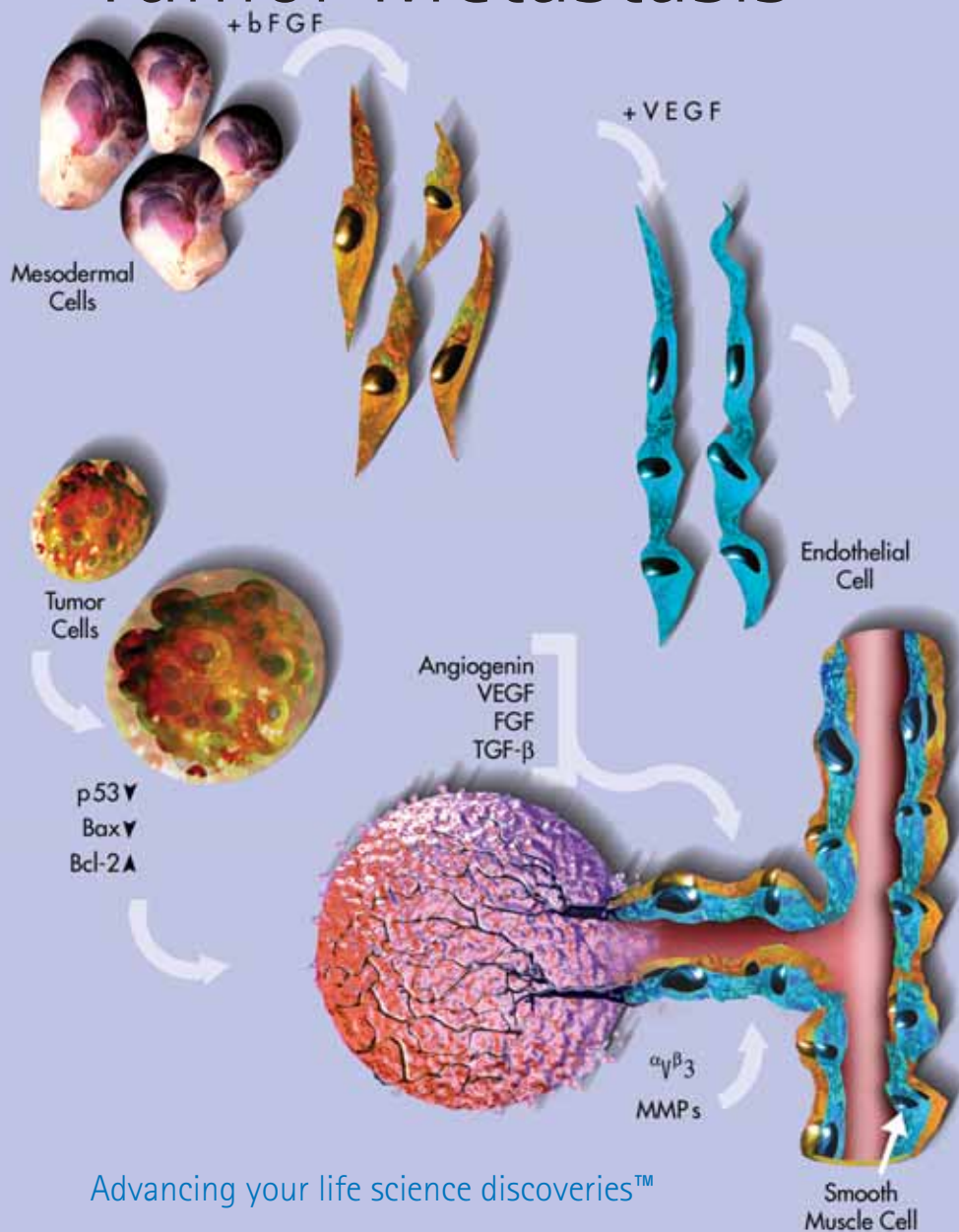


# Angiogenesis and Tumor Metastasis



Advancing your life science discoveries™



# Angiogenesis and Tumor Metastasis

## Angiogenesis: Role in Tumor Growth and Metastasis

Chandra Mohan, Ph.D. and Kate Thomas, Ph.D.  
EMD Biosciences, Inc.  
San Diego, CA 92121



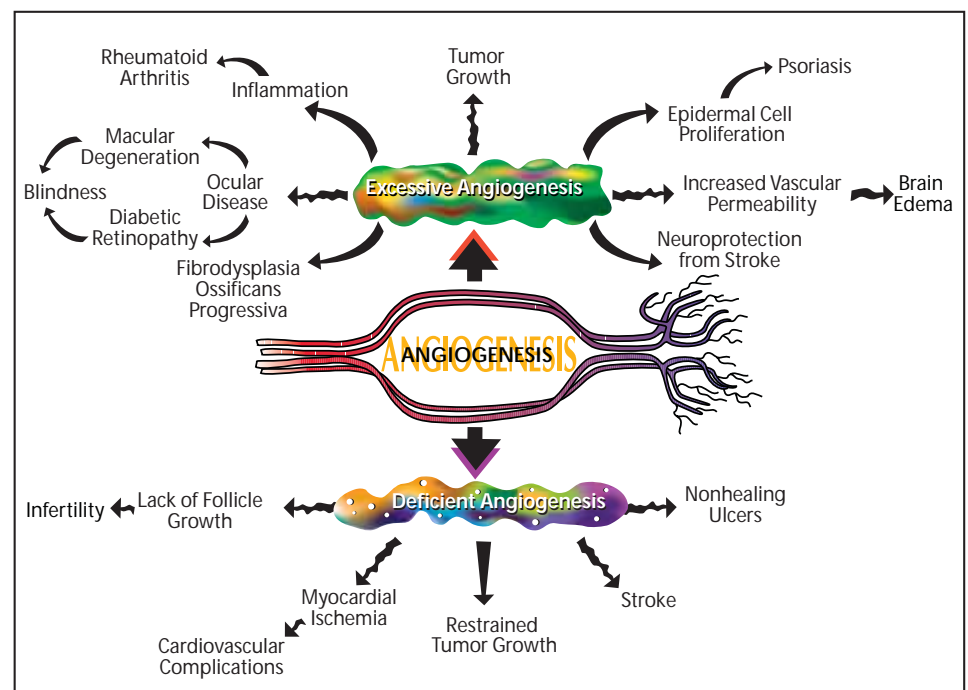
### TABLE OF CONTENTS

Angiogenesis Kits and Set .....	3
Promoters of Angiogenesis .....	3
Antibodies to Angiogenesis Promoters .....	5
Inhibitors of Angiogenesis .....	8
Antibodies to Angiogenesis Inhibitors .....	10
Cathepsins .....	12
Antibodies to Cathepsins .....	13
Enzymes and Proteins .....	13
Cathepsin Substrates .....	14
Cathepsin Inhibitors .....	14
MMP Kits and Assays .....	15
MMP Enzymes and Related Products .....	16
Antibodies to MMPs and Related Products .....	17
MMP Substrates and Related Products .....	20
MMP Inhibitors and Related Products .....	22
Tissue Inhibitors of Metallo-Proteinases (TIMPs) .....	24

The vascular system is formed through a combination of vasculogenesis and angiogenesis. In vasculogenesis, blood vessels are formed *de novo* by the assembly of angioblasts of mesodermal origin. Angiogenesis is the formation of new capillaries from preexisting vasculature by migration and proliferation of endothelial cells.<sup>1</sup> Angiogenesis is a fundamental process required for a number of physiological and pathological events and is considered a key step in tumor growth, invasion, and metastasis.<sup>2,3</sup> Angiogenesis is required for proper nourishment and removal of metabolic wastes from tumor sites. Under physiological conditions, angiogenesis is a

highly regulated phenomenon. The progression of angiogenesis is controlled by a delicate balance between the positive and negative regulators of this process. Although angiogenesis occurs during embryonic development, wound healing, and the menstruation cycle, unregulated angiogenesis is seen under pathological conditions such as tumor growth, diabetic retinopathy, and psoriasis. Angiogenesis is not only a prerequisite for tumor growth and expression but also a major factor affecting the metastatic spread of malignant cells.<sup>4-6</sup>

Angiogenesis is a multi-step process that begins with the degradation of basement membrane at post-capillary venule.<sup>7</sup>



During angiogenesis, the assembly of a vascular network occurs in several sequential steps which include:

- (a) Release of proteases from activated endothelial cells
- (b) Degradation of basement membrane surrounding the existing blood vessel
- (c) Migration of endothelial cells to the tumor
- (d) Proliferation of endothelial cells
- (e) Canalization and branching
- (f) Creation of new basement membrane and enrollment of pericytes for vascular stability
- (g) Fusion of newly formed blood vessels
- (h) Establishment of blood flow

Angiogenic growth factors such as acidic and basic fibroblast growth factors, tumor necrosis factor- $\alpha$ , vascular endothelial growth factor, angiogenin, and others secreted by tumors, endothelial cells, and supporting cells accelerate the process of angiogenesis. These factors act as autocrine or paracrine growth factors to produce angiogenesis.<sup>8</sup>

Dormant tumors secrete inhibitory factors such as angiostatin, thrombospondins, and tissue inhibitors of metalloproteinases that prevent tumors from switching to the angiogenic phenotype and arrest the growth of tumors. For angiogenesis to occur, proangiogenic molecules have to overcome the effect of those inhibitory factors. To trigger angiogenesis, either the production of proangiogenic factors must increase or the level of inhibitors must decrease. Tumor-associated angiogenesis allows the tumor to maintain its growth and facilitates metastasis spread by establishing connections to the existing blood vessels. Tumor-induced angiogenesis begins with the dissolution of the basement membrane surrounding a pre-existing blood vessel, a process aided

by matrix metalloproteinases (MMPs) produced by the tumor cells and supporting cells. The non-mitotic endothelial cells then migrate towards the tumor through the disintegrated tissue extracellular matrix. The dissolution of extracellular matrix facilitates the release of sequestered angiogenic factors.<sup>9</sup> An augmentation in MMP activity is positively linked to the increase in metastatic and angiogenic potential of tumors.<sup>8</sup> Upregulation of MMP-2, MMP-7, MMP-9, and stromelysin-3 mRNA has been reported in tumor invasion and metastasis.<sup>10-13</sup>

Most tumors persist for years without any angiogenic activity, incapable of growing beyond 2 to 3 mm in size.<sup>3,14</sup> However, when they switch to the angiogenic phenotype they grow rapidly.<sup>15</sup> Avascular, microscopic tumors proliferate and grow at a rate similar to rapidly growing tumors.<sup>16</sup> However, in the dormant stage, the rate of tumor cell proliferation is balanced by apoptosis of tumor cells.<sup>8</sup> The acquisition of angiogenic phenotype results in a diminution in the apoptotic rate and a shift in balance in favor of cell proliferation. During angiogenic neovascularization a selective expression of adhesion receptor integrin  $\alpha_v\beta_3$  has also been reported.<sup>17</sup> The binding of integrin  $\alpha_v\beta_3$  to the receptor provides a specific signal that enhances the survival of angiogenic endothelial cells. This signal is also linked to a decrease in p53, p21<sup>WAF1</sup> and bax expression and an increase in Bcl-2 expression, thereby facilitating a switch to the angiogenic phenotype.<sup>18</sup>

