



Carcinoma Cell Detection Kit

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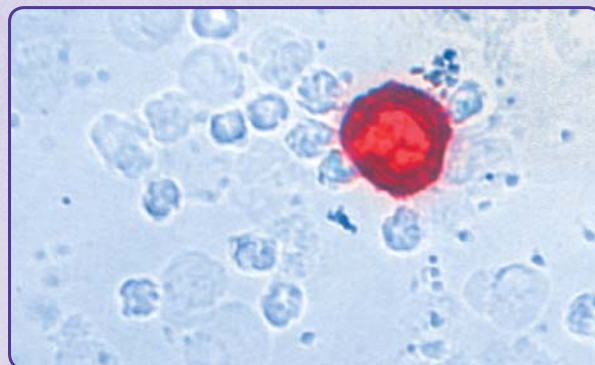
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Carcinoma Cell Detection Kit human

For 100 tests with 10⁶ cells

Order no. 130-090-463



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1. Description

1.1 Background and product applications

The Carcinoma Cell Detection Kit has been developed for highly specific immunocytochemical detection of epithelium-derived tumor cells in a preparation of mononuclear cells (MNCs) from human blood or bone marrow. Disseminated tumor cells are detected according to their expression of epithelium-specific antigens, e.g. cytokeratins, in a non-epithelial environment, e.g. peripheral blood or bone marrow.

Cytokeratins are typical intermediate filaments of the cytoskeleton of epithelial cells.^{1,2} Most malignant cells which have their origin in epithelial tissue express cytokeratins and can be recognized by an anti-cytokeratin antibody.

The Carcinoma Cell Detection Kit can also be used for the detection of epithelial tumor cells in blood or bone marrow after their magnetic enrichment.

Examples of applications

- Detection of circulating epithelial tumor cells.

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1.2 Principle of detection

For immunocytochemical staining, cells are spun onto a microscopic slide using a cytocentrifuge. The cytocentrifuged cells are fixed, permeabilized and subjected to intracellular staining, using a cocktail of two cytokeratin-specific antibodies conjugated to alkaline phosphatase and a substrate which forms a red precipitate. Cytokeratin⁺ cells are specifically labeled with the enzyme-conjugated antibodies and can be identified by their red, cytoplasmic staining.

1.3 Kit size and storage

Kit size	100 tests
Test size	One test corresponds to the analysis of 1×10 ⁶ MNCs
Storage	Store reagents protected from light at 4–8 °C. Do not freeze. The expiration date is indicated on the vial and box label.

1.4 Kit components

250 µL Anti-Cytokeratin-Alkaline-Phosphatase

Cocktail of monoclonal antibodies CK3-3E4 (isotype: mouse IgG2a) and CK-11D5 (isotype: mouse IgG1) conjugated to alkaline phosphatase supplied in a solution containing 50% glycerine and 0.05% sodium azide.

250 µL Control Reagent

Cocktail of monoclonal antibodies (isotype: mouse IgG2a and mouse IgG1) conjugated to alkaline phosphatase supplied in a solution containing 50% glycerine and 0.05% sodium azide.

30 mL Fixation Reagent

1.85% formaldehyde in PBS (phosphate buffered saline) (EU Hazard Classification: Xn harmful R40/20/21/22-43).

25 mL Permeabilisation Reagent

PBS containing 0.5% BSA, 0.25% Casein and detergent.

25 Substrate tablets

SIGMA FAST™ Fast Red TR/Naphthol AS-MX substrate tablets and 25 Tris/HCl tablets.

1.5 Description of kit components

Anti-Cytokeratin-Alkaline Phosphatase

The Anti-Cytokeratin-Alkaline Phosphatase cocktail is a pre-mixed cocktail of two cytokeratin-specific antibodies CK3-11D5 and CK3-3E4, which are directly conjugated to alkaline phosphatase. CK3-11D5 is a multicytokeratin-specific antibody and recognizes cytokeratins 7, 8, 18 and possibly 19. It crossblocks Cam5.2, an antibody known to be specific for cytokeratin 7 and 8. CK3E4 binds specifically to cytokeratin 8. It almost completely crossblocks A45B/B3, an antibody known to recognize cytokeratin heterodimers 8/18 and 8/19.

