

MedixMAB™  
**TUMOR  
MARKERS**

# Technical Note

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# Introduction

Tumor markers are a diverse group of proteins and other molecules that are secreted by cancer cells, or normal cells, in response to tumors and related conditions. Most tumor markers are also produced under noncancerous circumstances; their expression, however, is upregulated during cancer. Determining the presence and concentration of tumor markers in bodily fluids thus supports early tumor detection and can aid treatment follow-up and efficient choice of therapy. Improved cancer management will become increasingly important in the future, as patients continue to live longer and cancers become more and more prevalent.

Various tumor markers are currently used in clinical practice to monitor treatment success, characterize disease, as well as to support cancer diagnosis and detection. An elevated tumor marker level can also result from benign conditions. On the other hand, cancer can be present in the absence of typical tumor markers. In practice, tumor marker immunoassays are therefore often combined with other tests to ensure reliable results. For example, immunoassays for human prostate-specific antigen (PSA) are commonly used to evaluate the pathological grade of prostate cancer and to aid early prostate cancer detection. As PSA overexpression is also related to some noncancerous conditions, measurements for both the total PSA concentration and the free form of PSA are often combined to improve cancer-specificity. Another example is carcinoembryonic antigen (CEA). Immunoassay can be a useful tool in predicting the therapeutic effect, progression, and prognosis of the several cancers.

Medix Biochemica has more than three decades of experience in producing premium-quality monoclonal antibodies for tumor marker detection. The company's optimized, industrial-scale *in vitro* production methods, certified batch-to-batch consistency, and expert customer service have made Medix Biochemica one the most important antibody suppliers for the IVD community.

# CA15-3

Cancer antigen 15-3 (CA15-3), produced by the *mucin 1* gene, is a well-characterized serum marker for breast cancer.<sup>1-3</sup> Originally, CA15-3 was defined as part of the mucin 1 (MUC-1) glycoprotein detected with two antibodies, one recognizing a tandem repeat in the peptide core and the other a carbohydrate epitope. Later, antibodies against various parts of CA15-3 have been developed.<sup>4,5</sup>

The primary clinical use of CA15-3 immunoassays is breast cancer follow-up. CA15-3 is known to be an independent prognostic serum marker for the disease, and it is routinely used for monitoring treatment responses and postoperative

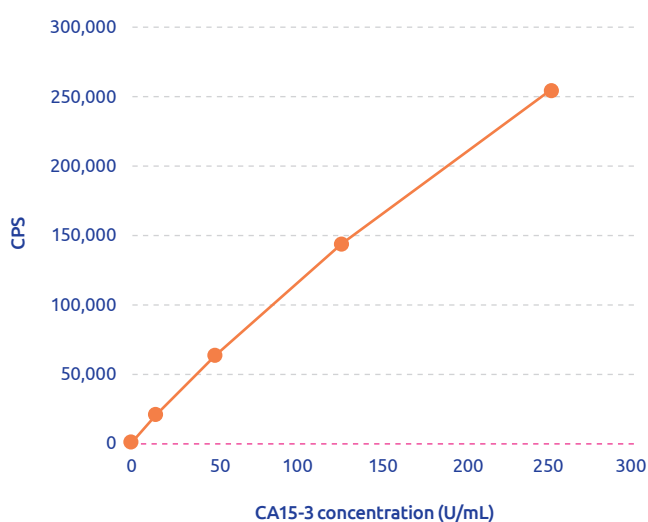
disease recurrence. Identifying an increase in the level of CA15-3 can be used to detect metastatic disease in approximately 70 percent of asymptomatic patients. In addition to breast cancer, elevated CA15-3 levels have also been detected in some other carcinomas, including ovarian cancer.<sup>3,6,7</sup>

Medix Biochemica offers four monoclonal antibodies (4404, 4403, 4402, and 4401) for the detection of human CA15-3. These antibodies recognize the tandem repeat APDTRPAPGSTAPPAHGVTs of the MUC-1 core protein of CA15-3.

## Anti-human CA15-3 monoclonal antibodies

CA15-3 antibody	Product code	Concentration (mg/mL)	Shelf life (months at +2–8°C)	Subclass	Applications tested
4401	100591	5	N/D	IgG <sub>1</sub> , λ light chain	ELISA
4402	100595	5	N/D	IgG <sub>1</sub> , λ light chain	ELISA
4403	100583	5	N/D	IgG <sub>1</sub> , λ light chain	ELISA
4404	100584	5	24	IgG <sub>1</sub> , λ light chain	ELISA

## CA15-3 standard curve



Capture: **4404**  
 Detection: **Commercial CA15-3 carbohydrate-specific mAb (Ma695, Fujirebio Diagnostics)**

## Control levels

Sample	CA15-3 level (U/mL)	
	FIA with antibody 4404	Reported level in the control
CA15-3 Ctrl Level 1	30	21–39
CA15-3 Ctrl Level 2	87	72–108

(Tumor Marker Controls: Fujirebio Diagnostics)

# CA125

Cancer antigen 125 (CA125) is a peptide epitope produced by the *mu*cin 16 (MUC16) gene. CA125 was among the first tumor biomarkers discovered, defined by the binding of murine monoclonal antibody OC125.<sup>12</sup> Other CA125 antibodies have subsequently been developed, and they are classified as OC125-like (group A), M11-like (group B), or OV197 (C).<sup>55</sup> Epithelial cells in the respiratory tract, female reproductive tract, and cornea express CA125 on their membranes, from where it can be cleaved and released.<sup>13-15</sup>

CA125 is the most widely used serum biomarker to monitor epithelial ovarian cancer; it is overexpressed in 80 percent of