The obligatory neovascularization, a rather uncommon process under normal conditions, for tumor growth and metastasis makes angiogenesis a prominent target for therapeutic intervention.<sup>19-21</sup> Most of the antitumor agents used in cancer therapy are cytotoxic in nature, designed mainly to prevent tumor growth. However, to be useful, an ideal therapeutic agent should exhibit selectivity and minimal acute or chronic toxicity. Angiogenic inhibitors

could prove to be useful agents in this arena. Their selective effect on vasculature may not only have an overall reduced toxicity, they may also be able to overcome drug resistance commonly seen in solid tumors. Any specific inhibitor of angiogenesis will be well tolerated by tumor patients because under physiological conditions there is minimal, if any, angiogenesis (e.g., wound healing). Several modes of treatment, separately or combined, are under consideration and include agents that act directly on the tumor cells to prevent the release of angiogenic agents, drugs that inactivate already released angiogenic molecules, and agents that obliterate endothelial cell response to angiogenic stimulators.<sup>22,23</sup> Contrary to the above, some questions have been raised relating to the efficacy of anti-angiogenic agents. Blocking the action of any one specific agent may induce tumors to overexpress another activator; also, it is not clear whether anti-angiogenic agents will reduce the size of the tumor or simply inhibit further tumor growth.<sup>24</sup>

#### References:

1. Beck, L., and D'Amore, P.A. 1997. *FASEB J.* **11**, 365.
2. Uhr, J.W., et al. 1997. *Nature Med.* **3**, 505.
3. Gastl, G., et al. 1997. *Oncology* **54**, 177.
4. Liekens, S., et al. 2001. *Biochem. Pharmacol.* **61**, 253.
5. Tanigawa, N., et al. 1997. *Cancer Res.* **57**, 1043.
6. Bicknell, R., and Harris, A.L. 1996. *Curr. Opin. Oncol.* **8**, 60.
7. Ausprunk, D.H., and Folkman, J. 1977. *Microvasc. Res.* **14**, 53.
8. Pluda, J.M. 1997. *Sem. Oncol.* **24**, 203.
9. Bhushan, M. and Griffiths, C.E. 2002. *Br. J. Dermatol.* **147**, 418.
10. Hashimoto, K., et al. 1997. *Nippon Hin. Gakk. Zasshi* **88**, 852.
11. Polette, M., et al. 1993. *Invasion Metastasis* **13**, 31.
12. Hahnel, E., et al. 1993. *Int. J. Cancer* **55**, 771.
13. Yu, A.E., et al. 1997. *Drugs Aging* **11**, 229.
14. Hori, A., et al. 1991. *Cancer Res.* **51**, 6180.
15. Folkman, J. 1995. In: *Molecular Basis of Cancer* (Mendelsohn, J., et al. Eds.), Philadelphia, W.B. Sanders, pp 206-232.
16. Holmgren, L., et al. 1995. *Nat. Med.* **1**, 149.
17. Brooks, P.C., et al. 1994. *Cell* **79**, 1157.
18. Stromblad, S., et al. 1996. *J. Clin. Invest.* **98**, 426.
19. Twardowski, P., and Gradishar, W.J. 1997. *Curr. Opin. Oncol.* **9**, 584.
20. Weinstat-Saslow, D., and Steeg, P.S. 1994. *FASEB J.* **8**, 401.
21. Le Querrec, A., et al. 1993. *Baillieres Clin. Haematol.* **6**, 711.
22. Petruzzelli, G.J. 1996. *Head and Neck* **18**, 283.
23. Folkman, J., and Ingber, D. 1992. *Sem. Cancer Biol.* **3**, 89.
24. Terman, B.I., and Stoleto, K.V. 2001. *Einstein, Q.J. Biol. Med.* **18**, 59.

## Products for Angiogenesis and Tumor Metastasis Research

Product	Cat. No.	Size	Price
Angiogenesis Research Discovery Pack™	DSV04	1 Set	
Endostatin™ Protein, Accucyte® EIA Kit, Human	QIA65	1 Kit	
Endostatin™ Protein, Accucyte® EIA Kit, Mouse	QIA66	1 Kit	
Fibroblast Growth Factor, Basic, Human, ELISA Kit	QIA64	1 Kit	
Fibroblast Growth Factor, Basic, Accucyte® EIA Kit	QIA67	1 Kit	
Interleukin-8 Accucyte® EIA Kit	QIA68	1 Kit	
VEGF Accucyte® EIA Kit	QIA69	1 Kit	
VEGF (Human) ELISA Kit	QIA51	1 Kit	
VEGF (Mouse) ELISA Kit	QIA52	1 Kit	
VEGF Receptor 1 ELISA Kit, Human	QIA100	1 Kit	

### Angiogenesis Kits and Set

### Angiogenesis Research Discovery Pack™ Cat. No. DSV04

A collection of antibodies suitable for studying the pathways involved in angiogenesis. Contains 20 µg of each of the following antibodies: Anti-VEGF (Cat. No. PC315), Anti-VEGFR1 (Cat. No. PC322), Anti-bFGF (Cat. No. PC16), Anti-Angiostatin (Cat. No. PC371), and Anti-MMP-2 (Cat. No. IM33).

## Promoters of Angiogenesis

Product	Cat. No.	Size	Price
ADAMTS4, Truncated, His•Tag®, Human, Recombinant	PF113	5 µg	
Angiogenin, Human, Recombinant, <i>E. coli</i>	175600	50 µg	
Angiogenin (108-123)	175602	1 mg	
Angiopoietin-2, His•Tag®, Human, Recombinant, Mouse, Biotin Conjugate	176600	10 µg	
Fibroblast Growth Factor, Acidic, Recombinant, Human, <i>E. coli</i>	341591	25 µg	
Fibroblast Growth Factor, Basic, Human, Recombinant, <i>E. coli</i>	341595	25 µg	
Fibroblast Growth Factor, Basic, Human, Recombinant	PF003	10 µg 25 µg	
Interleukin-8, Human, Recombinant, <i>E. coli</i>	407673	10 µg	
Insulin-Like Growth Factor-I, Human, Recombinant, <i>E. coli</i>	407240	50 µg	
Insulin-Like Growth Factor-II, Human, Recombinant, <i>E. coli</i>	407245	50 µg	
Laminin Hexapeptide	428030	1 mg	
PIGF-1, Human, Recombinant, <i>Spodoptera frugiperda</i>	526610	5 µg	
PIGF-2, Human, Recombinant, <i>Spodoptera frugiperda</i>	526612	5 µg	
Platelet-Derived Growth Factor, Human Platelets	521200	1 µg	
Platelet-Derived Growth Factor, BB Homodimer, Human, Recombinant, <i>E. coli</i>	521225	10 µg	
Platelet-Derived Growth Factor, Porcine Platelets	521300	5 µg	
PR-39, Porcine, Synthetic	529645	100 µg	
D-erythro-Sphingosine-1-phosphate	567727	1 mg	

### Angiogenesis Promoters

## Products for Angiogenesis and Tumor Metastasis Research

### Angiogenesis Promoters, continued

### Promoters of Angiogenesis, cont.

Product	Cat. No.	Size	Price
Thymidine Phosphorylase (PD-ECGF), Human, Recombinant	PF081	10 µg	
Transforming Growth Factor-α, Human, Recombinant, <i>E. coli</i>	616430	100 µg	
Transforming Growth Factor-β1, Human Platelets	616450	1 µg	
Transforming Growth Factor-β1, Human, Recombinant, CHO Cell Line	616455	2 µg	
Transforming Growth Factor-β1, Porcine Platelets	616460	1 µg	
Transforming Growth Factor-β3, Human, Recombinant	PF073	2 µg	
Tumor Necrosis Factor-α, Human, Recombinant, <i>E. coli</i>	654205	10 µg	
Tumor Necrosis Factor-α, Mouse, Recombinant, <i>E. coli</i>	654245	10 µg	

### Vascular Endothelial Growth Factors and Receptors

Vascular endothelial growth factor (VEGF), one of the most potent angiogenic cytokines, regulates both vascular proliferation and permeability, and acts as an anti-apoptotic factor for newly formed blood vessels. Alternative splicing of a single VEGF gene has generated five isoforms (VEGF<sub>121</sub>, VEGF<sub>145</sub>, VEGF<sub>165</sub>, VEGF<sub>189</sub> and VEGF<sub>206</sub>), which differ in their molecular weights and in their ability to bind to cell-surface heparan sulfate proteoglycans. VEGF<sub>121</sub> and VEGF<sub>165</sub> are reported to be the most dominantly expressed variants in all tumor cell lines investigated. VEGF<sub>145</sub> is either very weakly or not expressed at all in breast and ovarian cancers. VEGF<sub>189</sub> expression is related to angiogenesis and prognosis in certain human solid tumors. The biological effects of VEGF are mediated through two VEGF receptors, VEGFR-1 (Flt-1) and VEGFR-2 (KDR/Flk-1), whose expression is largely limited to the vascular endothelium. Studies have shown that mitogenic and chemotactic effects of VEGF are mediated via KDR. VEGF-induced cellular responses, including the inhibition of apoptosis and expression of MMPs are mediated via its interaction with KDR.

VEGF has been implicated as the major prognostic factor in tumor growth and angiogenesis. Its expression is enhanced in response to hypoxia, oncogenes, and other cytokines, and is associated with poor prognosis in several types of cancer. Recently, vascular targeting agents, such as SU 5416, that selectively block neovascularization have become attractive agents for the treatment of solid tumors. Their action differs from other anti-angiogenic agents because they target the mature, blood-conducting vessels of the tumors.

#### References:

Stimpfl, M., et al. 2002. *Clin. Cancer Res.* **8**, 2253.  
 Nakamura, M., et al. 2002. *Pathol. Int.* **52**, 331.  
 Rosen L.S. 2002. *Cancer Control* **9** (2 Suppl), 36.

Brekken, R.A., and Thorpe, P.E. 2001. *Anticancer Res.* **21**, 4221.  
 Terman, B.I., and Stoletov, K.V. 2001. *Einstein, Q.J. Biol. Med.* **18**, 59.