Components of the Anti-Cytokeratin-Alkaline Phosphatase

Antibody	Specificity	Crossblocks
CK3-11D5	7, 8, 18, (19)	Cam5.2
CK3-3E4	8	A45B/B3

Control Reagent

The Control Reagent contains monoclonal antibodies which match the isotype of the anti-cytokeratin-specific antibodies in the Anti-Cytokeratin-Alkaline Phosphatase, but have irrelevant specificities (isotype control). Thereby non-specific cell staining, e.g. via Fc receptors is determined. For reliable analysis of epithelium-derived tumor cells, an isotype control should always be included in the analysis.

Fixation Reagent

By addition of the Fixation Reagent, cells are fixed in a final concentration of 1.85% formaldehyde. Formaldehyde conserves the cell structure and intracellular antigenicity by cross-linking protein amino groups without considerable changes in the cell morphology.

Permeabilisation Reagent

The Permeabilisation Reagent, a mild non-ionic detergent, is used to permeabilize the cells for intracellular staining. It also serves as antibody diluent. The reagent formulation is optimized to reduce non-specific staining.

▲ **Note:** Cell permeabilisation is a reversible process. It is important to keep the cells in the presence of the Permeabilisation Reagent during intracellular staining.

Substrate tablets

The substrate Naphthol AS-MX-Phosphate, dissolved in tris buffer, is hydrolyzed and further reacts with the colorless chromogen Fast Red TR to form an intense red precipitate in the presence of alkaline phosphatase.

▲ **Note:** The reaction product is soluble in alcoholic and organic solvents. Use aqueous-based counterstain solution and mounting medium.

1.6 Starting material

The assay is designed for the analysis of mononuclear cells isolated from peripheral blood, buffy coat, or bone marrow by density gradient centrifugation. For best results use blood within 8 hours after collection.

Peripheral blood Peripheral blood has to be supplemented with an anticoagulant e.g. EDTA, heparin, citrate, acid citrate dextrose acid (ACD-A) or citrate phosphate dextrose (CPD). Whole blood should be stored at room temperature until analysis.

Bone marrow Bone marrow has to be supplemented with an anticoagulant e.g. EDTA, heparin, citrate, acid citrate dextrose (ACD) or citrate phosphate dextrose (CPD). Bone marrow should be stored at 4 °C until analysis.

1.7 Additional reagent and instrument requirements

- Buffer (degassed): Prepare a solution containing PBS (phosphate buffered saline) pH 7.2, 0.5% BSA and 2 mM EDTA by diluting MACS BSA Stock Solution (# 130-091-376) 1:20 with autoMACS™ Rinsing Solution (# 130-091-222). Keep buffer cold (4–8 °C).
- PBS (phosphate buffered saline) pH 7.2
- Deionized water
- Tubes
- Staining jars, type Hellendahl
- Incubation chamber
- Micropipettes with tips
- Vortex mixer
- Liquid repellent pen, e.g. Dako Pen, DakoCytomation, Hamburg, Germany
- Cytospin centrifuge, e.g. Hettich, Tuttlingen, Germany
- Silane coated slides, e.g. Histobond® Marienfeld, Bad Mergentheim, Germany
- Coverslips
- (Optional) Mayer's hemalum solution Merck, Darmstadt, Germany
- (Optional) 100 mM Tris/HCl, pH 8.2, Merck, Darmstadt, Germany

- Mounting medium, e.g. Faramount Aqueous Mounting Medium, DakoCytomation, Hamburg, Germany