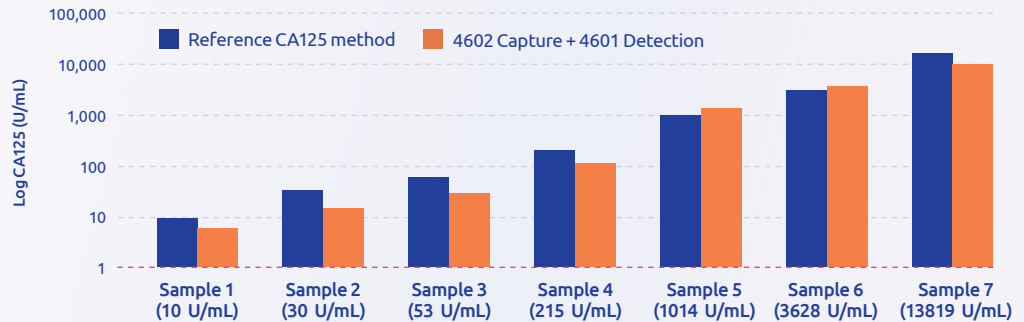
all disease cases, and in 90 percent of patients who have stage III/IV disease. Currently, CA125 is used to monitor ovarian cancer treatment and detect residual or recurrent disease, as well as for the differential diagnosis of pelvic masses. To improve specificity and sensitivity, assays for CA125 and HE4 (another marker for ovarian cancer) are often combined.<sup>13-18</sup>

Medix Biochemica offers two monoclonal antibodies (4601 and 4602) for the detection of CA125. Based on their specificities, antibody 4601 is OC125-like and 4602 M11-like.

## Anti-human CA125 monoclonal antibodies

CA125 antibody	Product code	Concentration (mg/mL)	Shelf life (months at +2-8°C)	Subclass
4601	100598	5	12	IgG <sub>1</sub>
4602	100628	5	12	IgG <sub>1</sub>

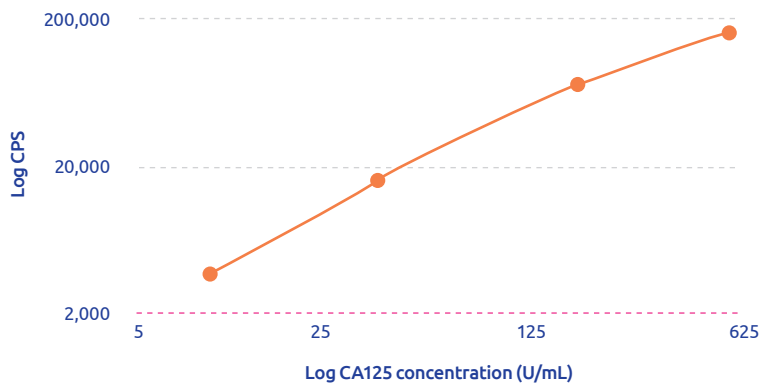
## Comparison to reference CA125 method



## CA125 standard curve

Capture: 4602  
Detection: 4601

Normal values in serum are less than 35 U/mL.





# CA19-9

Carbohydrate antigen 19-9 (CA19-9) assays detect proteins containing a specific carbohydrate epitope, the so-called sialylated Lewis-a pentasaccharide also known as sLea antigen. This epitope is found on several glycoproteins, including MUC-1.<sup>8,9</sup>

In healthy individuals, the serum concentration of CA19-9 is low, but it increases during gastrointestinal malignancy, including pancreatic cancer, pancreatic or hepatobiliary adenocarcinoma, or colon cancer. CA19-9 has been verified to be an independent prognostic factor for advanced pancreatic adenocarcinoma, and it provides a tool for pancreatic and gastrointestinal cancer monitoring.

To date, CA19-9 is the only FDA-approved biomarker for early detection and establishing a prognosis of pancreatic cancer. However, benign conditions, such as pancreatitis, can also lead to increased serum CA19-9 concentrations. On the other hand, up to 10 percent of population is not able to produce CA19-9 at all. To improve specificity and sensitivity, CA19-9 immunoassay is often combined with determination of carcinoembryonic antigen (CEA).<sup>7,8,10,11</sup>

Medix Biochemica offers a monoclonal antibody (4701) for the detection of human CA19-9. Immunoassays for CA19-9 typically utilize the same CA19-9 monoclonal antibody for both capturing and detecting the antigen.

## Anti-human CA19-9 monoclonal antibody

CA19-9 antibody	Product code	Concentration (mg/mL)	Shelf life (months at +2–8°C)	Subclass	Applications tested
4701	100609	5	18	IgG <sub>3</sub>	ELISA

## Specificity

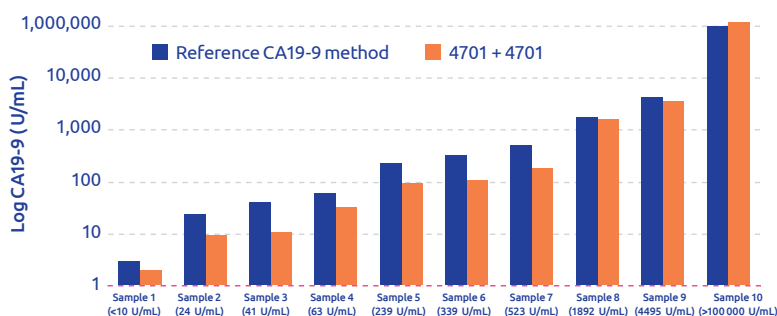
Specificity of CA19-9 antibody 4701 against selected Lewis antigens. The antibody demonstrates similar specificity as the antibody 1116-NS-19-9 which was originally used to define the CA19-9 antigen.

