| **Target:** | Carcinoembryonic antigen (CEA) | |
| **Target Category:** | Antibody to antigen binding | |
| **Method of detection:** | Single-photon emission computed tomography (SPECT), gamma planar imaging | |
| **Source of signal/ contrast:** | $^{131}$I, $^{123}$I, $^{125}$I | |
| **Activation:** | No | |
| **Studies:** | • *In vitro*<br>• Rodents<br>• Non-primate non-rodent mammals<br>• Humans | Click on protein, nucleotide (RefSeq), and gene for more information about CEA. |

## Background

[PubMed]

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Radioiodinated anti-carcinoembryonic antigen (CEA) monoclonal antibody (MAb) NP-4 F(ab′)$_2$ fragment ($^{123}$I/$^{131}$I/$^{125}$I-NP-4 F(ab′)$_2$), which is formed by the conjugation of radioiodine with a murine anti-CEA MAb F(ab′)$_2$ fragment, can be used for imaging and therapy of CEA-expressing cancers (1, 2). $^{125}$I has a relatively long physical half-life ($t_{½}$) of 60 days and a gamma energy that makes it suitable for imaging only in small animals. $^{131}$I has a physical half-life ($t_{½}$) of 8.02 days with a gamma energy that is high but acceptable for *in vivo* imaging. $^{123}$I, another radioiodine, has better physical properties for single-photon emission computed tomography (SPECT) and planar gamma imaging in humans.

CEA was first identified from extracts of human adenocarcinoma of the colon (3). It is a β-glycoprotein, and its predominant expression on the cell surface is increased in a variety of carcinomas, particularly of the gastrointestinal tract, as well as in fetal gastrointestinal tissues and in certain inflammatory states, such as inflammatory bowel disease (4, 5). CEA, which exhibits extensive heterogeneity in its physicochemical and immunologic properties (2, 3), has a molecular mass of 200 kDa and can be shed and detected in the serum (2). It has been used as a serum marker for monitoring disease status in patients who have various CEA-secreting tumors (gastrointestinal, lung, medullary, thyroid, uterine, ovarian, and bladder carcinomas). Other cross-reactive, but genetically distinct, CEA variants have been identified, including nonspecific cross-reactive antigen (NCA) and meconium antigen (MA) (6).

Radiolabeled MAbs have been developed for both the diagnosis and treatment of tumors (4). Primus et al. (2) studied the immunologic heterogeneity of CEA by use of four MAbs to differentiate the antigenic sites on colonic cancer CEA. They classified the MAbs into three general classes based on their reactivity with CEA, NCA, and MA. The class I antibody, NP-1, had high affinity for CEA and MA but low affinity for NCA. The class II antibodies, NP-2 and NP-3, had moderate affinities for CEA and MA. The class III antibody, NP-4, appeared to recognize determinants unique to CEA and had no affinity for NCA or MA. Because of this specificity, NP-4 MAb has been labeled with radionuclides for CEA tumor imaging and therapy (7). Intact NP-4 MAb can be covalently linked to $^{131}$I, $^{123}$I, or $^{125}$I by direct radioiodination with Na$^{131}$I, Na$^{123}$I, or Na$^{125}$I, using an appropriate oxidizing agent. Because of differences in their radiation physical properties, $^{131}$I can be used for both therapy and imaging, $^{123}$I is used only for imaging, and $^{125}$I is used mainly for *in vitro* studies. The *in vivo* pharmacokinetics of intact radiolabeled immunoglobulin G (IgG) in humans are characterized by high liver uptake and slow blood elimination. Therefore, the intact radiolabeled NP-4 MAb is generally not ideal for imaging. Smaller radiolabeled MAb fragments such as Fob or F(ab′)$_2$ may have better imaging pharmacokinetics because they are rapidly excreted by the kidneys. Covell et al. (8) reported that the percentages of total body catabolism of an i.v.-administered $^{131}$I-labeled MAb and its fragments by the kidney were 1.7% (intact IgG), 50.3% (F(ab′)$_2$), and 73.4% (Fab′).