Product	Cat. No.	Size	Price
Vascular Endothelial Growth Factor, Human, Recombinant, <i>Spodoptera frugiperda</i>	676472	10 µg	
VEGF <sub>121</sub> , Human, Recombinant, <i>Spodoptera frugiperda</i>	676473	5 µg	
VEGF <sub>164</sub> , Mouse, Recombinant, <i>Spodoptera frugiperda</i>	676474	5 µg	
VEGF <sub>165</sub> , Human, Recombinant	PF074	10 µg	
VEGF-C, Rat, Recombinant, <i>Spodoptera frugiperda</i>	676476	20 µg	
VEGF Receptor 1 (Flt-1), Human, Recombinant	PF082	50 µg	
VEGF Receptor 1 <sub>D1-5</sub> , Human, Recombinant, <i>Spodoptera frugiperda</i>	676478	20 µg	
VEGF Receptor 1 <sub>D1-6</sub> , Human, Recombinant, <i>Spodoptera frugiperda</i>	676479	20 µg	
VEGF Receptor 2 <sub>D1-7</sub> , Human, Recombinant, <i>Spodoptera frugiperda</i>	676490	50 µg	

## Products for Angiogenesis and Tumor Metastasis Research

### Antibodies and Standards to Angiogenesis Promoters

Antibody	Cat. No.	Species Reactivity	Applications	Size	Price
Anti-Angiogenin (Ab-1) (Goat)	PC317L	Human	IB, NT	100 µg	
Anti-Angiopoietin-2, Mouse (Rabbit)	176002	Human, Mouse	ELISA, IB	50 µg	
Anti-Angiopoietin-3 (Ab-1)	PC671	Mouse	ELISA, FS, IB	100 µg	
Anti-Angiopoietin-Like Factor (Ab-1)	PC672	Human	ELISA, IB	100 µg	
Anti-BMP-2/4, N-Terminal, Human (Rabbit)	203640	Human	ELISA, IB, IP	100 µg	
Anti-EDG-1 (Ab-1) (Rabbit)	PC620	Human	IB	50 µg	
EDG-1 Transfected Cell Lysate	PF109	-	-	100 µl	
Anti-EDG-2 (328-344), Human (Rabbit)	324635	Human, Rat	IB	50 µg	
EDG-2 Transfected Cell Lysate	PF110	-	-	100 µl	
Anti-EDG-3 (Ab-1) (Mouse)	GR41	Human, Rat	IB	50 µg	
Anti-EDG-3 (Ab-2) (Mouse)	GR42	Human, Rat	IB	50 µg	
Anti-EDG-4 (Ab-1) (Mouse)	GR43	Human	IB	50 µg	
EDG-4 Transfected Cell Lysate	PF111	-	-	100 µl	
Anti-EDG-5 (Ab-1) (Mouse)	GR44	Human, Rat	IB	50 µg	
Anti-EDG-7 (Ab-1) (Rabbit)	PC621	Human	IB	50 µg	
EDG-7 Transfected Cell Lysate	PF112	-	-	100 µl	
Anti-EDG-8 (Ab-1) (Rabbit)	PC622	Human	IB	50 µg	
Anti-Endothelin (Ab-1) (Mouse)	CP43	Broad range	ELISA	100 µl	
Anti-Endothelin-1 (Ab-1) (Mouse)	CP44	Broad range	IC, PS, RIA	100 µl	
Anti-Endothelin-1 (Ab-2) (Rabbit)	PC266	Broad range	ELISA, PS, RIA	50 µl	
Anti-Fibroblast Growth Factor, Acidic (Ab-1) (Rabbit)	PC316L	Bovine, Human	ELISA, IB, NT	100 µg	
Anti-Fibroblast Growth Factor, Basic (Ab-1) (Rabbit)	PC15	Human	ELISA, PS	100 µg	
Fibroblast Growth Factor Blocking Peptide 1	PP23	-	-	100 µg	
Anti-Fibroblast Growth Factor, Basic (Ab-2) (Rabbit)	PC16	Human, Rat	IB, PS	20 µg 100 µg	
Fibroblast Growth Factor Blocking Peptide 2	PP26	-	-	100 µg	
Anti-Fibroblast Growth Factor, Basic (Ab-3) (Mouse)	GF22	Human	ELISA, IB, IP, NT, PS,	100 µg	
Anti-Fibroblast Growth Factor, Basic (Ab-4) (Mouse)	GF23L	Human	ELISA	100 µg	
Anti-Fibroblast Growth Factor, Basic (Ab-5) (Mouse)	GF24L	Human	ELISA	100 µg	
Anti-Fibroblast Growth Factor Receptor (Ab-1) (Mouse)	GR21	Bovine, Chicken, Guinea Pig, Human, Mouse, Rat	FS, IB, IP, PS	100 µg	
Anti-Fibroblast Growth Factor Receptor (Ab-2) (Rabbit)	PC99	Human	IB	100 µl	
Anti-Fli-1 (Ab-1) (Rabbit)	PC425	Human, Mouse	IB	250 µg	
Anti-Flt-4, Mouse (Rabbit)	343009	Mouse, Rat	ELISA, IB	50 µg	
Anti-HGF (Scatter Factor) (Ab-1) (Mouse)	GF39	Human	IB, IP	100 µg	
Anti-Hypoxia-Inducible Factor 1α, Human (Mouse)	400080	Bovine, Ferret, Human, Monkey, Mouse, Rat, Sheep	IB, IP, PS	100 µl	

### Antibodies and Standards to Angiogenesis Promoters

**Applications:** **ELISA:** Enzyme-Linked Immunosorbent Assay; **FC:** Flow Cytometry; **FS:** Frozen Sections; **IB:** Immunoblotting (Western Blotting); **IC:** Immunocytochemistry; **IF:** Immunofluorescence; **IH:** Immunohistochemistry; **IP:** Immunoprecipitation; **NT:** Neutralization; **PS:** Paraffin Sections; **RIA:** Radioimmunoassay

## Products for Angiogenesis and Tumor Metastasis Research

### Antibodies and Standards to Angiogenesis Promoters, continued

### Antibodies and Standards to Angiogenesis Promoters, cont.

Antibody	Cat. No.	Species Reactivity	Applications	Size	Price
Anti-Hypoxia-Inducible Factor 2 $\alpha$ /EPAS1, Mouse (Rabbit)	400082	Human, Mouse	IB	100 $\mu$ l	
Anti-Hypoxia-Inducible Factor 1 $\beta$ /ARNT, Human (Mouse)	400081	Bovine, Ferret, Human, Mouse, Rat, Sheep	IB	100 $\mu$ l	
Anti-KDR/Flk-1, Mouse (Rabbit)	420401	Human, Mouse, Rat	ELISA, IB, IF, IH	50 $\mu$ g	
Anti-Mast Cell Chymase, Human (Mouse)	444904	Human	ELISA, IB, PS	100 $\mu$ g	
Anti-Mast Cell Tryptase, Human (Mouse)	444905	Cat, Dog, Human, Monkey	FS, IB, PS	100 $\mu$ g	
Anti-MDM2 Sampler Kit-Human	ASK26	-	-	1 Kit	
Anti-MDM2 Sampler Kit-Mouse/Human	ASK27	-	-	1 Kit	
Anti-MDM2 (Ab-1) (Mouse)	OP46T OP46	Human	FS, IB, IF, IP, PS	10 $\mu$ g 20 $\mu$ g 100 $\mu$ g	
Anti-MDM2 (Ab-2) (Mouse)	OP115T OP115	Human	IB, IF, IP, PS	10 $\mu$ g 100 $\mu$ g	
Anti-MDM2 (Ab-3) (Mouse)	OP143	Human, Mouse	IB, IF, IP, PS	10 $\mu$ g 100 $\mu$ g	
Anti-MDM2 (Ab-4) (Mouse)	OP144T OP144	Human, Mouse	IB, IF, IP, PS	10 $\mu$ g 20 $\mu$ g 100 $\mu$ g	
Anti-MDM2 (Ab-5) (Mouse)	OP145T OP145	Human	IB, IF, IP, PS	10 $\mu$ g 100 $\mu$ g	
Anti-MDM2 (Ab-6) (Mouse)	OP146T OP146	Human	IB, IF, IP, PS	10 $\mu$ g 100 $\mu$ g	
Anti-PIGF, N-Terminal, Human (Rabbit)	526615	Human	ELISA, IB, IP	100 $\mu$ g	
Anti-pTEN (Ab-4) (Sheep)	PC623	Human	IB	250 $\mu$ g	
Anti-Thymidine Phosphorylase (Ab-1) (Mouse)	GF40	Human	FS, IB, PS	100 $\mu$ g	
Anti-TIE2, Human (Mouse)	610205	Human, Mouse, Pig, Rat	FS, IB, IP	50 $\mu$ g	
Anti-Phospho-TIE2, Phospho-Specific (Ab-1) (Rabbit)	PC449	Human	ELISA, PS	5 $\mu$ l 25 $\mu$ l	
Anti-Phospho-TIE2, Phospho-Specific (Ab-2) (Rabbit)	PC450	Human	ELISA, PS	25 $\mu$ l	
Anti-Tryptase, Human Lung (Rabbit)	650367	Human	IB	500 $\mu$ g	
Anti-uPA (Ab-1) (Mouse)	IM13L	Human	FS, IB, IP, PS	100 $\mu$ g	
Anti-uPA (Ab-2) (Mouse)	IM14L	Human	FS, IB, IP	100 $\mu$ g	
Anti-uPA (Ab-3) (Mouse)	IM15L	Human	IB, IP	100 $\mu$ g	
Anti-uPA Receptor (Ab-1) (Mouse)	GR35	Human	FS	100 $\mu$ g	
Anti-VASP, Phospho-Specific (Ser <sup>157</sup> ), Human (Mouse)	676604	Human, Mouse	ELISA, IB, IC, IP	100 $\mu$ g	
Anti-VEGF (Ab-1) (Rabbit)	PC36	Human, Mouse	IB, PS	100 $\mu$ g	
Anti-VEGF (Ab-2) (Rabbit)	PC37	Human	IB, PS	100 $\mu$ g	
Anti-VEGF (Ab-3) (Mouse)	GF25	Human	PS, IB	100 $\mu$ g	

**Applications:** **ELISA:** Enzyme-Linked Immunosorbent Assay; **FS:** Frozen Sections; **IB:** Immunoblotting (Western Blotting); **IF:** Immunofluorescence; **IH:** Immunohistochemistry; **IP:** Immunoprecipitation; **PS:** Paraffin Sections

## Products for Angiogenesis and Tumor Metastasis Research

### Antibodies and Standards to Angiogenesis Promoters, cont.

Antibody	Species Reactivity	Applications	Cat. No.	Size	Price
Anti-VEGF (Ab-4) (Rabbit)	PC315	Human, Rodent	IB, IP, FS (rodent only), PS (rodent only)	20 µg, 500 µg	
Anti-VEGF (Ab-5) (Mouse)	GF41	Human, Rabbit	FS, IP, NT, PS	100 µg	
Anti-VEGF (Ab-6) (Mouse)	GF46	Bovine, Human, Porcine	IB	50 µg	
Anti-VEGF (Ab-7) (Mouse)	GF48	Human	IB, IP	100 µg	
Anti-VEGF Receptor-1 (Flt-1) (Ab-1) (Goat)	PC322L	Human	ELISA, IB	100 µg	
Anti-VEGF Receptor-2, Mouse (Mouse)	676486	Human, Mouse	IB	50 µg	
Anti-VEGF Receptor-2, Mouse (Rabbit)	676488	Human, Mouse	IB, IP	50 µl	
Anti-VEGF-Receptor 3, Mouse (Rabbit)	343009	Mouse, Rat	ELISA, IB	50 µg	
Anti-VEGF Receptor-1 Phospho-Specific (Ab-1) (Rabbit)	PC458	Human	PS	5 µl, 25 µl	
Anti-VEGF Receptor-1 Phospho-Specific (Ab-2) (Rabbit)	PC459	Human	PS	25 µl	
Anti-VEGF Receptor-2, Phospho-Specific (Ab-1) (Rabbit)	PC462	Human	ELISA, PS	25 µl	
Anti-VEGF Receptor-2/3, Phospho-Specific (Ab-1) (Rabbit)	PC460	Human	ELISA, IB, PS	25 µl	

**Applications:** **ELISA:** Enzyme-Linked Immunosorbent Assay; **FS:** Frozen Sections; **IB:** Immunoblotting (Western Blotting); **IC:** Immunocytochemistry; **IF:** Immunofluorescence; **IH:** Immunohistochemistry; **IP:** Immunoprecipitation; **PS:** Paraffin Sections

Antibodies and Standards to Angiogenesis Promoters, continued



### Angiogenesis Inhibitors

### Inhibitors of Angiogenesis

Kate Thomas, Ph.D.  
EMD Biosciences, Inc.  
San Diego, CA 92121

Dormant tumors secrete inhibitory factors such as angiostatin, endostatin, thrombospondins, and tissue inhibitors of metalloproteinases that prevent the tumor from switching to the angiogenic phenotype. Recent research has led to the identification of several proteolytic fragments or cryptic domains of proteins that act as inhibitors of angiogenesis. These include fragments of plasminogen such as Angiostatin (kringles 1-4, kringles 1-3, and kringles 1-5), the C-terminal proteolytic fragment of collagen XVIII (Endostatin), the NC10 domain of collagen XV, the C-terminal hemopexin-like domain of MMP-2 (PEX), the N-terminal fragment of prolactin, and the N-terminally truncated platelet factor 4.