\*Based on Consortium for Functional Glycomics Nomenclature

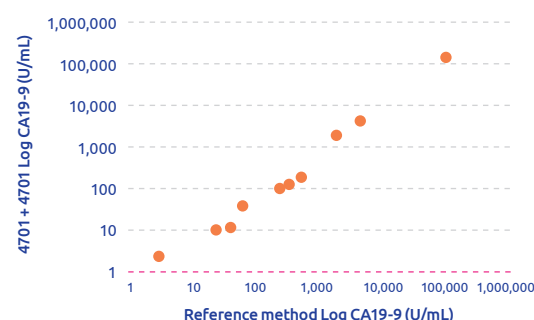
- Galactose (Gal)
- N-acetylglucosamine (GlcNAc)
- ◆ Sialic acid (Neu5Ac)
- ▲ Fucose (Fuc)

Structure	Symbol*	Anti-CA19-9	
		4701	1116-NS-19-9
Sialyl Lewis A		+++	+++
Sialyl Lewis C		+	+
Sialyl Lewis X		–	–
Lewis Y		–	–

## CA19-9 detection



## Correlation to reference method





# HE4

Human epididymis protein 4 (HE4) is a member of the whey acidic protein family, and contains two whey acidic protein domains. HE4 is synthesized mainly in the trachea and salivary gland, but it is also expressed in the ovary, lung, prostate, pituitary gland, thyroid, and kidney. The physiological role of HE4 remains unclear, but it is presumed to play a role in innate immunity.<sup>19-21</sup>

The normal HE4 concentration in human blood is less than 140 pmol/L. HE4 overexpression is associated with ovarian and endometrial cancer, which makes HE4 a promising biomarker for these malignancies. In comparison to CA125, HE4 is less frequently elevated in benign gynecological

conditions. Furthermore, HE4 is expressed by some ovarian and endometrial carcinomas that do not express CA125. HE4 immunoassays can therefore be useful in complementing CA125 immunoassays in discriminating between benign and malign adnexal masses. The "risk of ovarian malignancy algorithm" (ROMA) which combines measurement of CA125 and HE4, and the woman's menopausal status, has been approved by the FDA for this purpose. When combined with CA125, HE4 also improves the sensitivity of early-stage ovarian cancer detection.<sup>19-22</sup>

Medix Biochemica offers five monoclonal antibodies (4501, 4502, 4505, 4506) for HE4 detection.

## Anti-human HE4 monoclonal antibodies

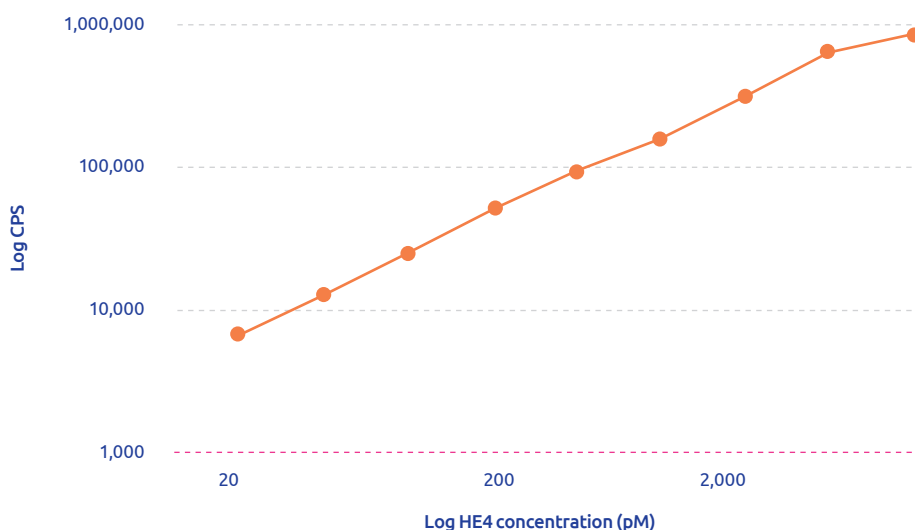
HE4 antibody	Product code	Concentration (mg/mL)	Shelf life (months at +2–8 °C)	Subclass	Applications tested
4501	100589	5	N/D	IgG <sub>1</sub>	ELISA
4502	100592	5	N/D	IgG <sub>1</sub>	ELISA
4503	100608	5	24	IgG <sub>1</sub>	ELISA
4505	100593	5	24	IgG <sub>1</sub>	ELISA
4506	100594	5	N/D	IgG <sub>1</sub>	ELISA

## Pair recommendations

	Detection				
	4501	4502	4503	4505	4506
Capture	4501	4502	4503	4505	4506
4501	–	–	+	+	+
4502	–	–	+	+	+
4503	–	–	–	–	–
4505	–	–	–	–	–
4506	–	–	–	–	–



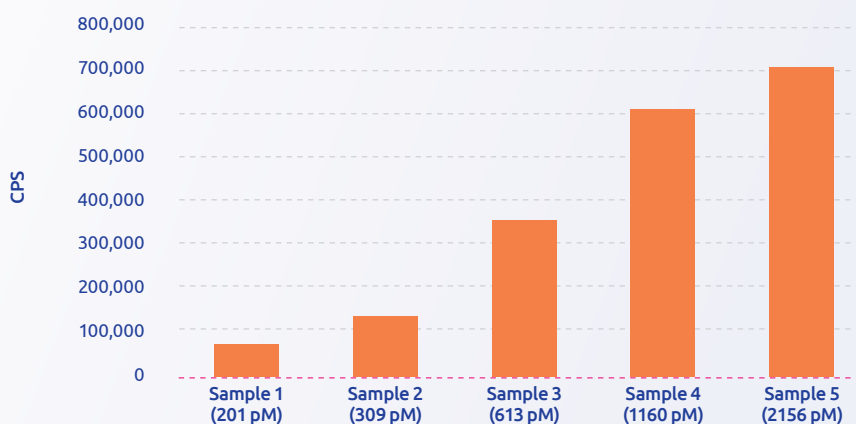
## HE4 standard curve



Capture: 4501  
Detection: 4503

Normal values in serum are less than 140 pM.