## Synthesis

[PubMed]

NP-4 MAb is an $IgG_1$ subtype and has a CEA affinity in the range of $10^8$ $M^{-1}$ (2, 5). NP-4 MAb was initially produced by Primus et al. (2) in 1983; they used the hybridoma technique and CEA isolated from liver metastases of a colonic adenocarcinoma. The NP-4 MAb was produced in mice and purified from ascites fluid by protein A and ion-exchange column chromatography at 4 °C (9). Sharkey et al. (10-13) and Blumenthal et al. (2) first reported the preparation of NP-4 F(ab′)$_2$ by pepsin digestion in 0.1 M sodium citrate buffer, pH 3.5, at 37 °C for 45-90 min. The reaction was stopped by increasing the pH to 7.0. The preparation was desalted on a fractogel column. Isolation was done by either protein A or ion-exchange chromatography. The final purity and identity were confirmed by immunoelectrophoresis, sodium dodecyl sulfate gel electrophoresis, and size-exclusion high-performance liquid chromatography. Direct radioiodination of the NP-4 F(ab′)$_2$ with $^{131}I$ was performed by the chloramine-T method using a ratio of 0.06 mg of F(ab′)$_2$ per mCi of $^{131}I$. Unbound radioactive iodine was separated from $^{131}I$-NP-4 F(ab′)$_2$ by gel filtration. The specific activity obtained was 444-555 MBq/mg (12-15 mCi/mg), or 20.4-55.5 GBq/μmol (1.2-1.5 Ci/μmol) based on a molecular weight of 100,000 for the F(ab′)$_2$ fragment. The radiochemical purity was 95-98%, and there was <1% aggregated antibody. Goldenberg et al. (14) achieved similar labeling efficiency with $^{123}I$. Juweid et al. (15) used the IodoGen method for $^{131}I$ radioiodination and obtained a similar specific activity of 444-592 MBq/mg (12-16 mCi/mg), or 20.4-59.2 GBq/μmol (1.2-1.6 Ci/μmol). Radiochemical purity was >98%, and there was <7% aggregated antibody.

## *In Vitro* Studies: Testing in Cells and Tissues

Primus et al. (2) first reported the production of NP-4 anti-CEA MAb. Using a competitive radioimmunoassay method, they obtained an affinity constant ($K$) for CEA of $8.9 \times 10^8$ $M^{-1}$. NP-4 MAb did not appear to bind to NCA or MA. Sharkey et al. (10-13) and Blumenthal et al. (2) determined the immunoreactivity of $^{131}I$-NP-4 F(ab′)$_2$ by affinity chromatography on a CEA immunoabsorbent. The $^{131}I$-NP-4 F(ab′)$_2$ prepared by the chloramine-T method had 75-85% binding. Juweid et al. (15) found that the $^{131}I$-NP-4 F(ab′)$_2$ prepared by the IodoGen method had >70% binding.

## Animal Studies

### Rodents

Sharkey et al. (11) studied the biodistribution of $^{131}I$-NP-4 F(ab′)$_2$ and the intact $^{131}I$-NP-4 MAb in athymic nude mice bearing the CEA-producing human colorectal cancer, GW-39. $^{131}I$-NP-4 F(ab′)$_2$ tumor uptake was highest (10-20% of injected dose (ID)/g) on days 1 and 2. Tumor accretion of $^{131}I$-NP-4 F(ab′)$_2$ was highest (4-5% ID/g) at 6 h after injection and remained constant from day 1 to day 3. In comparison, maximum tumor localization of $^{131}I$-NP-4 MAb occurred on day 3 and reached about 30% ID/g. On day 1,

the $^{131}$I-NP-4 F(ab´)$_2$ tumor/nontumor ratios ($n$ = 4-6) were 2.0 ± 0.7 (tumor/blood), 3.2 ± 0.8 (tumor/lung), 7.1 ± 1.6 (tumor/liver), and 3.7 ± 1.2 (tumor/kidney). For the intact $^{131}$I-NP-4 MAb, these ratios were 0.9 ± 0.3 (tumor/blood), 2.1 ± 0.8 (tumor/lung), 3.8 ± 1.3 (tumor/liver), and 2.5 ± 0.9 (tumor/kidney). On day 3, the $^{131}$I-NP-4 F(ab´)$_2$ tumor/nontumor ratios were increased to 9.1 ± 3.0 (tumor/blood), 14.5 ± 4.8 (tumor/lung), 26.6 ± 6.6 (tumor/liver), and 14.2 ± 3.6 (tumor/kidney). For the $^{131}$I-NP-4 MAb, these ratios were 2.2 ± 0.8 (tumor/blood), 5.3 ± 1.8 (tumor/lung), 8.6 ± 2.8 (tumor liver), and 7.1 ± 2.7 (tumor/kidney).

In another study, Sharkey et al. (12) reported radiation dose estimates of $^{131}$I-NP-4 F(ab´)$_2$ in GW-39 tumor-bearing nude mice. The estimates were based on a dose of 50.69 MBq (1.37 mCi), which would give a 50-Gy (5,000 rads) radiation absorbed dose to the tumor. The doses for the blood, kidney, liver, lung, and spleen were 8.54, 7.01, 3.74, 8.09, and 3.86 Gy (854, 701, 374, 809, and 386 rads), respectively.