Endostatin, a 20 kDa fragment generated by cleavage of the Ala-His linkage at the C-terminus of collagen XVIII, has been implicated in the inhibition of tumor progression and induction of endothelial cell apoptosis. Recent evidence suggests that several members of the elastase family can mediate the processing of Endostatin. Immunohistology of adult mouse tissues shows that elastic fibers of the aorta and other large arteries are rich in this anti-angiogenic peptide. Endostatin has a  $Zn^{2+}$ -binding site formed by three histidines at the N terminus and an aspartic acid at residue 76. Studies have shown that the binding of  $Zn^{2+}$  in a 1:1 molar ratio is essential for its antiangiogenic activity. The human endostatin  $Zn^{2+}$  binding site is localized to the N-terminal loop, which makes a dimeric contact in endostatin crystals and involves His<sup>1,3,11</sup> and Asp<sup>76</sup>. Endostatin is reported to bind directly to KDR/Flk-1 and blocks the VEGF-induced tyrosine phosphorylation of KDR/Flk-1 in endothelial cells. This suppresses the downstream effects of KDR/Flk-1 signaling, such as the activation of ERK, p38 MAPK, and p125FAK, and thus blocks cell proliferation.

Studies have shown that administration of Endostatin to mice bearing Lewis lung carcinoma, T24 fibrosarcoma or B16F10 melanoma caused regression of these tumors without the development of drug resistance. Endostatin treatment has been reported to reduce the levels of antiapoptotic proteins Bcl-2 and Bcl-x<sub>L</sub> and increase apoptosis of endothelial cells. However, these effects are not observed in several types of nonendothelial cells. Angiostatin, another important natural inhibitor, is an approximate 38 kDa internal fragment comprised of the first four kringle regions of plasminogen. Systemic administration of Angiostatin has been reported to inhibit primary carcinomas in mice. Studies to determine the endogenous source of Angiostatin have shown that the matrix metalloproteinase-2 (MMP-2, Gelatinase A) produced by Lewis lung carcinoma cells, can process plasminogen to yield active angiostatin. Differential processing of plasminogen can yield two additional fragments with antiangiogenic properties, kringles 1-3 and kringles 1-5.

Studies of endothelial cell inhibition have shown that the kringles 1-3 fragment has a greater inhibitory activity than the kringles 1-4 fragment (ED<sub>50</sub> for kringles 1-3 = 70 nM vs 135 nM for kringles 1-4). However, one *in vivo* study suggests that both fragments are equipotent; administration of 30 nmol/kg/day of either fragment resulted in the inhibition of experimental B16-BL6 lung metastases by greater than 80%. The smaller sized, non-glycosylated kringles 1-3 fragment has also been shown to inhibit brain tumor growth by 71% when administered subcutaneously, and by 85% when administered systemically. Systemic administration of kringles 1-5 also suppressed the growth of murine T241 fibrosarcoma in mice and significantly reduced neovascularization. Use of Angiostatin as a therapeutic agent is still in question due to the high doses and repeated injections required in animal studies, however, potential does exist in the area of gene therapy.

#### References:

- |   |   |   |
|---|---|---|
| Young-Mi, K., et al. 2002. <i>J. Biol. Chem.</i> <b>277</b> , 27872.      | MacDonald, N.J., et al. 1999. <i>Biochem. Biophys. Res. Commun.</i> <b>264</b> , 469. | Boehm, T., et al. 1998. <i>Biochem. Biophys. Res. Commun.</i> <b>252</b> , 190. |
| Bleizinger, P., et al. 1999. <i>Nat. Biotechnol.</i> <b>17</b> , 343.     | Meneses, O.I., et al. 1999. <i>Clin. Cancer Res.</i> <b>5</b> , 3689.                 | Brooks, P.C., et al. 1998. <i>Cell</i> <b>92</b> , 391.                         |
| Cao, Y. 1999. <i>Haematologica</i> <b>84</b> , 643.                       | Miosge, N., et al. 1999. <i>FASEB J.</i> <b>13</b> , 1743.                            | Ding, Y.H., et al. 1998. <i>Proc. Natl. Acad. Sci. USA</i> <b>95</b> , 10443.   |
| Cao, R., et al. 1999. <i>Proc. Natl. Acad. Sci. USA</i> <b>96</b> , 5728. | O'Reilly, M.S., et al. 1999. <i>J. Biol. Chem.</i> <b>274</b> , 29568.                | Hohenester, E., et al. 1998. <i>EMBO J.</i> <b>17</b> , 1656.                   |
| Dhanabal, M., et al. 1999. <i>J. Biol. Chem.</i> <b>274</b> , 11721.      | Ramchandran, R., et al. 1999. <i>Biochem. Biophys. Res. Commun.</i> <b>255</b> , 735. | Boehm, T., et al. 1997. <i>Nature</i> <b>390</b> , 404.                         |
| Joe, Y.A., et al. 1999. <i>Int. J. Cancer</i> <b>82</b> , 694.            | Wen, W., et al. 1999. <i>Cancer Res.</i> <b>59</b> , 6052.                            | O'Reilly, M.S., et al. 1997. <i>Cell</i> <b>88</b> , 277.                       |
| John, H., et al. 1999. <i>Biochemistry</i> <b>38</b> , 10217.             | Yoon, S.S., et al. 1999. <i>Cancer Res.</i> <b>59</b> , 6251.                         | Sim, B.K., et al. 1997. <i>Cancer Res.</i> <b>57</b> , 1329.                    |
|   |   | Cao, Y., et al. 1996. <i>J. Biol. Chem.</i> <b>271</b> , 29461.                 |
|   |   | O'Reilly, M.S., et al. 1994. <i>Cell</i> <b>79</b> , 315.                       |

## Products for Angiogenesis and Tumor Metastasis Research

### Inhibitors of Angiogenesis

Product	Cat. No.	Size	Price
AG 1433	658553	5 mg	
Amiloride, HCl	129876	100 mg	
Angiogenin (108-123)	175602	1 mg	
Angiopoietin-2, His•Tag®, Human, Recombinant, Mouse, Biotin Conjugate	176600	10 µg	
Angiostatin® Protein, Human <sup>1</sup>	176700	500 µg	
Angiostatin K1-3, Human	176705	250 µg	
Angiostatin K1-5, Human	176706	250 µg	
Apigenin	178278	5 mg	
Aurintricarboxylic Acid	189400	100 mg	
Captopril	211875	1 g	
Castanospermine, <i>Castanospermum australe</i>	218775	1 mg	
D609, Potassium Salt	251400	5 mg	
Daidzein	251600	25 mg	
DL-α-Difluoromethylornithine, HCl	288500	25 mg	
Endostatin™ Protein, Mouse, Recombinant, <i>Pichia pastoris</i> <sup>2</sup>	324733	250 µg 1 mg	
Endostatin™ Protein, His•Tag®, Mouse, Recombinant, <i>Spodoptera frugiperda</i> <sup>2</sup>	324743	250 µg 500 µg	
Endostatin™ Protein, Human, Recombinant, <i>Pichia pastoris</i> <sup>2</sup>	324746	250 mg 1 mg	
Eriochrome® Black T	329740	1 g	
Fumagillin, <i>Aspergillus fumigatus</i>	344845	500 µg	
Genistein	345834	20 mg 50 mg	
Herbimycin A, <i>Streptomyces</i> sp.	375670	100 µg	
4-Hydroxyphenylretinamide	390900	5 mg	
α-Interferon, Mouse, Recombinant, <i>E. coli</i>	407293	100 TU**	
γ-Interferon, Human, Recombinant, <i>E. coli</i>	407306	1 MU**	
γ-Interferon Inducible Protein 10, Human, Recombinant, <i>E. coli</i>	407350	10 µg	
Laminin Hexapeptide	428030	1 mg	
Laminin Pentapeptide	05-23-3700	5 mg	
Lavendustin A	428150	1 mg	
Medroxyprogesterone Acetate	444400	500 mg	
2-Methoxyestradiol	454180	10 mg 50 mg	
Mifepristone	475838	50 mg	
Minocycline, HCl	475843	50 mg	
Neomycin Sulfate	4801	25 g	
Plasminogen Activator Inhibitor-1, Human, Recombinant	528205	50 µg	

Angiogenesis  
Inhibitors,  
continued

\*Not for sale in the United States

\*\*1 TU = 1,000 units / 1 MU = 1,000,000 units

1 Sold under license of U.S. Patent 6,024,688 and corresponding patents

2 Sold under license of U.S. Patent 5,854,205

## Products for Angiogenesis and Tumor Metastasis Research

### Angiogenesis Inhibitors, continued

### Inhibitors of Angiogenesis, cont.

Product	Cat. No.	Size	Price
Plasminogen Activator Inhibitor-1, Mutant, Human, Recombinant	528208	50 µg	
Plasminogen Activator Inhibitor-1, Mutant, Mouse, Recombinant	528213	50 µg	
Plasminogen Activator Inhibitor-1, Rat, Recombinant	528214	50 µg	
Platelet Factor 4, Human Platelets	521726	100 µg	
Prolactin, Human Pituitary, Iodination Grade	869039	5 µg	
Radical, <i>Diheterospora chlamydosporia</i>	553400	500 µg	
Rapamycin	553210	100 µg 1 mg	
RHC-80267	554994	10 mg	
Ribonuclease Inhibitor, Human Placental, Recombinant	556883	2500 U	
Shikonin	565850	10 mg	
SMC Proliferation Inhibitor-2w	573117	5 mg	
SU1498	572888	5 mg	
SU5614*	572632	1 mg	
Suramin, Sodium Salt	574625	50 mg 200 mg	
(±)-Thalidomide	585970	100 mg	
Thrombospondin, Human Platelets	605225	25 µg	
Tranilast	616400	10 mg	
Troponin I, Human Heart	648480	100 µg	
TSRI265	654100	1 mg	
VEGF Inhibitor, Flt <sub>2-11</sub> <sup>3</sup>	676493	1 mg	
VEGF Inhibitor, Je-11	676494	500 µg 1 mg	
VEGF Inhibitor, V1	676495	1 mg	
VEGF Receptor Tyrosine Kinase Inhibitor	676475	1 mg	
VEGF Receptor 2 Inhibitor I	676480	1 mg	
VEGF Receptor 2 Inhibitor II	676485	1 mg	

### Antibodies to Angiogenesis Inhibitors

### Antibodies to Angiogenesis Inhibitors

Antibody	Cat. No.	Species Reactivity	Applications	Size	Price
Anti-Angiopoietin-2, Mouse (Rabbit)	176002	Human, Mouse	ELISA, IB	50 µg	
Anti-Angiostatin (Ab-1) (Rabbit)	PC371	Human	IB, IF	20 µg 100 µg	
Anti-Angiostatin (Ab-2) (Mouse)	GF47	Human	IB, IP	10 µg 100 µg	
Anti-Angiostatin (Ab-3) (Mouse)	GF49	Human	IB, IP	10 µg 100 µg	
Anti-Angiostatin (Ab-4) (Mouse)	GF50	Human	IB, IP	10 µg 100 µg	