## Results with patient samples

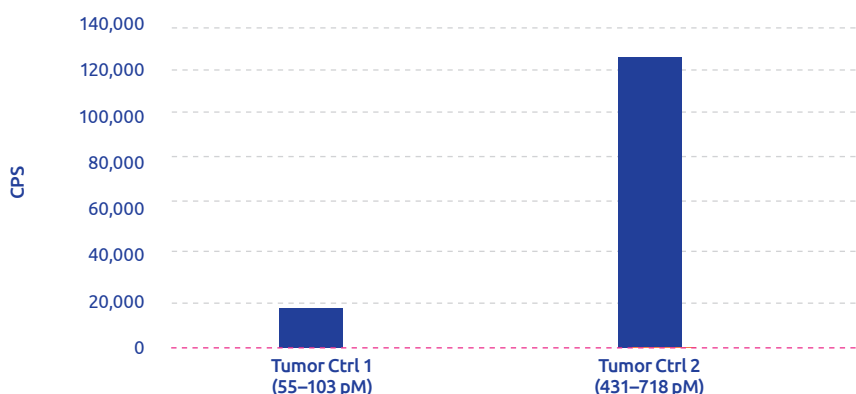


Capture: 4501  
Detection: 4503

Samples 1-5 had been measured earlier with Roche Elecsys® HE4 assay.

## HE4 results with Tumor Marker Controls

(Fujirebio Diagnostics, 108-20W)



Capture: 4501  
Detection: 4503

# CEA

Carcinoembryonic antigen (CEA), also known as CD66e and CEACAM5, is a 180–200 kDa glycoprotein involved in cell adhesion. It is normally produced in the fetal digestive tract, but since the production is repressed after birth, CEA levels are usually very low in normal adult colon and blood. Elevated CEA serum levels are, however, raised by various types of carcinomas, including colorectal, lung, and breast cancer. Therefore, CEA has been widely used as a broad-spectrum tumor marker. CEA is not specific to any cancer type, but its concentrations in blood may predict the therapeutic effect, progression, and prognosis of the disease.

CEA is most widely used in detecting gastrointestinal cancers, especially colorectal cancer. Several organizations recommend the measurement of both preoperative and postoperative levels of CEA in patients with colorectal cancer.<sup>30–32</sup> Furthermore, CEA is suggested as the marker of choice for monitoring the efficacy of systemic therapy against metastatic disease.

For patients with lung cancer, serum levels of CEA may carry prognostic and predictive information of risk of

recurrence.<sup>33</sup> Similarly, elevated CEA levels serve as an independent predictor of decreased survival in pancreatic adenocarcinoma.<sup>34</sup> Increased CEA levels are also associated with a number of benign conditions, such as inflammatory bowel disease, liver cirrhosis, pancreatitis, and smoking.

Along with CEA, members of the CEA-related gene family include cross-reacting antigens, such as CD66c (also called NCA, NCA50/90, and CEACAM6), CD66a (also called BGP, BGP-1, and CEACAM1), and meconium CEA (also called NCA-2). These CEA-like proteins share common epitopes with CEA, but they also have protein domains distinctive to each molecule.

Medix Biochemica offers five different monoclonal antibodies for CEA detection. Two of them are specific to CEA (5909 and 5910) with no known cross-reactivity to other CEA-like molecules. Of the three remaining antibodies, two cross-react with NCA-2 (5911 and 5912) and one has negligible cross-reactivity to both NCA and NCA-2 (5905).

**Scientific references: page 18**

## Anti-human CEA monoclonal antibodies

CEA antibody	Product code	Concentration (mg/mL)	Shelf life (months at +2–8°C)	Subclass	Applications tested
5905	100044	1	36	IgG <sub>1</sub>	ELISA, CLIA
5909	100428	5	36	IgG <sub>1</sub>	ELISA, CLIA
5910	100047	5	36	IgG <sub>1</sub>	ELISA, CLIA
5911	100048	1	24	IgG <sub>1</sub>	ELISA, CLIA
5912	100049	1	36	IgG <sub>1</sub>	ELISA, CLIA

## Pair recommendations

	Detection				
	5905	5909	5910	5911	5912
Capture	5905	–	–	–	–
	5909	+	–	+	–
	5910	–	+	–	+
	5911	–	–	–	–
	5912	–	–	+	–

## Kinetic parameters

CEA antibody	Affinity constant, K <sub>A</sub>
5905	5 x 10 <sup>10</sup> 1/M
5909	3 x 10 <sup>10</sup> 1/M
5910	1 x 10 <sup>11</sup> 1/M
5911	1.5 x 10 <sup>10</sup> 1/M
5912	4 x 10 <sup>9</sup> 1/M



# PSA

Prostate-specific antigen (PSA) is a glycoprotein produced by the epithelial cells of the prostate gland. PSA belongs to the kallikrein protein family, and has chymotrypsin-like protease activity. It is secreted into seminal plasma, where it catalyzes the liquefaction of the seminal coagulation formed immediately after ejaculation.