Blumenthal et al. (16) evaluated the targeting of $^{131}$I-NP-4 F(ab´)$_2$ to micrometastases in a micrometastatic lung model. Intravenous injection of GW-39 tumor cells into nude mice resulted in 40-80 tumor nodules (50-200 μm in diameter within 7 days) throughout the lungs. Each mouse received 370 kBq (10 μCi)/6 μg of MAb. The radioactivities (% ID/g; $n$ = 5) at 24 h for the lung tumor nodules, s.c. tumor, and blood were 2.3 ± 0.5, 6.3 ± 0.7, and 3.8 ± 0.7, respectively. On the basis of a highest possible dose resulting in no animal death (maximum tolerated dose) of 44.4 MBq (1.2 mCi), the radiation absorbed doses were 5.5 (lung tumor nodules), 22.57 (s.c. tumor), and 8.95 Gy (blood) (550, 2,257, and 895 rads, respectively). Fand et al. (17) also studied tumor metastases in the lung and liver, using whole-body macroautoradiography. Each mouse received 555 kBq (15 μCi) of $^{125}$I-NP-4 F(ab´)$_2$. The densitometrically derived tumor/nontumor ratios on day 1 for the metastatic lung tumor were 1.9 (tumor/blood), 4.3 (tumor/liver), 2.8 (tumor/kidney), and 2.8 (tumor/lung). On day 3, all of these ratios were 11. For the metastatic liver tumor on day 1, the ratios were 6.3 (tumor/blood), 14.3 (tumor/liver), 9.5 (tumor/kidney), and 9.5 (tumor/lung), and all of these ratios increased to 57 on day 3.

## Other Non-Primate Mammals

[PubMed]

Sharkey et al. (10) studied the biodistribution of $^{131}$I-NP-4 F(ab´)$_2$ and intact $^{131}$I-NP-4 in hamsters bearing the human colorectal carcinoma GW-39 in the hind leg muscle. Each tumor-bearing hamster received intracardiac injections containing 5,550-7,400 kBq (150-200 μCi)/10-15 μg of $^{131}$I-NP-4 F(ab´)$_2$ or $^{131}$I-NP-4. Both $^{131}$I-NP-4 F(ab´)$_2$ and $^{131}$I-NP-4 showed a preferential localization for GW-39. $^{131}$I-NP-4 F(ab´)$_2$ was cleared from the blood and normal tissues more rapidly than the intact $^{131}$I-NP-4. By day 3, there was 2.5 times less radioactivity in the tumor with $^{131}$I-NP-4 F(ab´)$_2$ compared with the intact $^{131}$I-NP-4. In the blood, there was 4 times less radioactivity with $^{131}$I-NP-4 F(ab´)$_2$ compared with $^{131}$I-NP-4.

Blumenthal et al. (13) evaluated the *in vivo* uptake, therapeutic potential, and host toxicity of $^{131}I$-NP-4 F(ab´)$_2$ in GW-39 tumors grown in hamster check pouches. The animals received i.p. injections containing 3.7 MBq (0.1 mCi)/6 μg (MAb) of either $^{131}I$-NP-4 F(ab´)$_2$ or $^{131}I$-NP-4. The tumor radioactivity concentrations (% ID/g; $n$ = 10-18) for $^{131}I$-NP-4 F(ab´)$_2$ on days 1 and 2 were 0.92 ± 0.44 and 1.24 ± 0.46, respectively. The tumor radioactivity concentrations (% ID/g; $n$ = 10-21) for $^{131}I$-NP-4 on days 1 and 3 were 1.20 ± 2.1 and 5.57 ± 0.56, respectively. The radioactivity concentrations (% ID/g; $n$ = 5-9) on day 1 for $^{131}I$-NP-4 F(ab´)$_2$ were 0.99 ± 0.23 (blood), 0.51 ± 0.22 (lungs), 0.53 ± 0.18 (kidney), 0.28 ± 0.13 (spleen), and 0.27 ± 0.09 (liver). On day 3, these values decreased to 0.11 ± 0.04 (blood), 0.05 ± 0.02 (lungs), 0.07 ± 0.02 (kidney), 0.03 ± 0.01 (spleen), and 0.03 ± 0.01 (liver). For $^{131}I$-NP-4, the % ID/g values in the same organs on day 1 were 2.48 ± 0.09 (blood), 1.05 ± 0.06 (lungs), 0.82 ± 0.1 (kidney), 0.66 ± 0.03 (spleen), and 0.83 ± 0.02 (liver), On day 3, these values decreased to 1.34 ± 0.12 (blood), 0.79 ± 0.09 (lungs), 0.58 ± 0.06 (kidney), 0.36 ± 0.03 (spleen), and 0.47 ± 0.03 (kidney), The $^{131}I$-NP-4 F(ab´)$_2$ cumulative absorbed doses were 0.11 (tumor), 0.014 (liver), 0.01 (spleen), 0.02 (kidney), and 0.018 (lung) Gy/MBq (420, 52, 36, 77, and 68 rads/mCi, respectively).