**Applications:** **ELISA:** Enzyme-Linked Immunosorbent Assay; **IB:** Immunoblotting (Western Blotting);  
**IF:** Immunofluorescence; **IP:** Immunoprecipitation

\* Not for sale in the United States

<sup>3</sup> Sold under license of U.S. Patent 6,200,954

## Products for Angiogenesis and Tumor Metastasis Research

### Antibodies to Angiogenesis Inhibitors, cont.

Antibody	Cat. No.	Species Reactivity	Applications	Size	Price
Anti-Angiostatin (Ab-5) (Mouse)	GF55T GF55	Human	ELISA, IB	10 µg 100 µg	
Anti-Endostatin (Ab-2) (Rabbit)	PC541T PC541	Human	IB	10 µg 100 µg	
Anti-Endostatin (Ab-3) (Mouse)	GF56	Human	ELISA, IB	100 µg	
Anti-Endostatin (Ab-4) (Rabbit)	PC599	Human	IB	100 µl	
Anti-Endostatin (Ab-5) (Mouse)	GF57	Human	IB	100 µg	
Anti-METH-1 (Ab-1) (Rabbit)	PC507	Human	PS	10 µl 100 µl	
Anti-METH-1 (Ab-2) (Rabbit)	PC509T PC509	Human	PS	10 µl 100 µl	
Anti-METH-2 (Ab-1) (Rabbit)	PC508T PC508	Human	IB, PS	10 µl 100 µl	
Anti-Plasminogen, Kringles 1-3, Human (Mouse)	528176	Human	IB	500 µg	
Anti-Thrombospondin (Ab-1) (Mouse)	BA18	Human	FC, FS, IF, IP, PS	100 µg	
Anti-Thrombospondin (Ab-2) (Mouse)	BA23	Bovine, Human, Rat	FC, FS, IB, IF, IP, NT	100 µg	
Anti-Thrombospondin (Ab-3) (Mouse)	BA24	Bovine, Dog, Horse, Human, Pig, Rat	FC, FS, IB, IF	100 µg	
Anti-VEGI (Ab-1) (Rabbit)	PC564T PC564	Human, Mouse	PS	10 µg 100 µg	

Antibodies to  
Angiogenesis  
Inhibitors,  
continued



**A**

**B**

**Panel A** shows detection of angiostatin using Angiostatin (Ab-1), Cat. No. PC371, and a FITC-conjugated secondary antibody.

**Panel B:** Cell nuclei stained with propidium iodide.

**Applications:** **ELISA:** Enzyme-Linked Immunosorbent Assay; **FC:** Flow Cytometry; **FS:** Frozen Sections; **IB:** Immunoblotting (Western Blotting); **IC:** Immunocytochemistry; **IF:** Immunofluorescence; **IH:** Immunohistochemistry; **IP:** Immunoprecipitation; **NT:** Neutralization; **PS:** Paraffin Sections

## Cathepsins and Related Products

### Cathepsins

Cathepsins, the lysosomal proteases, are widely distributed in normal tissues and are involved in a variety of physiological processes. They are synthesized as pre-proenzymes that are post-translationally glycosylated and phosphorylated to active enzyme. Oncogenic factors, chemokine stimulation, and other signaling events may lead to disturbances in their transport to lysosomes, resulting in cytosolic cathepsin activity or secretion of the proenzyme to the extracellular matrix. Higher levels of several cathepsins have been associated with the pathological destruction of the extracellular matrix, leading to tumor metastasis, atherosclerosis, emphysema, osteoporosis, and rheumatoid arthritis.

Cathepsins B, H, K, L, and S are endopeptidases that belong to the papain cysteine protease superfamily. However, Cathepsin B has been shown to exhibit dipeptidylcarboxypeptidase activity and Cathepsin H has aminopeptidase activity. Cathepsin K is selectively produced by osteoclasts and is involved in bone resorption. It has the ability to completely dissolve insoluble type I collagen of human cortical bone by cleaving the molecule at multiple points. Cathepsin L is widely expressed in various tissues. Increased expression of Cathepsin L by metastatic bone tumors suggests this enzyme may participate in tumor invasion by either directly degrading barriers such as the basement membrane or indirectly by processing other latent extracellular matrix proteases and degrading their protein inhibitors.

Cathepsin D is an aspartyl lysosomal protease expressed in all tissues. It exhibits a catalytic pH in the range of 3 and 5. It is reported to be involved in the degradation of the tissue plasminogen activator/plasminogen activator complexes internalized by human monocytes. Following hypoxia or necrosis, Cathepsin D undergoes a translocation from lysosomes to the cytosol and the extracellular matrix. Metastatic breast cancer cell lines exhibit higher levels of 52 kDa pro-cathepsin D, which is cleaved to the enzymatically active 48 kDa heterodimer (two chains of 14 and 34 kDa) that may promote metastasis. Cathepsin D may also be involved in the processing of growth factors and inhibitors that allow metastatic foci to form.

Cathepsin G is a serine protease produced by neutrophils. Priming of neutrophils with TNF- $\alpha$  or LPS and subsequent stimulation with chemoattractants such as fMLP results in approximately 160 ng of catalytically active Cathepsin G per  $10^6$  cells. This focused catalytic activity may alter the endothelial barrier and extracellular matrix to allow neutrophil migration to the site of injury, but may also cause excessive tissue destruction during periods of acute inflammation.

#### References:

- Garnero, P., et al. 1998. *J. Biol. Chem.* **273**, 32347.  
 Ishidoh, K., and Kominami, E. 1998. *Biol. Chem.* **370**, 131.  
 Turk, B., et al. 1997. *Biol. Chem.* **378**, 141.  
 Bankowska, A., et al. 1997. *Rocz. Akad. Med. Bialymst.* **42**, 79.  
 Gacko, M., et al. 1997. *Rocz. Akad. Med. Bialymst.* **42**, 60.  
 Park, I.C., et al. 1996. *J. Korean Med. Sci.* **11**, 144.  
 Berquin, I.M., and Sloane, B.F. 1996. *Adv. Exp. Med. Biol.* **389**, 281.  
 Simon, D.I., et al. 1995. *Biochim. Biophys. Acta* **59**, 63.  
 Owen, C.A. et al. 1995. *J. Immunol.* **155**, 5803.  
 Chapman, H.A., et al. 1991. *Annu. Rev. Physiol.* **59**, 63.

#### Total Cathepsin D ELISA Kit

Format: 96 well plate      Sensitivity: = 4 ng/ml  
 Assay Range: 0 - 100 ng/ml      Assay Time: 5 hours

A non-isotopic immunoassay for the *in vitro* measurement of human cathepsin D in tissue cytosol extracts and cell culture extracts. Suitable for 96 determinations.

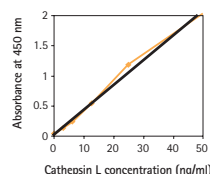


Cat. No. QIA29      1 Kit

#### Cathepsin L ELISA Kit

Format: 96 well plate      Sensitivity:  $\leq 2.6$  ng/ml  
 Assay Range: 3 - 50 ng/ml      Assay Time: 3.5 hours

Can be used to measure human cathepsin L in prostate carcinoma, breast cancer, malignant melanoma, colorectal carcinoma, rheumatoid arthritis, aortic aneurysm, and parietal thrombus. Species reactivity: Human.



Cat. No. QIA94      1 Kit

## Cathepsins and Related Products

### Antibodies to Cathepsins

Product	Cat. No.	Species Reactivity	Applications	Size	Price
Anti-Cathepsin B (Ab-1) (Mouse)	IM27L	Bovine, Human, Porcine	IB, IP	20 µg 100 µg	
Anti-Cathepsin B (Ab-3) (Rabbit)	PC41	Human	IB, PS	100 µg	
Anti-Cathepsin B, Human (Rabbit)	219408	Human	ELISA, IB, RID	1 ml	
Anti-Cathepsin D (Ab-1) (Mouse)	IM03	Human	IB, PS	100 µg	
Anti-Cathepsin D (Ab-2) (Rabbit)	IM16	Human	FS, IB, PS	100 µg	
Anti-Cathepsin D, Human (Rabbit)	219361	Human	ELISA	1 ml	
Anti-Pro-Cathepsin D (Ab-1) (Rabbit)	IM04L	Human	IB, PS	100 µg	
Pro-Cathepsin D Blocking Peptide	PP42	—	—	100 µg	
Anti-Cathepsin G, Human (Rabbit)	219358	Human	ELISA, IB	1 ml	
Anti-Cathepsin K (Ab-1) (Mouse)	IM55L	Human	IB	100 µg	
Anti-Cathepsin K, Human (Rabbit)	219386	Human	IB	100 µl	
Anti-Cathepsin L, Human (Rabbit)	219387	Human	IB	100 µl	
Anti-Cathepsin S, Bovine (Rabbit)	219389	Bovine, Human	IB	100 µl	
Anti-Cathepsin S, Human (Rabbit)	219384	Human	IB	100 µl	

**Applications:** **ELISA:** Enzyme-Linked Immunosorbent Assay; **FS:** Frozen Sections; **IB:** Immunoblotting (Western Blotting); **IF:** Immunofluorescence; **IP:** Immunoprecipitation; **PS:** Paraffin Sections; **RID:** Radial Immunodiffusion

#### Cathepsin Antibodies

### Cathepsins

Product	Cat. No.	Size	Price
Cathepsin B, Bovine Spleen	219366	10 U	
Cathepsin B, Human Liver	219362	50 µg	
Cathepsin B, Human Liver	219364	5 U	
Cathepsin D, Bovine Kidney	219398	300 U	
Cathepsin D, Bovine Spleen	219396	1000 U	
Cathepsin D, Human Liver	219401	15 U 30 U	
Cathepsin D, Human Spleen	219394	50 µg	
Cathepsin G, Human Neutrophil	219373	100 mU*	
Cathepsin H, Bovine Kidney	219416	100 µg	
Cathepsin H, Human Liver	219404	25 µg	
Cathepsin L, Bovine Kidney	219418	300 mU*	
Cathepsin L, Human Liver	219402	25 µg	
Cathepsin L, <i>Paramecium tetraurelia</i>	219412	500 mU*	
Cathepsin S, Bovine Spleen	219388	25 µg	
Chymase, Human Skin	230780	10 µg	
Trypsin, Human Lung	650366	25 µg	

\* 1 mU = 0.001 units

#### Enzymes and Proteins

## Cathepsins and Related Products

### Cathepsin Substrates

### Cathepsin Substrates

Product	Cat. No.	Size	Price
Z-Arg-Arg-7-amido-4-methylcoumarin, DiHCl	03-32-1570	5 mg 25 mg	
Cathepsin B Substrate I, Colorimetric	219405	5 mg	
Cathepsin B Substrate II	219391	25 mg	
Cathepsin B Substrate III, Fluorogenic	219392	25 mg	
Cathepsin D Substrate I	219399	10 mg	
Cathepsin G Substrate I, Colorimetric	219407	25 mg	
Cathepsin G Substrate II, Colorimetric	219410	25 mg	
Cathepsin G Substrate III, Water-Soluble, Colorimetric	219438	5 mg	
Cathepsin H Substrate II, Fluorogenic	219414	25 mg	