Small quantities of PSA are found in the serum of men with healthy prostate, but elevated serum PSA levels indicate the presence of prostate cancer or other prostate disorders. PSA is the most widely used marker for early detection of prostate cancer. Increased concentrations of serum PSA are associated with elevated prostate cancer risk, a higher pathological grade of the cancer, and a higher risk of metastatic disease. Since the 1980s, PSA screening has significantly improved prostate cancer survival rates and the overall disease management.<sup>35,36</sup>

PSA is organ specific, and expressed only in the prostate. However, it is not a cancer-specific biomarker, since elevated

PSA levels may also reflect benign conditions. Thus, there is an ongoing debate over PSA-based screening and whether it will lead to overdiagnosis and overtreatment. The cancer-specificity of PSA-based screening can be improved by measuring the free form PSA (fPSA) and comparing it to the total PSA (tPSA), which consists of fPSA and complex PSA attached to serum protease inhibitors. fPSA accounts for 5-35% of tPSA.<sup>36,37</sup> Low fPSA/tPSA ratio is associated with cancer, whereas high fPSA/tPSA indicates the presence of nonmalignant conditions.

Medix Biochemica offers four different anti-PSA monoclonal antibodies (8301, 8311, 8312, and 8313). The selection includes two antibodies that recognize both complex PSA and fPSA (8301 and 8311). Antibody 8312 has a binding profile that favors fPSA, with 15% cross-reactivity with PSA-ACT (antichymotrypsin) complex; antibody 8313 is fPSA-specific without cross-reactivity with the complex form.

**Scientific references:** page 18

## Anti-human PSA monoclonal antibodies

PSA antibody	Product code	Concentration (mg/mL)	Shelf life (months at +2–8°C)	Subclass	Applications tested
8301	100102	5	36	IgG <sub>1</sub>	ELISA
8311	100103	1	36	IgG <sub>2a</sub>	ELISA
8312	100139	5	36	IgG <sub>1</sub>	ELISA
8313 (free)	100488	5	18	IgG <sub>1</sub>	ELISA

## Pair recommendations

		Detection			
		8301	8311	8312	8313
Capture	8301	–	+	+	+
	8311	–	–	–	+
	8312	–	–	–	+
	8313	–	–	–	–

## Kinetic parameters

PSA antibody	Association rate constant, $k_{on}$	Dissociation rate constant, $k_{off}$	Affinity constant, $K_A$
8301	N/D	N/D	$1 \times 10^{11}$ 1/M
8311	N/D	N/D	$1 \times 10^{10}$ 1/M
8312	N/D	N/D	$3 \times 10^9$ 1/M
8313 (free)	$2.0 \times 10^6$ 1/Ms	$1.5 \times 10^{-5}$ 1/s	$K_A = 1.3 \times 10^{11}$ 1/M, $K_D = 7.5 \times 10^{-12}$ M (= 7.5 pM)

# PG I and PG II

Pepsinogen is a proenzyme for pepsin, a digestive enzyme that breaks down the protein in food. Pepsinogen is secreted by chief cells in the stomach wall. Once it reaches the strongly acidic environment of the stomach, pepsinogen is cleaved and converted to active pepsin. Based on their biochemical and immunochemical properties, human pepsinogens are classified into two types: pepsinogen I (PG I) and pepsinogen II (PG II).

Although pepsinogens are mainly secreted into the gastric lumen, approximately 1% of the expressed protein can be found in serum. Serum PG I and PG II levels serve as commonly accepted biomarkers reflecting functional and morphologic status of gastric mucosa. Conditions leading to alterations in serum pepsinogen concentrations include *Helicobacter pylori* infections, atrophic gastritis, and gastric cancer.<sup>38-41</sup> These conditions are causally related, since chronic atrophic gastritis, an important precursor of gastric cancer, is predominantly caused by *H. pylori* infections. Identifying the precursor lesions as early as possible is crucial for reducing the morbidity and

mortality of gastric cancer.<sup>40</sup> Population screening of gastric cancer has been adopted in many Asian countries due to the high incidence of the disease.

The concentrations of serum PG I and PG II increase in *H. pylori*-related chronic gastritis; the more severe the condition, the higher the pepsinogen levels. However, when the condition includes loss of fundic gland mucosa and the cells secreting PG I, the level of PG I becomes lower while PG II level remains high or stable. This leads to a stepwise decrease of the PG I/PG II ratio. Therefore, monitoring the serum levels of PG I and PG II, as well as their ratio, offers an alternative for invasive endoscopic biopsy.

Medix Biochemica's selection of mouse monoclonal antibodies includes seven anti-pepsinogen products. Four of the antibodies are specific to PG I (8003, 8009, 8015, and 8016), while three of them are PG II-specific (8101, 8102, and 8103). In addition, Medix Biochemica offers recombinant PG I and PG II antigens.

## Anti-human PG I and PG II monoclonal antibodies and recombinant antigens

PG I antibody	Product code	Concentration (mg/mL)	Shelf life (months at +2–8°C)	Subclass	Applications tested
8003	100120	5	36	IgG <sub>1</sub>	ELISA, LF, IT
8009	100093	1	36	IgG <sub>1</sub>	ELISA, LF, IT
8015	100143	5	36	IgG <sub>1</sub>	ELISA, LF, IT
8016	100095	1	36	IgG <sub>1</sub>	ELISA, LF, IT

PG II antibody	Product code	Concentration (mg/mL)	Shelf life (months at +2–8°C)	Subclass	Applications tested
8101	100097	5	36	IgG <sub>1</sub>	ELISA, LF, IT
8102	100098	1	24	IgG <sub>1</sub>	ELISA, LF, IT
8103	100121	5	24	IgG <sub>1</sub>	ELISA, LF, IT

PG antigens	Product code
Recombinant PG I, 100 µg	610000
Recombinant PG II, 100 µg	610001

## Pair recommendations

PG I		Detection			
		8003	8009	8015	8016
Capture	8003	-	+	+	+
	8009	-	-	+	-
	8015	+	-	-	-
	8016	+	+	-	-