## Non-Human Primates

PubMed]

No publication is currently available.

# Human Studies

[PubMed]

Murray et al. (18) conducted a tumor localization study of $^{131}I$-NP-4 F(ab´)$_2$ in 5 patients with either liver metastases from colorectal cancer or intact primary tumors. Patients received both $^{131}I$-NP-4 F(ab´)$_2$ (1 mg of F(ab´)$_2$ labeled with 10 mCi of $^{131}I$) and intact $^{125}I$-NP-4 MAb (1 mg of NP-4 labeled with 2 mCi of $^{125}I$) in a mixture. Gamma imaging and autoradiography of tissues from biopsies were used to determine radioactivity localization. For $^{131}I$-NP-4 F(ab´)$_2$, the pharmacokinetic parameters plasma half-life ($t_{½}$), volume of distribution, plasma clearance, and 48-h urinary excretion were 29.0 ± 3.2 h, 3.8 ± 0.4 liters, 1.5 ± 0.2 ml/kg/min, and 50.2 ± 5.0%, respectively. For $^{125}I$-NP-4 MAb, these parameters were 43.2 ± 7.3 h, 3.3 ± 0.2 liters, 0.9 ± 0.2 ml/kg/min, and 56.7 ± 4.7%, respectively. The tumor radioactivity uptakes (% ID/kg) of $^{131}I$-NP-4 F(ab´)$_2$ and $^{125}I$-NP-4 MAb were 2.0 ± 0.57 and 2.6 ± 0.94, respectively. The $^{131}I$-NP-4 F(ab´)$_2$ tumor/normal tissue ratios were 6.0 ± 2.1 (tumor/liver), 0.83 ± 0.21 (tumor/blood), and 7.6 ± 2.3 (tumor/other tissue). For $^{125}I$-NP-4 MAb, these ratios were 3.1 ± 0.61 (tumor/liver), 0.88 ± 0.21 (tumor/blood), and 7.3 ± 3.5 (tumor/other tissue).

Juweid et al. (15) studied the feasibility of $^{131}I$-NP-4 F(ab´)$_2$ for use in therapy in 13 cancer patients (8 colorectal, 3 lung, 1 pancreatic, and 1 medullary thyroid cancer). The mean plasma CEA level was 120 ng/ml with 11 patients having ≤100 ng/ml. The

radioactivity dose was based on a prescribed red marrow dose, which was determined by a tracer study dose, of 370-555 MBq (10-15 mCi). The average blood and total-body $t_{½}$ values in the 12 patients with a human anti-mouse antibody (HAMA) level <100 ng/ml were 15.3 ± 4.7 and 49.5 ± 13.1 h, respectively. Dosimetry studies showed that the absorbed doses (cGy/mCi) were 0.5 ± 0.1 (whole body), 1.8 ± 0.4 (red marrow), 3.3 ± 1.9 (kidneys), 1.6 ± 0.7 (liver), 2.1 ± 0.6 (lung), and 4.4 ± 2.7 (spleen).

Goldenberg et al. (14) evaluated colorectal cancer imaging with $^{123}$I-NP-4 F(ab´)$_2$ in a prospective, randomized multicenter study of 58 patients. Patients received doses of 296-370 MBq (8-10 mCi) in1 or 10 mg of either $^{123}$I-NP-4 F(ab´)$_2$ or $^{123}$I-NP-4 Fab´. Imaging was performed at 2-4, 24, and 48 h after antibody administration. Of the 58 patients, 17 received 1 mg and 14 received 10 mg of $^{123}$I-NP-4 F(ab´)$_2$. For $^{123}$I-NP-4 Fab ´, 12 patients received 1 mg and 15 patients received 10 mg. The median biological blood $t_{½\alpha}$ and $t_{½\beta}$ values for $^{123}$I-NP-4 F(ab´)$_2$ were 1.6 and 26 h, respectively. For $^{123}$I-NP-4 Fab´, these values were 2.4 and 19 h, respectively. No difference was observed between the imaging results of the 4 groups. No dose dependence for the antibody targeting was found. There appeared to be no correlation between sensitivity and size of lesions or serum CEA level. Single-photon emission computed tomography (SPECT) evaluation was judged to be more beneficial than planar imaging in 47% of the cases. Sensitivity, specificity, and accuracy for all regions and all four arms of the studies were 86, 89, and 89%, respectively. The positive predictive value by tumor lesions was 91%. Only one patient developed a low level of HAMA.

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