For the preparation of mononuclear cells

- PBS containing anticoagulant, e.g. 2 mM EDTA or 0.6% ACD-A
- Ficoll-Paque™ (1.077 density), e.g. GE Healthcare companies
- Conical test tubes, 50 mL, e.g. Falcon tubes, BD Biosciences, Bedford, USA
- Pipettes
- Centrifuge with swinging bucket rotor

For the isolation of cells from bone marrow

- PBS containing anticoagulant, e.g. 2 mM EDTA, 0.6% ACD-A or 200 U/mL heparin
- RPMI 1640 (# 130-091-440) containing 0.02% collagenase B and 100 U/mL DNase
- Ficoll-Paque™ (1.077 density), e.g. GE Healthcare companies
- Conical test tubes, 50 mL, e.g. Falcon tubes, BD Biosciences, Bedford, USA
- Pipettes
- Centrifuge with swinging bucket rotor

2. Protocol overview

1. Preparation of the slides

Cytospin $0.5-1 \times 10^6$ cells onto a slide and create a hydrophobic barrier around the cell spot



2. Fixation of the cells



3. Intracellular staining of the cytokeratin-positive cells with Anti-Cytokeratin-Alkaline Phosphatase



4. Substrate incubation



5. (Optional) Counterstaining and mounting

6. Microscopic evaluation of stained slides

3. Experimental set-up

3.1 Controls

Negative reagent control

For reliable detection of epithelial tumor cells, a negative control reagent sample per patient sample should always be included. This sample should show absence of specific staining. The negative control reagent sample slide will help to evaluate non-specific staining e.g. of hematopoietic cells. The negative control reagent sample slides should be treated exactly the same as the test samples slides except for the Anti-Cytokeratin-Alkaline Phosphatase which is replaced by the Control Reagent.

Batch controls

A. Positive sample control

When setting up a new experiment, it is recommended to include a positive control cell sample. This positive control slide helps to assure the correct performance of sample preparation and staining. A sample of peripheral blood mononuclear cells (PBMCs) spiked with cells of an epithelial tumor cell line, e.g. SK-BR-3, MCF-7, as positive control cell sample, may be included in the experiment.

B. Negative sample control

To evaluate specific background staining, e.g. antibody cross-reactivity with non-epithelial cells, a negative control cell sample should be included. This sample should show absence of specific staining. As a negative control cell sample, PBMCs of a normal donor may be included in the experiment.

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3.2 Counterstaining of carcinoma cells

For additional cytomorphological investigation of the stained cells, slides can be stained with, e.g. Mayer's hemalum solution. Using Mayer's hemalum solution, nuclei are selectively stained blue, dark violet or black.

3.3 Detection with prior magnetic enrichment

(Optional, reagents not included) If the frequency of tumor cells is less than 10^6 or if larger volumes are screened, magnetic cell enrichment can be performed in order to increase the sensitivity of detection. Tumor cells can be enriched by using the Carcinoma Cell Enrichment Kit (# 130-060-101), the CD326 (EpCAM) MicroBeads (# 130-061-101) or the Anti-ErbB-2 MicroBeads (# 130-090-482). Negative cell enrichment by depletion of leukocytes can be performed using the CD45 MicroBeads (130-045-801). Detailed protocols are included in the data sheets of the respective products and are available from our website www.miltenyibiotec.com/protocols.



4. Protocol

4.1 Sample preparation

When working with anticoagulated peripheral blood or buffy coat, PBMCs should be isolated by density gradient centrifugation.

Preparation of peripheral blood mononuclear cells

▲ The peripheral blood or buffy coat should not be older than 8 hours and supplemented with anticoagulants.