PG II		Detection		
		8101	8102	8103
Capture	8101	-	+	+
	8102	-	-	-
	8103	-	+	-

## Kinetic parameters

PG I antibody	Affinity constant $K_A$
8003	$4 \times 10^{10} 1/M$
8009	$2 \times 10^{10} 1/M$
8015	$4 \times 10^{10} 1/M$
8016	$3 \times 10^{10} 1/M$

PG II antibody	Affinity constant $K_A$
8101	$3 \times 10^{10} 1/M$
8102	$1 \times 10^9 1/M$
8103	$3.5 \times 10^9 1/M$

# Hemoglobin

Hemoglobin (Hb) is an oxygen-carrying metalloprotein. It is found abundantly in red blood cells, constituting 97% of their dry weight.<sup>23</sup> The main function of Hb is to transport oxygen (O<sub>2</sub>) from the lungs to tissues, but it also interacts with other biologically important gases: carbon dioxide (CO<sub>2</sub>), carbon monoxide (CO), and nitric oxide (NO).<sup>24</sup> Hb is a heterotetramer consisting of two alpha chains and two beta chains. Each subunit contains a heme group with an iron atom that is able to bind one O<sub>2</sub> molecule.

Microscopic amounts of Hb in fecal samples may indicate tumor-induced gastrointestinal bleeding. Therefore, detection of Hb in feces through fecal occult blood (FOB) testing can be used for non-invasive colorectal cancer

screening.<sup>25,26</sup> FOB tests that are specific for human Hb do not require dietary restrictions prior to sampling.

Hb is also an important biomarker for hemolytic anemia. In addition, the level of free Hb in serum may serve as a potential biomarker for conditions such as ovarian cancer or acute ischemic stroke.<sup>27-29</sup>

Medix Biochemica offers two anti-Hb monoclonal antibodies (7202 and 7204) that specifically recognize human Hb without cross-reactivity with ovine, equine or porcine Hb. Cross-reactivity of antibody 7204 is 5% with bovine Hb. These antibodies can be used as a sandwich pair for diagnostic tests.

## Anti-human Hb monoclonal antibodies

Hb antibody	Product code	Concentration (mg/mL)	Shelf life (months at +2–8°C)	Subclass	Applications tested
7202	100079	5	36	IgG <sub>1</sub>	ELISA, LF
7204	100080	5	36	IgG <sub>1</sub>	ELISA, LF

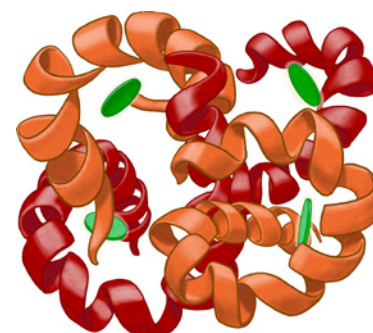
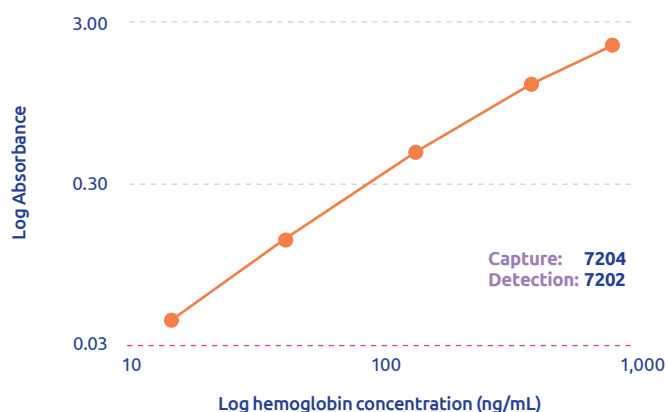
## Pair recommendations

		Detection	
		7202	7204
Capture	7202	–	+
	7204	+	–

## Kinetic parameters

Hb antibody	Affinity constant, K <sub>A</sub>
7202	1 × 10 <sup>10</sup> 1/M
7204	6 × 10 <sup>8</sup> 1/M

## Hb standard curve



Hemoglobin is the oxygen binding protein of red blood cells. It is a tetramer consisting of two alpha chains and two beta chains.



# NSE

Enolases are glycolytic enzymes that catalyze the conversion of 2-phosphoglycerate into phosphoenolpyruvate. This catalysis is dependent on two Mg<sup>2+</sup> ions bound to the catalytic active site of the enolase. Vertebrates express three different enolase isoforms that consist of three different monomeric units forming either homo- or heterodimers.<sup>42-44</sup>

Neuron-specific enolase (NSE), or  $\gamma$ -enolase, is specifically expressed by neurons and neuroendocrine cells. NSE occurs either as a homodimer consisting of two 47 kDa  $\gamma$ -monomers or as a heterodimer of a  $\gamma$ - and  $\alpha$ -subunit ( $\gamma$ - and  $\alpha\gamma$ -isoenzymes, respectively). Under physiological conditions, NSE is mostly present in the brain; it has been linked to neural maturation and is a commonly used biomarker for identifying neurons and neuroendocrine cells.<sup>43-45</sup>

As NSE is normally expressed in a tissue-specific manner, an increased NSE concentration in serum or cerebrospinal fluid concentration often indicates neuronal damage or malignancies. In clinical diagnostics, NSE is thus a widely used marker for neuroendocrine tumors (NETs), including

neuroblastoma and small-cell lung cancer (SCLC). NSE level in bodily fluids has been reported to correlate with extent of disease and response to treatment, allowing the marker to be used as a tool for diagnosis, prognosis, as well as treatment follow-up. Identification of NSE in cord blood allows early postnatal confirmation of neuroblastoma diagnosis in newborn babies.<sup>43,44</sup>