### Cathepsin Inhibitors

### Cathepsin Inhibitors

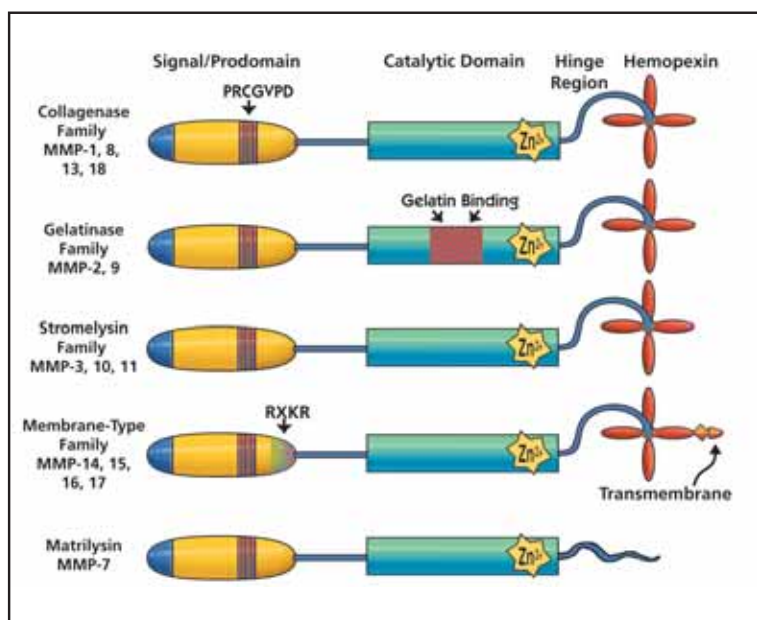
Product	Cat. No.	Size	Price
CA-074	205530	1 mg	
CA-074 Me	205531	1 mg	
Cathepsin Inhibitor I	219415	1 mg	
Cathepsin Inhibitor II	219417	1 mg	
Cathepsin Inhibitor III	219419	1 mg	
Cathepsin B Inhibitor I (Caspase Inhibitor, Negative Control)	342000	1 mg 5 mg	
Cathepsin B Inhibitor II	219385	1 mg	
Cathepsin K Inhibitor I	219377	5 mg	
Cathepsin L Inhibitor I	219421	1 mg	
Cathepsin L Inhibitor II	219426	5 mg	
Cathepsin L Inhibitor III	219427	5 mg	
Cathepsin L Inhibitor IV	219433	1 mg	
Cathepsin L Inhibitor V	219435	1 mg	
Cathepsin S Inhibitor	219393	1 mg	
Cathepsin/Subtilisin Inhibitor	219420	1 mg	
Cystatin, Egg White	240891	500 µg 1 mg	
Cystatin C, Human Urine	240896	50 µg	

## Matrix Metalloproteinases (MMPs) and Related Products

### Matrix Metalloproteinases

Matrix Metalloproteinases (MMPs) are a family of zinc metallo-endorpeptidases secreted by normal and tumor cells that are responsible for much of the turnover of extracellular matrix components. MMPs are involved in a wide range of proteolytic events, in normal and pathological circumstances. Normal physiological roles for MMPs include neurite growth, cell migration, bone elongation, wound healing, angiogenesis, ovulation, sperm maturation, uterine involution, menstruation, mammary gland development, and embryo implantation. Pathological processes involving MMPs include tumor growth and migration, fibrosis, arthritis, glaucoma, lupus, scleroderma, cirrhosis, multiple sclerosis, aortic aneurysms, infertility, and many more diseases.

MMPs and  
Related Products



### Assay Kits

Product	Cat. No.	Size	Price
Active MMP Purification Kit	QIA102	1 Kit	
MMP-1 ELISA Kit*	QIA55	1 Kit	
MMP-1/TIMP-1 ELISA Kit*	QIA49	1 Kit	
MMP-2 ELISA Kit*	QIA63	1 Kit	
MMP-3 ELISA Kit	QIA73	1 Kit	
MMP-3/TIMP-1 ELISA Kit*	QIA50	1 Kit	
MMP-3 Inhibitor Screening Assay, Colorimetric	QIA103	1 Kit	
MMP-3 Inhibitor Screening Assay, Fluorometric	QIA104	1 Kit	
MMP-9 ELISA Kit	QIA56	1 Kit	
TIMP-1 ELISA Kit*	QIA54	1 Kit	
TIMP-2 ELISA Kit*	QIA40	1 Kit	

\* Not for sale in Japan

Assay Kits

## Matrix Metalloproteinases (MMPs) and Related Products

### MMPs and Related Products

Product	Cat. No.	Size	Price
p-Aminophenylmercuric Acetate (1 Set = 5 x 700 mg)	164610	700 mg 1 Set	
Atrolysin C, <i>Crotalus atrox</i>	189350	10 µg 50 µg	
ADAM10, His•Tag®, Recombinant Protein	PF124	20 µg	
ADAMTS4, Truncated, His•Tag®, Human, Recombinant	PF113	5 µg	
Aggrecan Interglobular Domain, His•Tag®, Human, Recombinant	PF114	100 µg	
MMP/TIMP Positive Control, Human Fibroblast	PF069	250 µl	
MMP-1, Human Protein	PF067	5 µg	
MMP-1 Proenzyme, Human Rheumatoid Synovial Fibroblast	444208	5 µg	
Active MMP-2 Enzyme, Human	PF023	5 µg	
Proenzyme MMP-2, Human Rheumatoid Synovial Fibroblast	444213	5 µg	
Proenzyme MMP-2, Human	PF037	10 µg	
Proenzyme MMP-2, Mouse Calvariae	PF118	5 µg	
MMP-2/TIMP-2 Complex, Human Rheumatoid Synovial Fibroblast	444214	5 µg	
MMP-2/TIMP-2, Mouse Calvariae	PF119	5 µg	
Proenzyme MMP-2, Murine Macrophage	444227	10 µg	
MMP-3, Catalytic Domain, Human, Recombinant	444217	5 µg	
Proenzyme MMP-3, Human	PF063	10 µg	
MMP-7, Active, Human, Recombinant, <i>E. coli</i>	444270	100 µg	
Proenzyme MMP-7, Human, Recombinant, <i>E. coli</i>	538540	100 µg	
MMP-8, Human Neutrophil	444229	5 µg	
MMP-9, Human, Recombinant	PF024	5 µg	
MMP-9, Monomer, Human Neutrophil	444231	5 µg	
MMP-9, Dimer, Human Neutrophil	444232	5 µg	
MMP-9-Lipocalin Complex, Human Neutrophil	444233	5 µg	
MMP-9-Lipocalin-TIMP-1 Complex, Human Neutrophil	444234	5 µg	
MMP-9/TIMP-1, Human Neutrophil	PF120	5 µg	
Proenzyme MMP-9	PF038	10 µg	
Proenzyme MMP-9, Mouse, Recombinant	PF068	5 µg	
MMP-12 Positive Control, Human	PF093	250 µl	
MMP-13 Positive Control, Human	PF094	250 µl	
Proenzyme MMP-13, His•Tag®, Human, Recombinant, <i>Spodoptera frugiperda</i>	444248	10 µg	
MT1-MMP, Catalytic Domain, Human, Recombinant, <i>E. coli</i>	475935	10 µg	
MT1-MMP Hemopexin Domain, His•Tag®, Human, Recombinant	PF115	20 µg	
MT1-MMP, Prodomain-Catalytic Domain, His•Tag®, Human, Recombinant, <i>E. coli</i>	475936	10 µg	
MT1-MMP, Soluble Proenzyme, His•Tag®, Human, Recombinant, <i>E. coli</i>	475937	10 µg	
MT2-MMP, Catalytic Domain, Human, Recombinant, <i>E. coli</i>	475938	10 µg	
MT2-MMP Hemopexin Domain, His•Tag®, Human, Recombinant	PF116	20 µg	

#### MMPs and Related Products

## Antibodies to MMPs and Related Products

### MMPs and Related Products, cont.

Product	Cat. No.	Size	Price
MT3-MMP, Catalytic Domain, Human, Recombinant, <i>E. coli</i>	475939	10 µg	
MT4-MMP, Catalytic Domain, His•Tag®, Human, Recombinant, <i>E. coli</i>	475940	10 µg	
MT5-MMP, Catalytic Domain, His•Tag®, Human, Recombinant	PF117	10 µg	
TACE, His•Tag®, Recombinant Protein	PF133	10 µg	

MMPs and  
Related Products,  
continued

### Antibodies to MMPs and Related Products

Product	Cat. No.	Species Reactivity	Applications	Size	Price
Anti-ADAM9 (Ab-1) (Goat)	PC669	Human	ELISA, IB, IP	100 µg	
Anti-ADAM10 (Ab-1) (Rabbit)	PC528	Human	IB	100 µg	
Anti-ADAM10 (240-259), Mouse (Rabbit)	422750	Human, Mouse	IB	100 µl	
Anti-ADAM10 (735-749), Mouse (Rabbit)	422751	Hamster, Human, Mouse	IB	100 µl	
Anti-ADAM15 (Ab-1) (Rabbit)	PC670	Human, Mouse	IB, IF, IP	100 µl	
Anti-BMP-1 (Ab-1) (Rabbit)	PC571T PC571	Human	IB	5 µg 50 µg	
Anti-BMP-1 (Ab-2) (Rabbit)	PC572T PC572	Human	IB	5 µg 50 µg	
Anti-BMP-1 (Ab-3) (Rabbit)	PC573T PC573	Human	IB	5 µg 50 µg	
Anti-BMP-2/4, N-Terminal, Human (Rabbit)	203640	Human	ELISA, IB, IP	100 µg	
MMP/TIMP Family Antibody Sampler Kit I	ASK10			1 Kit	
MMP/TIMP Family Antibody Sampler Kit II	ASK17			1 Kit	
Anti-MMP-1 (Ab-1) (Mouse)*	IM35L	Human	FS, IB, PS	20 µg 100 µg	
Anti-MMP-1 (Ab-2) (Mouse)*	IM52T IM52L	Human	IB	10 µg 100 µg	
Anti-MMP-1 (Ab-3) (Rabbit)	PC311T PC311	Human	IB	10 µg 200 µg	
Anti-MMP-1 (Ab-5) (Mouse)*	IM66T IM66	Human	IF	10 µg 100 µg	
Anti-MMP-1 (Ab-6) (Mouse)*	IM67T IM67	Human	IB, IP	10 µg 100 µg	
Anti-MMP-1, Human (Rabbit)	444209	Human, Marmoset, Rabbit	ELISA, IB IF, IH, IP	500 µl	
Anti-MMP-2 (Ab-3) (Mouse)*	IM33T IM33L	Bovine, Human, Mouse, Rat	FS, IB, PS	10 µg 100 µg	
Anti-MMP-2 (Ab-4) (Mouse)*	IM51L	Human, Rat	FS, IB, IH, PS	20 µg 100 µg	
Anti-MMP-2 (Ab-5) (Sheep)	PC312T PC312	Human	IB	10 µg 200 µg	
Anti-MMP-2 (Ab-6) (Mouse)	IM53T IM53	Human	FS, IB, IP, IS	10 µg 100 µg	
Anti-MMP-2 (Ab-7) (Rabbit)	PC342	Human, Mouse	IB, IP	100 µg	

\* Not for sale in Japan

**Applications:** **ELISA:** Enzyme-Linked Immunosorbent Assay; **FC:** Flow Cytometry; **FS:** Frozen Sections; **IB:** Immunoblotting (Western Blotting); **IC:** Immunocytochemistry; **IF:** Immunofluorescence; **IH:** Immunohistochemistry; **IP:** Immunoprecipitation; **PS:** Paraffin Sections