1. Start with fresh human blood treated with an anticoagulant, e.g. EDTA, heparin, citrate, ACD-A or citrate phosphate dextrose (CPD), or leukocyte-rich buffy coat not older than 8 hours.
2. Dilute cells with 2–4 volumes of PBS containing 2 mM EDTA or 0.6% ACD-A.
 - ▲ Note: The more diluted the blood sample, the better the purity of the mononuclear cells.
3. Carefully layer 35 mL of diluted cell suspension over 15 mL Ficoll-Paque in a 50 mL conical tube and centrifuge at $400\times g$ for 30–40 minutes at 20°C in a swinging bucket rotor without brake.
4. Aspirate the upper layer leaving the mononuclear cell layer undisturbed at the interphase.
5. Carefully transfer the interphase cells (lymphocytes and monocytes) to a new 50 mL conical tube.
6. Fill the conical tube with PBS containing 2 mM EDTA or 0.6% ACD-A, mix and centrifuge at $300\times g$ for 10 minutes at 20°C . Carefully remove the supernatant completely.

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7. Resuspend cell pellet in PBS at a final volume of 1 mL of buffer per 1×10^6 total cells. For fewer than 1×10^6 total cells, use 1 mL. Proceed to immunocytochemical staining (4.3).

▲ Note: PBMCs may be stored in the refrigerator overnight in PBS containing 0.5% BSA supplemented with autologous serum after the last washing step.

Preparation of bone marrow cells

1. Collect bone marrow in 50 mL tubes containing 5 mL PBS supplemented with 2 mM EDTA or 0.6% ACD-A or 200 U/mL heparin. Store at 4°C if the cells cannot be processed immediately.
2. For release of the cells, dilute sample in 10-fold excess of RPMI 1640 containing 0.02% collagenase B and 100 U/mL DNase and shake gently at room temperature for 45 minutes.
3. Pass cells through $30\ \mu\text{m}$ nylon mesh (Pre-Separation Filters # 130-041-407). Wet filter with buffer before use.
4. Carefully layer 35 mL of diluted cell suspension over 15 mL of Ficoll-Paque in a 50 mL conical tube and centrifuge for 35 minutes at $400\times g$ at 20°C in a swinging bucket rotor without brake.
5. Aspirate the upper layer leaving the mononuclear cell layer undisturbed at the interphase.
6. Carefully transfer the interphase cells (lymphocytes and monocytes) to a new 50 mL conical tube.



- Fill the conical tube with PBS containing 2 mM EDTA or 0.6% ACD-A, mix and centrifuge at 300×g for 10 minutes at 20 °C. Carefully remove the supernatant completely.
- Resuspend cell pellet in PBS at a final volume of 1 mL of buffer per 1×10⁶ total cells. For fewer than 1×10⁶ total cells, use 1 mL. Proceed to immunocytochemical staining (4.3).
 - ▲ **Note:** BMMCs may be stored in the refrigerator overnight in PBS containing 0.5% BSA supplemented with autologous serum after the last washing step.

4.2 Preparation of working solutions

Anti-Cytokeratin-Alkaline Phosphatase

Dilute the Anti-Cytokeratin-Alkaline Phosphatase 1:100 with Permeabilisation Reagent. Prepare 250 µL of diluted antibody solution per spot.

Control Reagent

Dilute the Control Reagent 1:100 with Permeabilisation Reagent. Prepare 250 µL of diluted antibody solution per spot.

Fast Red TR/Naphthol AS-MX substrate solution

Dissolve 1 Tris/HCl tablet in 1 mL of double distilled water. Add 1 tablet of Fast Red TR/Naphthol AS-MX substrate tablets to this solution and mix by using a Vortex mixer until tablet is dissolved completely.

▲ **Note:** Prepare immediately before use.

(Optional) Mayer's hemalum solution

Dilute Mayer's hemalum solution 1:2 in 100 mM Tris/HCl, pH 8.2 and filter the diluted hemalum solution.

4.3 Immunocytochemical staining

The volumes indicated in this protocol are appropriate for cell spots on a cytoentrifuge slide of 1.75 cm (0.69 in) in diameter or 240 mm² (0.95 in²) (0.5–1×10⁶ mononuclear cells per spot). If the spots differ in size adjust the volumes accordingly.



- Transfer 0.5–1×10⁶ mononuclear cells resuspended in PBS onto silanised slides using a cytoentrifuge. Air-dry slides for 2–18 hours at room temperature. Alternatively dry for 30 minutes at 37 °C.