Besides cancer, increased NSE may also reflect the presence of other conditions, such as brain damage, cerebral accidents, myocardial infarctions, Guillain-Barré syndrome, or Creutzfeldt-Jakob disease. Hemolysis can occasionally cause false positive test results, because erythrocytes also contain NSE.<sup>43,46</sup>

Medix Biochemica currently offers two high-quality monoclonal antibodies for NSE detection (9601 and 9602). According to an evaluation of 12 commercially available anti-NSE antibodies, by four independent working groups, Medix Biochemica's antibodies showed the highest affinities towards the NSE  $\gamma$ -isotype, while the 9602/9601 assay combination also recognized the  $\alpha\gamma$ -isotype.<sup>44</sup>

## Anti-human NSE monoclonal antibodies

NSE antibody	Product code	Concentration (mg/mL)	Shelf life (months at +2–8°C)	Subclass	Applications tested
9601	100388	5	36	IgG <sub>1</sub>	ELISA, CLIA
9602	100408	5	24	IgG <sub>1</sub>	ELISA, CLIA

## Kinetic parameters

NSE antibody	Affinity constant, K <sub>A</sub>
9601	4.3 × 10 <sup>8</sup> 1/M
9602	2.2 × 10 <sup>8</sup> 1/M

# CYFRA 21-1

CYFRA 21-1 is a soluble fragment of cytokeratin 19. The name of the cytokeratin fragment derives from two monoclonal antibodies, BM 19-21 and KS 19-1, that were first used to measure it. The acidic cytokeratin 19 is produced by the simple and stratified squamous epithelia and the basal cells of the mucous membrane. Cytokeratins belong to the intermediate filament (IF) protein family, which is one of the three cytoskeletal systems found in eukaryotic cells. The main function of cytokeratins is to protect cells from mechanical and non-mechanical stress, which would otherwise eventually lead to cell death. Cytokeratins are also known to play a role in cell signaling and cellular stress responses.<sup>19,47,48</sup>

Cytokeratin 19 is typically found in malignant epithelial cells. Due to the cytokeratin structure, most tumors are hard. CYFRA 21-1 is released into the bloodstream during cell death, especially during necrosis. Thus, an increased CYFRA 21-1 level indicates the presence of a tumor mass in various squamous cell cancers, such as prostate cancer, carcinoma, breast cancer, colorectal cancer, and lung cancer.<sup>19,49</sup>

Medix Biochemica's product selection includes four different monoclonal antibodies for CYFRA 21-1 detection. The CYFRA 21-1 antibodies also recognize human cytokeratin 19.

## Anti-human CYFRA 21-1 monoclonal antibodies

CYFRA 21-1 antibody	Product code	Concentration (mg/mL)	Shelf life (months at +2–8°C)	Subclass	Applications tested
1602	100220	5	6	IgG <sub>1</sub>	ELISA
1603	100221	5	12	IgG <sub>2a</sub>	ELISA
1604	100222	5	12	IgG <sub>2a</sub>	ELISA
1605	100223	5	12	IgG <sub>1</sub>	ELISA

## Kinetic parameters

CYFRA 21-1 antibody	Association rate constant, $k_{on}$	Dissociation rate constant, $k_{off}$	Affinity constant, $K_A$
1602	N/D	N/D	N/D
1603	$1 \times 10^4$ 1/Ms	$4 \times 10^{-5}$ 1/s	$K_A = 3 \times 10^8$ 1/M, $K_D = 4 \times 10^{-9}$ M
1604	$3 \times 10^4$ 1/Ms	$6 \times 10^{-5}$ 1/s	$K_A = 5 \times 10^8$ 1/M, $K_D = 2 \times 10^{-9}$ M
1605	$5 \times 10^4$ 1/Ms	$6 \times 10^{-5}$ 1/s	$K_A = 8 \times 10^8$ 1/M, $K_D = 1 \times 10^{-9}$ M



# AFP

Alpha-fetoprotein (AFP) is an albumin-like glycoprotein produced by the fetal liver and yolk sac during embryonic development. In addition to its embryo-specific production, AFP was among the first proteins demonstrated to be tumor-associated.<sup>9,50,51</sup>

AFP is a secreted protein that consists of three homologous  $\alpha$ -helical domains. The size of the protein varies from 68 to 73 kDa, depending mainly on its carbohydrate content and origin. In fetal blood, AFP binds to various hydrophobic ligands, such as fatty acids, metal ions, and flavonoids, and is thought to be a carrier molecule for them in the blood stream. AFP concentration gradually decreases after birth and is generally very low but detectable, 5–10 ng/ml, in healthy non-pregnant adults.<sup>9,50,51</sup>

AFP is a widely used biomarker in clinical practice. An increased serum AFP level is detected in 70–80 percent

of hepatocellular carcinomas and 10–30 percent of other gastrointestinal cancers. In addition, AFP levels can be elevated in germ cell cancer. An increased AFP concentration in maternal blood or amniotic fluid is often related to neural tube developmental defects or nephrosis, while a decreased AFP level has been observed in relation to Down syndrome. Elevated AFP levels can also indicate liver disease or damage, such as hepatitis or cirrhosis. As AFP is not specific to a certain malignancy or disease, it is mostly used in combination with other diagnostic tools.<sup>9,51-54</sup>

Medix Biochemica has more than three decades of experience in producing high-quality monoclonal antibodies against AFP. Currently, the company produces two anti-AFP antibodies (5107 and 5108) that do not cross-react with human albumin, and can be used as a pair in diagnostic tests.