Antibodies to  
MMPs and  
Related Products

## Antibodies to MMPs and Related Products

### Antibodies to MMPs and Related Products, cont.

#### Antibodies to MMPs and Related Products, continued

Product	Cat. No.	Species Reactivity	Applications	Size	Price
Anti-MMP-2 (Ab-8) (Mouse)*	IM68T IM68	Human	IB, IF	10 µg 100 µg	
Anti-MMP-2 (Ab-9) (Mouse)	IM83T IM83	Rat	IB, PS	10 µg 100 µg	
Anti-MMP-2 (Ab-10) (Mouse)	IM84T IM84	Rat	PS	10 µg 100 µg	
Anti-MMP-2 (Ab-11) (Mouse)	IM85T IM85	Rat	PS	10 µg 100 µg	
Anti-MMP-3 (Ab-1) (Mouse)*	IM36T IM36L	Human, Pig, Sheep	FS, IB, PS	10 µg 100 µg	
Anti-MMP-3 (Ab-2) (Mouse)*	IM45T IM45L	Rabbit	FS, IB, PS	10 µg 100 µg	
Anti-MMP-3 (Ab-3) (Rabbit)	PC310T PC310	Human	IB	10 µg 200 µg	
Anti-MMP-3 (Ab-4) (Mouse)*	IM69T IM69	Human	IB, IF, IP	10 µg 100 µg	
Anti-MMP-3 (Ab-5) (Mouse)*	IM70T IM70	Human	FS, IB, IF, IP, PS	10 µg 100 µg	
Anti-MMP-3, Rabbit (Guinea Pig)	444222	Human, Marmoset, Rabbit	ELISA, IB, IF, IH, IP	500 µl	
Anti-MMP-7 (Ab-1) (Mouse)*	IM40T IM40L	Human	IB, PS	10 µg 100 µg	
Anti-MMP-7 (Ab-2) (Mouse)*	IM47T IM47L	Human	IB	10 µg 100 µg	
Anti-MMP-7 (Ab-3) (Mouse)*	IM71T IM71	Human	FS, IB, IF, PS	10 µg 100 µg	
Anti-MMP-7 (Ab-4) (Rabbit)	PC492	Human, Mouse, Rat	IB	50 µg	
Anti-MMP-8 (Ab-1) (Mouse)*	IM38L	Human	IB, PS	20 µg 100 µg	
Anti-MMP-8 (Ab-2) (Rabbit)	PC493	Human	FS, IB, IP, PS	50 µg	
Anti-MMP-9 (Ab-1) (Mouse)*	IM09T IM09L	Human	IB, IP, NT	10 µg 100 µg	
Anti-MMP-9 (Ab-3) (Mouse)*	IM37T IM37L	Guinea Pig, Human Rabbit, Rat	FS, IB, PS	10 µg 100 µg	
Anti-MMP-9 (Ab-5) (Sheep)	PC309	Human	IB	200 µg	
Anti-MMP-9 (Ab-6) (Mouse)*	IM60T IM60L	Human	IB	10 µg 100 µg	
Anti-MMP-9 (Ab-7) (Mouse)*	IM61T IM61	Human	FS, IB, IP, PS	10 µg 100 µg	
Anti-MMP-9 (Ab-8) (Mouse)*	IM72T IM72	Human	FS, IB, IF, PS	10 µg 100 µg	
Anti-MMP-9 (Ab-9) (Mouse)*	IM73T IM73	Rat	IB	10 µg 100 µg	
Anti-MMP-9 (Ab-10) (Mouse)*	IM74T IM74	Rat	IB, IF, NT	10 µg 100 µg	

\* Not for sale in Japan

**Applications:** **ELISA:** Enzyme-Linked Immunosorbent Assay; **FC:** Flow Cytometry; **FS:** Frozen Sections;  
**IB:** Immunoblotting (Western Blotting); **IC:** Immunocytochemistry; **IF:** Immunofluorescence;  
**IH:** Immunohistochemistry; **IP:** Immunoprecipitation; **NT:** Neutralization; **PS:** Paraffin Sections

## Antibodies to MMPs and Related Products

### Antibodies to MMPs and Related Products, cont.

Product	Cat. No.	Species Reactivity	Applications	Size	Price
Anti-MMP-9, Human (Rabbit)	444236	Human, Marmoset	ELISA, IB, IF, IH, IP	500 µl	
Anti-MMP-10 (Ab-1) (Mouse)*	IM54T IM54L	Human	IB	10 µg 100 µg	
Anti-MMP-10 (Ab-2) (Mouse)*	IM75T IM75	Human	IB	10 µg 100 µg	
Anti-MMP-10 (Ab-3) (Mouse)*	IM76T IM76	Human	FS, IB, PS	10 µg 100 µg	
Anti-MMP-11 (Ab-1) (Rabbit)	PC467T PC467	Human	IB	10 µg 500 µg	
Anti-MMP-11 (Ab-2) (Mouse)	IM86T IM86	Human	FS, IB, PS	10 µg 100 µg	
Anti-MMP-12 (Ab-1) (Rabbit)	PC494	Human	IB	50 µg	
Anti-MMP-13 (Ab-1) (Mouse)*	IM44L	Human	IB, PS	20 µg 100 µg	
Anti-MMP-13 (Ab-2) (Rabbit)	PC326T PC326	Human	IB	10 µg 200 µg	
Anti-MMP-13 (Ab-3) (Mouse)*	IM64T IM64L	Human	IB, PS	10 µg 100 µg	
Anti-MMP-13 (Ab-4) (Mouse)*	IM78T IM78	Human, Mouse	FS, IB, PS	10 µg 100 µg	
Anti-MMP-13 (Ab-5) (Mouse)*	IM79T IM79	Human, Mouse	FS, IB, IF, PS	10 µg 100 µg	
Anti-MMP-13 (Ab-6) (Mouse)*	IM80T IM80	Mouse, Rat	IB, IF	10 µg 100 µg	
Anti-MMP-13 (Ab-7) (Mouse)*	IM81T IM81	Mouse, Rat	IB, IF	10 µg 100 µg	
Anti-MMP-13 (Ab-8) (Rabbit)	PC542T PC542	Human	IB, PS	10 µg 100 µg	
Anti-MMP-13 (Ab-9) (Mouse)	IM87	Human	IB	100 µg	
Anti-MMP-18 (Ab-1) (Rabbit)	PC495T PC495	<i>Xenopus</i>	IB	5 µg 50 µg	
Anti-MMP-18, Human (Rabbit)	475869	Human	IB, IP	100 µl	
Anti-MMP-19 (Ab-1) (Rabbit)	PC374T PC374	Human	IB, PS	5 µg 100 µg	
Anti-MMP-19 (Ab-2) (Rabbit)	PC496T PC496	Human	IB	5 µg 50 µg	
Anti-MMP-20 (Ab-2) (Rabbit)	PC497T PC497	Human	IB	5 µg 50 µg	
Anti-MMP-23 (Ab-1) (Rabbit)	PC470	Human	IB	10 µg 100 µg	
Anti-MMP-23 (Ab-2) (Rabbit)	PC566	Human	IB	50 µg	
Anti-MMP-23 (Ab-3) (Rabbit)	PC567	Human	IB	50 µg	
Anti-MT1-MMP (Ab-1) (Mouse)*	IM39T IM39L	Human	IB, IP	10 µg 100 µg	
Anti-MT1-MMP (Ab-2) (Rabbit)	PC94T PC94	Human	IB	10 µg 100 µg	

Antibodies to MMPs  
and  
Related Products,  
continued

For Support Call Technical Service at 800-628-8470

\* Not for sale in Japan

## Antibodies to MMPs and Related Products

### Antibodies to MMPs and Related Products, cont.

#### Antibodies to MMPs and Related Products, continued

Product	Cat. No.	Species Reactivity	Applications	Size	Price
Anti-MT1-MMP (Ab-3) (Mouse) *	IM42L	Human	IB, IC, PS	20 µg 100 µg	
Anti-MT1-MMP (Ab-4) (Mouse) *	IM57T IM57	Human, Mouse, Rabbit, Rat	IB, IF, IP	10 µg 100 µg	
Anti-MT1-MMP (Ab-5) (Mouse)	IM88	Human	IB	100 µg	
Anti-MT2-MMP (Ab-1) (Mouse) *	IM48L	Human, Mouse	IB, IC, PS	20 µg 100 µg	
Anti-MT2-MMP, Human (Rabbit)	475930	Human	IB	100 µl	
Anti-MT3-MMP (Ab-1) (Mouse) *	IM50T IM50L	Human	IB	10 µg 100 µg	
Anti-MT3-MMP, Human (Rabbit)	475932	Human	IB, IP	100 µl	
Anti-MT4-MMP, Human (Rabbit)	475934	Human	IB, IP	100 µl	
Anti-MT5-MMP (Ab-1) (Rabbit)	PC499T PC499	Human, Mouse	IB	5 µg 50 µg	
Anti-MT5-MMP (Ab-2) (Rabbit)	PC568	Human, Mouse	IB	50 µg	
Anti-MT5-MMP (Ab-3) (Rabbit)	PC569	Human, Mouse	IB	50 µg	
Anti-MT5-MMP (Ab-4) (Rabbit)	PC570T PC570	Human, Mouse	IB	5 µg 50 µg	
Anti-PCOLE-1, Human (Rabbit)	208769	Human, Mouse, Porcine	IB	100 µg	
Anti-PCOLE-2, Human (Rabbit)	208770	Human, Mouse, Porcine	IB	100 µg	
Anti-TACE (Ab-1) (Rabbit)	PC491	Human, Mouse, Rat	IB	100 µg	
Anti-TACE (809-823), Human (Chicken)	616405	Human, Mouse	IB	100 µl	

\* Not for sale in Japan

#### MMP Substrates and Related Products

### MMP Substrates

Substrate specificity for MMPs is not yet fully characterized. Known substrates including most of the ECM components (fibronectin, vitronectin, laminin, entactin, tenascin, aggrecan, myelin basic protein, etc.), and the collagens (Types I, II, III, IV, V, VI, VII, VIII, IX, X, XIV), have been shown to be substrates with different efficacies. In addition to connective tissue and ECM components, proteinase inhibitors such as  $\alpha_1$ -proteinase inhibitor, antithrombin-III and  $\alpha_2$ -macroglobulin are selectively cleaved by MMPs. Growth factors such as IL-1 $\alpha$  and pro-TNF- $\alpha$  are cleaved, as are IGF binding protein-3 and IGFBP-5. The most common substrates used to study MMP activity are casein and gelatin. While gelatin (heat denatured collagen) might be considered a valid substrate for the gelatinases (MMP-2 and MMP-9), casein is not likely to be a physiologically relevant substrate. Casein is used as a generic proteinase substrate because it is digested by a wide range of proteinases. Intact Type-I collagen is cleaved at the same site on all three strands, releasing 1/4 and 3/4 length fragments. MMP-1 cleaves intact triple helical collagen efficiently, but does not work well on other substrates. Other MMPs, such as MMP-3 and MMP-7, cleave a broad range of substrates. For most of the MMPs, the substrate specificity *in vivo* is not yet defined.