Slides should be completely dry. Otherwise cells may be washed off during staining procedure.

▲ **Note:** Segregate negative sample controls (see 2. Experimental set-up) from sample slides.

▲ **Note:** If using cells of a tumor cell line as positive sample control (see 2. Experimental set-up) transfer a maximum number of 1×10⁵ tumor cells onto the slides using a cytoentrifuge.



- Using a liquid repellent pen (e.g. DAKO Pen) apply a hydrophobic line around the cell spot on the slides. Allow the barrier to dry for one minute at room temperature. Label slides using a permanent marker.



- Apply 300 µL of the Fixation Reagent to the cell spot of all slides and allow the cells to fix for 10 minutes at room temperature.

▲ **Note:** Make sure that the cell spots are completely covered with Fixation Reagent. Avoid drying of the cell spot.



- To remove excess of Fixation Reagent, carefully tap the end of the slides vertically on a paper towel and let the supernatant drain off. Carefully wipe off remaining solution outside the cell spot using a paper towel.

▲ **Note:** The Fixation Reagent contains formaldehyde and should be disposed of properly.



- Wash slides 3× for 5 minutes in PBS in a staining jar.

▲ **Note:** To avoid cross-contamination of slides change PBS after each washing step.

- Position slides in an incubation chamber.

▲ **Note:** Remove one slide at a time from the staining jar.



- Apply 250 µL of the prediluted Anti-Cytokeratin-Alkaline-Phosphatase to the cell spots on the sample slides (see 4.2 Preparation of working solutions).



- Apply 250 µL of the prediluted Control Reagent to the cell spots on the negative control reagent sample slides (see 4.2 Preparation of working solutions).

▲ **Note:** Make sure that the cell spots are completely covered with antibody solution. Avoid drying of the cell spot.

- Incubate both, control and test samples, in a moist chamber for 45 minutes at room temperature.



- To remove excess of antibody solution, carefully tap the end of the slides vertically on a paper towel and let the supernatant drain off. Carefully wipe off remaining solution outside the cell spot using a paper towel.



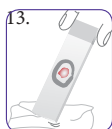
- Wash slides 3× for 5 minutes in PBS in a staining jar.

▲ **Note:** To avoid cross-contamination of slides change PBS after each washing step.



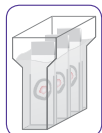
- Add 250 µL of freshly prepared Fast Red TR/Napthol AS-MX substrate solution (see 4.2 Preparation of working solutions) to the cell spots of all slides and incubate for 15 minutes at room temperature.

▲ **Note:** Make sure that the cell spots are completely covered with substrate solution. Avoid drying of the cell spot.



13. To remove excess of substrate solution, carefully tap the end of the slides vertically on a paper towel and let the supernatant drain off. Carefully wipe off remaining solution outside the cell spot using a paper towel.

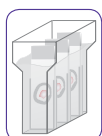
▲ **Note:** The substrate waste should be disposed of properly.



14. Wash slides for 5 minutes in double-distilled water in a staining jar.



15. (Optional) To counterstain cell nuclei incubate slides for 1 minute in filtered Mayer's hemalum solution in a staining jar.



16. To permanently blue the cells, wash slides for 2 minutes in tap water in a staining jar. Subsequently wash slides for 5 minutes in double distilled water in a staining jar.



17. (Optional) Remove slides from staining jar, and mount with aqueous-based mounting medium. Apply coverslip.

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5. Evaluation of stained slides

▲ Stained slides are examined by manual or automated light microscopy.

▲ Slides should be screened at 10× magnification for stained cells.

▲ Staining should be confirmed at 40× magnification.