**Scientific references: page 18**

## Anti-human AFP monoclonal antibodies

AFP antibody	Product code	Concentration (mg/mL)	Shelf life (months at +2–8°C)	Subclass	Applications tested
5107	100014	1	24	IgG <sub>1</sub>	ELISA
5108	100015	5	24	IgG <sub>1</sub>	ELISA

## Kinetic parameters

AFP antibody	Affinity constant, $K_A$
5107	$4 \times 10^{10}$ 1/M
5108	$3 \times 10^{10}$ 1/M

# Calcitonin

The polypeptide hormone thyrocalcitonin or calcitonin (CT) is a linear 32-amino-acid cleavage product of the 116-amino-acid procalcitonin (PCT) precursor. PCT is produced by parafollicular C-cells in the thyroid gland and cleaved into three peptides: CT, katalcalcin, and an N-terminal fragment.<sup>56</sup> PCT is a well-described biomarker for severe bacterial infection and sepsis, while its polypeptide products have diverse functions.<sup>57</sup> In healthy individuals, CT counteracts parathyroid hormone by inhibiting osteoclast activity in the bones and reducing the levels of calcium and phosphorus in the blood.<sup>56,57</sup>

While the baseline serum levels of CT are low in healthy individuals, CT is excessively produced by tumor cells in the thyroid gland in patients with medullary thyroid carcinoma (MTC).<sup>58,59</sup> CT is therefore a sensitive and potent biomarker for MTC and thus frequent quantification of CT is a crucial part of follow-up and disease monitoring in MTC patients.<sup>60,61</sup> MTC originates from C-cells and is responsible for 3.5–10% of all thyroid cancers.<sup>60,61</sup>

Routine measurement of serum CT in nodular thyroid disease has been shown to allow for an early and accurate preoperative diagnosis of MTC and efficient post-operative follow-up of thyroid nodules, which leads to improved survival.<sup>62,63</sup> Quantification of serum CT can also be utilized in the evaluation of treatment response to systemic therapies, including tyrosine kinase inhibitors.<sup>64</sup>

Recent research has shown that the CT receptor (CTR) dimerizes with the prostaglandin receptor EP2, forming a new G protein-coupled receptor EP2-CTR.<sup>65</sup> The EP2-CTR heterodimer may be involved in functional regulation, which has potential implications for yet unknown biological roles of CT.<sup>65</sup>

The MedixMAB product portfolio includes four high-quality monoclonal IgG antibodies (4050, 4051, 4004 and 4005) for the reliable detection of calcitonin.

## Anti-human calcitonin monoclonal antibodies

Calcitonin antibody	Product code	Concentration (mg/mL)	Shelf life (months at +2–8°C)	Subclass	Applications tested
4050	700019	> 1	60	IgG <sub>1</sub>	ELISA
4051	700020	> 1	60	IgG <sub>1</sub>	ELISA
4004	100563	5	24	IgG <sub>1</sub>	ELISA
4005	100564	5	24	IgG <sub>1</sub>	ELISA

## Pair recommendations

	Detection			
	4004	4005	4050	4051
Capture 4004	–	–	+	–
4005	–	–	+	–
4050	+	+	–	+
4051	–	–	+	–



# S100B

The S100 calcium-binding protein B (S100B, S100 $\beta$ , NEF) is a 21.5-kDa member of the EF-hand calcium-binding S100 protein family. S100B is involved in a wide range of cellular functions, including calcium homeostasis, cell-to-cell communication, cell cycle progression, differentiation, cytoskeletal dynamics, and cell morphology.<sup>66</sup>

S100B is a glial-specific protein primarily expressed by astrocytes in the central nervous system (CNS), but also by certain other cell types such as chondrocytes, adipocytes and melanocytes.<sup>66,67</sup> Secreted S100B penetrates the blood–brain barrier and is thus one of the leading biomarkers of traumatic CNS injuries, neuroinflammatory and neurodegenerative disorders, brain tumors, and certain psychiatric disorders.<sup>68</sup> Chromosomal rearrangements and altered expression of the S100B gene have been connected to several neurological and neoplastic diseases.<sup>66,67,68</sup>

Since the early 1980's S100B has been regarded as a reliable biomarker of melanoma malignancy.<sup>67,69,70</sup> S100B aids in the clinical staging of malignant melanoma and evaluation of patient prognosis. Elevated S100B levels are indicative of an advanced disease stage, poor therapeutic response, cancer progression, increased recurrence, and low overall survival.<sup>66</sup> S100B has been found to target p53 tumor suppressor, leading to efforts to develop innovative strategies to inhibit the S100B-p53 interaction and to eventually induce tumor cell death.<sup>66</sup>

The MedixMAB product portfolio includes high quality S100B monoclonal antibodies and a recombinant antigen in three product sizes.

## Anti-human S100B monoclonal antibodies and recombinant antigen

S100B antibody	Product code	Concentration (mg/mL)	Shelf life (months at +2–8°C)	Subclass	Applications tested
11401	100778	5	N/D	IgG <sub>1</sub>	ELISA
11402	100779	5	N/D	IgG <sub>1</sub>	ELISA
11404	100781	5	N/D	IgG <sub>1</sub>	ELISA

S100B antigen	Product code
Recombinant S100B, 50 $\mu$ g	710014
Recombinant S100B, 500 $\mu$ g	710045
Recombinant S100B, 1000 $\mu$ g	710044

## Pair recommendations

		Detection		
		11401	11402	11404
Capture	11401	–	+	–
	11402	+	–	+
	11404	–	+	–

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CPS = Counts per second  
CLIA = Chemiluminescence immunoassay  
ELISA = Enzyme-linked immunosorbent assay  
FIA = Fluoroimmunoassay  
IT = Immunoturbidimetry  
LF = Lateral flow  
N/A = Not Applicable  
N/D = Not Determined

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