Product	Cat. No.	Size	Price
Anthrax Lethal Factor Protease Substrate, Fluorogenic	176902	500 µg	
Anthrax Lethal Factor Protease Substrate II, Colorimetric	176903	1 mg	

## MMP Substrates and Related Products

### MMP Substrates, cont.

Product	Cat. No.	Size	Price
Anthrax Lethal Factor Protease Substrate III, Fluorogenic	176904	1 mg	
Aggrecan Interglobular Domain, His•Tag®, Human, Recombinant	PF114	100 µg	
MMP Substrate, Fluorogenic	444207	1 mg	
MMP Substrate II	444272	1 mg 5 mg	
MMP Substrate II, Control	444273	1 mg	
MMP Substrate III, Fluorogenic	444256	500 µg	
MMP Substrate IV, Fluorogenic	444257	500 µg	
MMP Substrate V, Fluorogenic	444254	500 µg	
MMP-1 Substrate I, Fluorogenic	444211	5 mg	
MMP-1 Substrate II	444216	1 mg	
MMP-1 Substrate III, Fluorogenic	444219	1 mg	
MMP-1/MMP-9 Substrate, Fluorogenic	444221	1 mg	
MMP-2 Substrate, Fluorogenic	444212	1 mg	
MMP-2/MMP-7 Substrate, Fluorogenic	03-32-5032	1 mg	
MMP-2/MMP-7 Substrate Control, Fluorogenic	03-32-5033	1 mg	
MMP-2/MMP-9 Substrate I, Fluorogenic	444215	5 mg	
MMP-2/MMP-9 Substrate II	444224	5 mg	
MMP-3 Substrate, Fluorogenic	444220	5 mg	
MMP-3 Substrate II, Fluorogenic	444223	500 µg	
MMP-7 Substrate, Fluorogenic	444228	1 mg	
MMP-8 Substrate, Fluorogenic	444230	5 mg	
MMP-13 Substrate, Fluorogenic	444235	1 mg	
MMP-14 Substrate I, Fluorogenic	444258	1 mg	
MMP-14 Substrate II, Fluorogenic	444259	1 mg	
NFF-2	480450	1 mg	
NFF-3	480455	1 mg	
NFF-2/NFF-3 Standard	480456	1 mg	
Plasminogen Activator Substrate	528198	25 mg	
Pro-Tumor Necrosis Factor-α-Processing Enzyme Substrate	539765	500 µg	
TACE Substrate I	616401	500 µg	
TACE Substrate II, Fluorogenic	616402	500 µg	
TACE Substrate III, Fluorogenic	616403	500 µg	
TACE Substrate IV, Fluorogenic	616407	1 mg	

MMP Substrates  
and  
Related Products,  
continued

## MMP Inhibitors and Related Products

### MMP Inhibitors and Related Products

### MMP Inhibitors and Related Products

MMPs are controlled by endogenous inhibitors, the Tissue Inhibitors of Metallo-Proteinases (TIMPs). There are currently four known TIMPs (1-4), which operate with different inhibition efficiencies against the different MMPs. The four TIMPs are also differentially expressed in tissues, and temporally follow the influx of MMPs. For example, TIMP-2 is constitutively produced, as is MMP-2, with which it is normally paired. This pairing is in fact required for the on-demand activation of MMP-2. The TIMPs are slow, tight-binding inhibitors with low nanomolar inhibition constants. TIMP-3 is localized in the extracellular matrix (ECM), and TIMP-4 is localized mostly in vascular tissue. The TIMPs have also been shown to inhibit ADAMs (A Disintegrin And Metalloproteinase), but with a much greater range of efficacy. Thus far, only TIMP-3 has been shown to be an effective ADAMs inhibitor, with inhibition constants similar to MMPs. Since there are more than forty known ADAMs family members, and no other endogenous inhibitors identified, the TIMPs may be responsible for inhibiting a large family of proteinases *in vivo*.

Product	Cat. No.	Size	Price
Anthrax Lethal Factor Protease Inhibitor, In-2-LF	176901	1 mg	
Chlorhexidine, DiHCl	220557	100 mg	
CL-82198	233105	5 mg	
Doxycycline, HCl	324385	1 g	
Fluvastatin	344095	25 mg	
GM 1489	364200	1 mg 5 mg	
GM 6001	364205	1 mg 5 mg	
GM 6001, Negative Control	364210	1 mg 5 mg	
Hinokitiol	377230	50 mg	
Minocycline, HCl	475843	50 mg	
MMP Inhibitor I	444250	10 mg	
MMP Inhibitor II	444247	1 mg	
MMP Inhibitor III	444264	1 mg	
MMP Inhibitor IV	444271	5 mg	
MMP Inhibitor Set I	444255	1 Set	
MMP-2 Inhibitor I	444244	10 mg	
MMP-2/MMP-3 Inhibitor I	444239	5 mg	
MMP-2/MMP-3 Inhibitor II	444240	2 mg	
MMP-2/MMP-9 Inhibitor I	444241	5 mg	
MMP-2/MMP-9 Inhibitor II	444249	1 mg	
MMP-2/MMP-9 Inhibitor III	444251	1 mg	
MMP-2/MMP-9 Inhibitor IV	444274	500 µg	
MMP-3 Inhibitor I	444218	5 mg	
MMP-3 Inhibitor II	444225	5 mg	
MMP-3 Inhibitor III	444242	2 mg	

## MMP Inhibitors and Related Products

### MMP Inhibitors and Related Products, cont.

Product	Cat. No.	Size	Price
MMP-3 Inhibitor IV	444243	2 mg	
MMP-3 Inhibitor V	444260	5 mg	
MMP-3 Inhibitor VI	444265	5 mg	
MMP-8 Inhibitor I	444237	1 mg	
MMP-8 Inhibitor I, Negative Control	444238	1 mg	
MMP-9/MMP-13 Inhibitor I	444252	1 mg	
MMP-9/MMP-13 Inhibitor II	444253	1 mg	
o-Phenanthroline	516705	500 mg	
Plasminogen Activator Inhibitor-1, Human, Recombinant	528205	50 µg	
Plasminogen Activator Inhibitor-1, Elastase Specific, Human, Recombinant, <i>E. coli</i>	528209	50 µg	
Plasminogen Activator Inhibitor-1, Mutant, Human, Recombinant	528208	50 µg	
Plasminogen Activator Inhibitor-1, Mutant, Mouse, Recombinant	528213	50 µg	
Plasminogen Activator Inhibitor-1, Rat, Recombinant	528214	50 µg	
TAPI-0	579050	1 mg	
TAPI-1	579051	1 mg	
TAPI-2	579052	1 mg	
DL-Thiorphan	598510	10 mg	
XG076	682300	5 mg	

MMP Inhibitors  
and  
Related Products,  
continued

### MMP Antisense Oligonucleotides

Product	Cat. No.	Size	Price
MMP-2 Antisense Oligonucleotide, Sodium Salt	444261	75 nmol	
MMP-2 Antisense Oligonucleotide, Negative Control, Sodium Salt	444262	75 nmol	
MMP-2 Antisense Oligonucleotide, Fluorescein-Labeled, Sodium Salt	444263	10 nmol	
MMP-7 Antisense Oligonucleotide, Sodium Salt	444266	75 nmol	
MMP-7 Antisense Oligonucleotide, Negative Control, Sodium Salt	444267	75 nmol	
MMP-7 Antisense Oligonucleotide, Fluorescein-Labeled, Sodium Salt	444268	10 nmol	
MMP-14 Antisense Oligonucleotide, Sodium Salt	444275	75 nmol	
MMP-14 Antisense Oligonucleotide, Negative Control, Sodium Salt	444276	75 nmol	
MMP-14 Antisense Oligonucleotide, Fluorescein-Labeled, Sodium Salt	444277	10 nmol	

For additional information on our  
Matrix Metalloproteinase related  
products, please ask for a free copy  
of our brochure and product guide...



## Tissue Inhibitors of Metallo-Proteinases (TIMPs)

### Tissue Inhibitors of Metallo-Proteinases (TIMPs)

## Tissue Inhibitors of Metallo-Proteinases (TIMPs)

Product	Cat. No.	Size	Price
TIMP-1, Human Neutrophil Granulocyte	612080	5 µg	
TIMP-1, Recombinant, Bovine*	PF020	3 µg	
TIMP-1, Recombinant, Human*	PF019	3 µg	
TIMP-2, Human, Recombinant* 4	PF021	3 µg	
TIMP-2, Human Rheumatoid Synovial Fibroblast	612084	5 µg	
TIMP-2, Mouse, Recombinant	PF098	5 µg	
TIMP-3, Human, Recombinant	PF095	5 µg	
TIMP-3, Mouse, Recombinant	PF096	5 µg	
TIMP-3, Positive Control, Human	WB35	250 µl	
TIMP-4, Human Fibroblast	PF097	5 µg	

4 Sold under license of U.S. Patents 5,595,885 and 5,698,671.

## Antibodies to Tissue Inhibitors of Metallo-Proteinases (TIMPs)

### Antibodies to Tissue Inhibitors of Metallo-Proteinases (TIMPs)

Product	Cat. No.	Species Reactivity	Applications	Size	Price
Anti-TIMP-1 (Ab-1) (Mouse)*	IM32T IM32L	Bovine, Human, Rat	IB, IC, PS	10 µg 20 µg 100 µg	
Anti-TIMP-1 (Ab-2) (Mouse)*	IM41T IM41L	Human	IB, PS	10 µg 100 µg	
Anti-TIMP-1 (Ab-3) (Mouse)*	IM62T IM62	Human, Rat	FS, IB	10 µg 100 µg	
Anti-TIMP-1 (Ab-4) (Mouse)*	IM63T IM63	Human	FS, IB, PS	10 µg 100 µg	
Anti-TIMP-1 (Ab-6) Human (Rabbit)	PC500	Human	IB	50 µg	
Anti-TIMP-2 (Ab-1) (Mouse)*	IM11T IM11L	Human	FS, IB, IP	10 µg 20 µg 100 µg	
Anti-TIMP-2 (Ab-2) (Mouse)*	IM56T IM56L	Bovine, Guinea Pig, Human, Mouse, Rabbit, Rat	FS, IB, PS	10 µg 100 µg	
Anti-TIMP-2 (Ab-4) (Mouse)*	IM82T IM82	Human	FS, IB, PS	10 µg 100 µg	
Anti-TIMP-3 (Ab-1) (Mouse)*	IM43T IM43L	Baboon, Human, Rabbit	FS, IB, PS	10 µg 100 µg	
Anti-TIMP-4 (Ab-1) (Rabbit)	PC434	Human	IB	50 µl	

\* Not for sale in Japan

**Applications:** **FS:** Frozen Sections; **IB:** Immunoblotting (Western Blotting); **IC:** Immunocytochemistry; **PS:** Paraffin Sections

Discovery Pack™ is a trademark of Calbiochem-Novabiochem Corp.  
His•Tag® is a registered trademark of Novagen, Inc.  
Accucyte® is a registered trademark of CytImmune Science, Inc.  
Angiostatin® is a registered trademark of EntreMed, Inc.  
Endostatin™ is a trademark of EntreMed, Inc.  
Erichrome® is a registered trademark of Ciba Specialty Chemicals

*Prices subject to change without notification.*

Copyright © 2003 EMD Biosciences, Inc., an affiliate of Merck KGaA, Darmstadt, Germany. All Rights Reserved.  
CALBIOCHEM® is a registered trademark of EMD Biosciences, Inc.; Oncogene Research Products™ is a trademark of EMD Biosciences, Inc.;  
His•Tag® is a registered trademark of Novagen, Inc.; the VWR International name and logo are trademarks of Scientific Holdings Corp.



[www.calbiochem.com](http://www.calbiochem.com)

[technical@calbiochem.com](mailto:technical@calbiochem.com)

or contact your local sales office