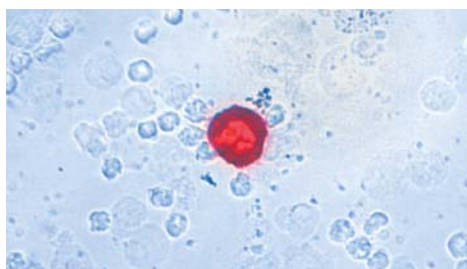
▲ Examination of the positive sample control should reveal intense red, cytoplasmic staining. No staining in the positive sample control indicates improper performance of prepared tissue or staining reagents.

▲ Examination of the negative sample control and negative reagent control should show absence of staining. Staining in the negative sample control or negative reagent control indicates antibody cross-reactivity to cells or cellular components.

▲ Positive staining or absence of staining in the patient samples should be assessed with regard to non-specific background staining in the negative sample control.

▲ **Note:** Stained slides can be stored in a dark and dry place at room temperature for several years.

6. Example of using the Carcinoma Cell Detection Kit for immunocytochemical staining of epithelial tumor cells



Cells of the tumor cell line SK-BR-3 spiked into PBMCs. Cell mixture was transferred to a slide by cytocentrifugation and stained using the Carcinoma Cell Detection Kit.

7. References

1. Kasper, M; Stosiek, P; Typlt, H; Karsten, U (1987) Eur. J. Cancer Clin. Oncol. 23:137-147.
2. Makin, C; Bobrow, L; Budmer, W (1984) Monoclonal antibody to cytokeratin for use in routine histopathology. J. Clin. Pathol. 37:975.

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8. Troubleshooting

No staining of any slides; neither controls nor test samples

- Reagents omitted or reagents not used according to protocol. Refer to 4.3 Immunocytochemical staining of carcinoma cells.
- Inappropriate dilution of staining reagent. Staining reagent diluted with inappropriate buffer. Refer to 4.2 Preparation of working solution.
- Inappropriate incubation time or temperature. Refer to 4.3 Immunocytochemical staining of carcinoma cells.
- Substrate solution was not prepared accordingly. Refer to 4.2 Preparation of working solution.
- Usage of alcohol-based counterstain and/or mounting medium, which would dissolve the red-colored product.
- Cell spot on the slides dried during staining procedure.

Weak specific staining of positive controls and samples

- Reagents not used according to protocol. Refer to 4.3 Immunocytochemical staining of carcinoma cells.
- One or more staining reagents may have expired. Check expiration date of the staining reagents.
- Check fixation time. Increased fixation time may mask the antigen.
- Too much liquid remained on the cell spot after removal from the staining jar. This may result in higher antibody dilution.

- Check incubation times. Shorter incubation time may lead to decreased staining intensity.
- Do not store the cells/slides for longer than 2 days between adding the antibodies and adding the substrate.
- Check if substrate solution was freshly prepared.
- Check incubation time with substrate and prolong by 5 to 10 minutes if appropriate.
- Check staining time of Mayer's hemalum solution and reduce if appropriate.

Non-specific staining of all slides

- Check substrate incubation times and temperature.
- Substrate solution was not prepared accordingly.
- Slides were not rinsed sufficiently.

Low recovery of tumor cells

- Do not use BSA containing buffer for cytocentrifugation.
- Use slides pre-coated with adherence factors.
- Let cells dry for at least 2 hours (best overnight) after cytocentrifugation.

Bad morphology of the cells

- Make sure that permeabilization time (exactly 5 minutes) is not exceeded.

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Warnings

Reagents contain sodium azide. Under acidic conditions sodium azide yields hydrazoic acid, which is extremely toxic. Azide compounds should be diluted with running water before discarded. These precautions are recommended to avoid deposits in plumbing where explosive conditions may develop.

MACS Fixation Reagent contains formaldehyde, which is classified as Xn harmful, R 40/20/21/22-43 according to EU Hazard Classification, EC Directive 91/155/EC. SIGMA FAST™ Fast Red TR/Naphthol AS-MX substrate tablets are classified Xn harmful, R 20/21/22-40-43, S 26-36/37/39 according to EU Hazard Classification, EC Directive 91/155/EC.

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